Clinical Ophthalmology

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Optimal Treatment of Retinal Vein Occlusion: An Updated Canadian Review and Recommendations

Nirojini Sivachandran[1–5], Filiberto Altomare[6], Ravi Dookeran[7], Jesia Hasan[8], James H Whelan[9]

[1]Toronto Retina Institute, North York, ON, Canada; [2]Department of Chemistry and Biology, Toronto Metropolitan University, Toronto, ON, Canada; [3]Department of Ophthalmology, University of Ottawa, Ottawa, ON, Canada; [4]Toronto Metropolitan University, School of Medicine, Toronto, ON, Canada; [5]Institute for Biomedical Engineering, Science and Technology (iBEST) at Toronto Metropolitan University and St. Michael's Hospital, Toronto, ON, Canada; [6]Department of Ophthalmology and Vision Sciences, University of Toronto, Toronto, ON, Canada; [7]Department of Ophthalmology, University of Manitoba, Winnipeg, MB, Canada; [8]Department of Ophthalmology and Visual Sciences, McGill University, Montreal, QC, Canada; [9]Department of Surgery, Memorial University of Newfoundland, St. John's, NL, Canada

Correspondence: Nirojini Sivachandran, Toronto Retina Institute, 6 Maginn Mews, North York, Ontario, Canada, M3C 0G6, Tel +001-647-886-5863, Email nsivacha@gmail.com

Abstract: Retinal vein occlusion (RVO) represents a heterogeneous group of disorders that remains the second most common retinal vascular disease and can be associated with vision loss. RVO confers a substantial burden of illness that affects patients, caregivers, medical systems, and physicians. Complications of RVO – including cystoid macular edema, macular ischemia, and neovascularization sequelae – may result in severe visual morbidity and blindness. Canadian expert consensus recommendations on the optimal treatment of patients with RVO were published in 2015. Since that time, advances in diagnosis and pharmacotherapy have been made, changing the clinical approach of retina specialists. This article presents updated data and recommendations for the management of patients with RVO.

Keywords: epidemiology, pathophysiology, pharmacotherapy, retinal vein occlusion, risk factors

Introduction

Retinal vein occlusions (RVO) are a heterogeneous group of disorders that have in common impaired venous return from the retinal circulation.[1] RVO is a chronic condition and remains the second most common cause of vision loss, after diabetic retinopathy (DR), due to retinal vascular disease.[1,2]

The global prevalence of RVO in people aged 30–89 years has been estimated at 0.77% in 2015, representing 28.06 million affected people, and the pooled 5- and 10-year cumulative incidence of RVO globally were 0.86% and 1.63%, respectively.[3] Epidemiology data for patients with RVO in Canada are scarce. A retrospective study of patient records from the Southwestern Ontario family practice database from 2008–2009 found that 73 of 47,166 patients aged >40 years had RVO (0.15%), including 0.11% with branch RVO (BRVO) and 0.04% with central RVO (CRVO); however, these data may severely underestimate incidence/prevalence due to the nature of the study.[4] The paucity of Canadian-based ophthalmological practice data underlines the need for a national registry or a populational eye health study to determine regional disease burden and treatment patterns to help guide policy and decision-making. In other countries, studies estimated prevalence rates of 0.50% in the United States (US; 2005–2008), 0.40% in Germany (study period not reported), and 2.1% in Japan (1998), as well as incidence rates of 48.09 per 100 000 population in Korea (2004–2015) and 1.9 per 100 persons in China (2001–2011).[5–9]

As with all sight-threatening conditions, RVO imposes a substantial burden of illness that affects patients, caregivers, medical systems, and physicians. Among the complications associated with RVO, cystoid macular edema (CME) is the most common.[10] Other complications include retinal ischemia and neovascularization of the retina or of the anterior segment (iris and trabecular meshwork), which can lead to vitreous hemorrhage or to neovascular glaucoma respectively, potentially causing severe visual morbidity and/or blindness.[10,11] Vision loss can occur secondary to CME, macular

https://doi.org/10.2147/OPTH.S577821
Received: 30 October 2025
Accepted: 13 February 2026
Published: 10 March 2026

Box 1 Summary of New Insights and Recommendations Since the 2015 Canadian Expert Consensus

- Clearer picture of the factors contributing to the development and exacerbation of RVO, notably the role of angiopoietin 2
- Growing understanding and ongoing investigation of potential biomarkers for RVO, such as hyperreflective foci, endothelin-1, pentraxin 3, fatty acid-binding protein 4, and ellipsoid zone integrity
- Expanded imaging options, notably the emergence of OCT-A as a powerful visualization tool for retinal and choroidal microvasculature
- Confirmation in multiple large, real-world RVO studies of the safety and effectiveness of anti-VEGF agents, and evidence of their usefulness in patients with ischemic RVO
- Updated treatment strategies recommend consideration to switch anti-VEGF agents in patients with inadequate response
- Approval of faricimab as a bispecific (anti-VEGF and anti-Ang-2) treatment option
- Introduction and increasing availability of biosimilar agents for cost-effective anti-VEGF treatment
- Ongoing study of new molecules, including caspase-9 inhibitors, minocycline, rho-kinase inhibitors, CD 34+ stem cells, and gene therapies

ischemia, tractional retinal detachment, and secondary macular atrophy.[12,13] A retrospective study of patients with RVO in a US hospital estimated that 24.1% of patients would develop RVO in the fellow eye over their life expectancy (mean 16 years), with a conversion rate of 1.5% per year.[14]

RVO-associated vision loss negatively impacts patients' quality of life.[15–17] An online survey of 32 patients in Canada (March-April 2024) revealed that RVO led to visual complications that render certain daily activities (eg, reading and driving) problematic or impossible.[18] RVO was also associated with acute emotional and psychological burdens, such as elevated levels of fear or anxiety regarding accelerated vision loss or when receiving their intravitreal injections (IVI).[18] Patients living in rural and remote regions likely face a particularly increased burden for themselves and their caregivers if they are required to regularly travel long distances for their IVI appointments.[18]

In response to the perceived need by retinal specialists, Berger et al developed a Canadian expert consensus in 2015 on optimal treatment of patients with RVO.[19] Since that time, improved understanding of the clinical picture of RVO and new advances in diagnosis and pharmacotherapy have refined these strategies (Box 1). This article updates Canadian expert recommendations on the management of patients with RVO.

Methods

An English-language literature search using the PubMed Library was performed with combinations of the terms "retinal vein occlusion", "disease burden", "classification", "clinical features", "epidemiology", "etiology", "imaging", "history, complications", "pathogenesis", "pathophysiology", "risk factors", "anti-VEGF", "ranibizumab", "aflibercept", "bevacizumab", "faricimab", "emerging therapies", "steroid", "triamcinolone acetonide", "dexamethasone", "diet", "therapy", "surgery", and "laser" to identify studies published from January 2014 to January 2024. This was followed by a manual search of references cited in selected papers published in peer-reviewed journals, including the original consensus article. Older publications and trials were taken into consideration if deemed relevant and applicable to current practice and/or in cases where recently published evidence was insufficient to make sound conclusions. Meta-analyses, systematic reviews, and randomized clinical trials with at least 1 year of follow-up were selected as preferred sources.

References identified by the literature searches were further reviewed by the expert panel members. Each member was assigned a specific topic, on which they presented to the entire group during a meeting that took place in Toronto, Ontario, on September 28, 2024. During this meeting, the experts reviewed the evidence, highlighted new RVO data, and formulated recommendations to update current clinical considerations from the 2015 consensus. Agreement was sought on all recommendation points.

Classification

Lesion Area

RVO can be classified into 4 subtypes depending on the area of the lesion: CRVO, BRVO, hemiretinal (HRVO), and macular (MRVO).[20–24] RVO cases can evolve into more than one subtype. BRVO is the most common subtype, and includes HRVO and MRVO, with population-based estimates from the US, Europe, Asia, and Australia that BRVO is approximately 3–6 times more common than CRVO.[23–25] HRVO is retinal hemorrhage or other biomicroscopic evidence

of RVO (eg telangiectatic capillary bed) and a dilated venous system (or previously dilated venous system) in 2 or 3 quadrants, typically 2 altitudinal quadrants.[22] While HRVO is often considered as a separate condition, its features are intermediate between BRVO and CRVO.[22,26] The literature on MRVO is sparse; studies by Hayreh et al identified MRVO as a distinct clinical entity from major BRVO.[21] MRVO refers to occlusion of a macular venule,[27] and it occurs primarily in the superior sector and manifests as retinal nerve fibre layer hemorrhages and CME.[20,28,29] Where previously there were specific therapeutic approaches for the RVO subtypes, current treatments have demonstrated efficacy in patients with CME secondary to both CRVO and BRVO.[30]

Perfusion Status

RVO can also be broadly classified by perfusion status into ischemic and nonischemic types based on the area of capillary nonperfusion, and this distinction is useful for clinical management;[10] however, an indeterminate type also exists where the amount of intraretinal hemorrhages can mask the underlying perfusion status.[31] Most of these cases are subsequently identified as ischemic or nonperfused. Ischemic status is also indicated by the presence of retinal and iris neovascularization, which typically arise secondary to severe macular ischemia and extensive peripheral ischemia.[32] Rates of neovascular complications are notably higher in ischemic than nonischemic eyes (66.7% versus 2.8%, respectively).[29] Additionally, although nonischemic RVO may resolve without complications, it can also convert to an ischemic RVO in approximately 25–34% and 29% of CRVO and BRVO cases, respectively.[31,33,34]

Pathogenesis and Pathophysiology

The pathogenesis and pathophysiology of RVO involve multiple factors and differ between CRVO and BRVO. Occlusion of the central retinal vein generally occurs posterior to or within the lamina cribrosa.[35–37] Because the vein and artery share a common adventitial sheath at the lamina cribrosa, CRVO pathogenesis is likely to be the result of mechanical narrowing of the vein's lumen.[37] Venous compression in the form of a rigid and hyperplasic thick arterial wall is caused by arteriosclerosis.[37] BRVO is usually found at an arteriovenous (AV) junction[37,38] and potentially occurs due to a combination of vein compression at the AV junction, vessel wall degeneration, and abnormal hematological factors.[39] RVO-associated ischemia and inflammation lead to upregulation of vascular endothelial growth factor (VEGF) and expression of inflammatory cytokines; this also contributes to disruption of the blood-retina barrier (BRB) that is already compromised by fluid accumulation and tissue swelling caused by hydrostatic and osmotic pressure.[40] VEGF upregulation also increases endothelial cell proliferation, vascular permeability, and angiogenesis.[41] VEGF is expressed by retinal pigment epithelial (RPE), retinal glial, and vascular endothelial cells and is the main cytokine that induces neovascularization, exacerbating ischemia.[40,42,43] Both direct venous occlusion and subsequent compromised vascular integrity from inflammation and ischemia result in capillary nonperfusion.

Beyond VEGF, a host of cytokines and chemokines have been found to be significantly correlated with RVO and CME, including proinflammatory interleukins (including IL-1, IL-6, IL-8, IL-12, IL-15, and IL-18), matrix metalloproteinase, platelet-derived growth factor A, and lysophosphatidic acid and autotaxin.[40,42] Placental growth factor (PGF), a member of the VEGF family, has been found to be active in pathological retinal angiogenesis and inflammation.[44] While PGF is expressed primarily by the placental trophoblast during pregnancy,[45] its expression increases during pathologic conditions in RPE and choroidal cells.[46,47] Increased expression of PGF has been found in retinal diseases such as BRVO,[48] DR,[49] and diabetic macular edema (DME).[50,51] PGF facilitates angiogenesis via induction of crosstalk between VEGFR-1 and VEGFR-2 receptors, which increases cell sensitivity to VEGF-A activity.[44]

More recently, the vascular destabilizing effects of angiopoietin 2 (Ang-2) have been studied, including increasing VEGF activity, weakening of endothelial cell junction integrity, and involvement in inflammatory cell recruitment.[52,53] Preclinical studies have also identified that Ang-2 negatively affects Tie2 integrin signaling, promoting angiogenesis and destabilization of the endothelium.[54,55] Intravitreal Ang-2 levels are higher in RVO compared to neovascular age-related macular degeneration (nAMD) and non-proliferative DR.[56]

Risk Factors (Table 1)

General or Systemic Factors

Advanced age is a well-established primary risk factor for RVO;[6,24,57,58] odds ratios (OR) for RVO per 10-year increase have been estimated at 1.60–1.93 (Figure 1).[3,5,25] The association between RVO prevalence and increased age may be partly attributed to the high prevalence of cardiovascular comorbidities among older patients, as the presence of systemic vascular and atherosclerotic diseases is a known risk factor for RVO.[3,8,9,58–64]

Several studies have demonstrated that hypertension is among the strongest risk factors for RVO;[3,9,58,59,61,63] this association may be stronger in BRVO than in CRVO.[8] Other cardiovascular diseases positively associated with RVO include stroke and myocardial infarction,[60,62] and obstructive sleep apnea (OSA) has a high prevalence among patients with RVO.[65–67] Many patients with RVO present with undiagnosed conditions such as hypertension or OSA,[64,68] which highlights the importance of communication between specialists and primary-care providers. However, patients lacking a primary-care physician may not receive proper management of their comorbidities.

Ocular Factors

Ocular risk factors for RVO include ocular hypertension and glaucoma.[69–71] A meta-analysis found the OR for RVO in the presence of glaucoma to be 4.01 (95% confidence interval [CI] 3.28, 4.91), and stronger associations noted for CRVO (OR 6.21; 95% CI 4.64, 8.31) and HRVO (OR: 4.60; 95% CI 2.26, 9.35) than for BRVO (OR 2.38; 95% CI 1.77, 3.19).[70] The increased risk for RVO was significant in patients with primary open-angle glaucoma (OR 5.03; 95% CI 3.97, 6.37; $P<0.001$) but not for primary angle-closure glaucoma.[70,72] Signs of RVO such as hemorrhage or cotton wool spots are similar to those observed in DR; thus, RVO should be considered in patients with diabetes mellitus presenting with acute loss of vision and asymmetric signs of DR.[73]

Thrombotic Factors

Data on the association between RVO and thrombotic risk factors appear conflicting. Patients with RVO have been reported to have higher prevalence of hyperhomocysteinemia and other thrombotic risk factors such as antithrombin, protein C or protein S deficiency, high factor VIII levels, and factor V Leiden, an R506Q mutation in the factor V gene;[63,71,74] however, other studies did not find significant differences in levels of these factors.[37,75] Coagulation disorders were found in 11.5% of 52 young (<40 years) patients with CRVO.[69]

Pharmacological Factors

Certain medications and recreational drugs may increase the risk of developing RVO, as found in case reports and case series of antipsychotics,[76,77] cancer therapies (inhibitors of mitogen-activated protein kinase or tyrosine kinase),[78,79] sildenafil,[80] and minoxidil.[81] Cigarette smoking, cocaine, and methamphetamines have all been linked to an increased risk of RVO.[59,71,82–84] The association between oral contraceptive pills (OCP) or hormone replacement therapy (HRT) and RVO is unclear, and most data in the literature are derived from case reports. A population-based cohort study involving records of more than 2 million women from the Korea National Health Insurance Service found no association between a history of HRT or OCP use and the incidence of RVO,[85] as did an observational case series of 60 patients aged ≤49 years in the US.[86] A few studies found appreciable levels of OCP or HRT use in patients with RVO; however, no causal analyses were conducted.[87–89] Of note, the study by Kirwan et al with the objective of determining whether OCP or HRT were independent risk factors for RVO found that 11 of 588 women with RVO had a history of HRT or OCP use, including 6 of 9 patients aged <35 years with a history of OCP use.[89] The authors recommended that RVO be a contraindication to the use of OCP.

Clinical Features and Potential Diagnostic Markers

Beyond general findings such as low vision and visual field or pupillary defects, clinical features of RVO can be classified as acute or chronic conditions (Box 2 and Figure 2). Ischemia is indicated by the presence of low vision (often

Table 1 Risk Factors for RVO

Modifiable			
Systemic Vascular/Atherosclerotic Diseases	**Ocular**	**Patient Characteristics**	**Medications and Recreational Drugs**
• Hypertension • Dyslipidemia • Diabetes mellitus • Peripheral artery disease • Obstructive sleep apnea • Multiple myeloma • Polycythemia vera • Leukemia • Syphilis	• Glaucoma (open- and closed-angle) • Ocular hypertension • Diabetic retinopathy • Retinal vasculitis	• Elevated body-mass index • Smoking • Low levels of folic acid • Reduced levels of nitric oxide	• Antipsychotics • Cancer therapies a. MEK inhibitors b. Systemic TK inhibitors • Minoxidil • Sildenafil • Cigarette smoking • Cocaine

Nonmodifiable				
Systemic Diseases	**Mechanical Compression**	**Ocular**	**Thrombotic**	**Patient Characteristics**
• Chronic renal failure • Systemic lupus erythematosus • Sarcoidosis • Stroke	• Atherosclerosis of retinal arteries (venous thrombosis at area of AV crossing) • External compression or disease of retinal venous wall i.e vasculitis • Changes in lamina cribrosa (CRVO)	• Hyperopia/short axial length • Central serous chorioretinopathy	• Hyperhomocysteinemia • Antiphospholipid syndrome • Anticardiolipin antibody • Prothrombin G20210A mutation • Factor V Leiden • Protein C/S deficiency • Antithrombin III deficiency	• Age

Abbreviations: AV, arteriovenous; MEK, Mitogen-activated protein kinase/extracellular signal-regulated kinase; POAG, primary open-angle glaucoma; TK, tyrosine kinase.

https://doi.org/10.2147/OPTH.S577821

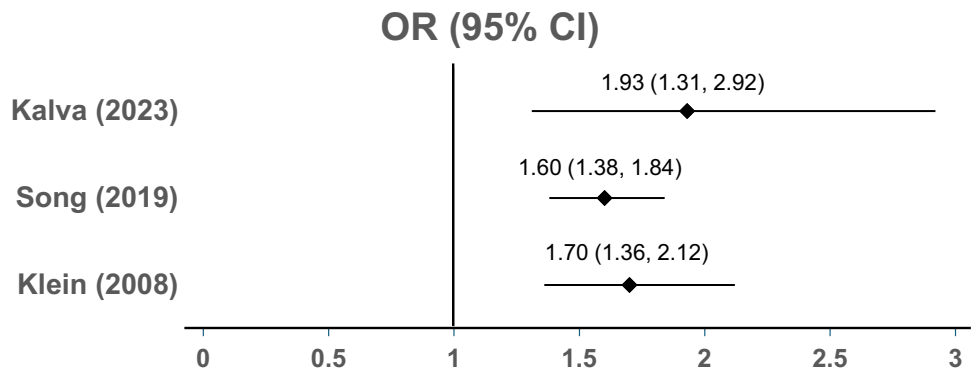

Figure 1 Odds ratios of RVO by 10-year increment in age.
Abbreviations: CI, confidence interval; OR, odds ratio.

20/200 or worse), visual field defect including central scotoma, a relative afferent pupillary defect, and/or neovascularization of the iris.

Potential diagnostic markers for RVO are listed in Box 3. RVO causes inflammation, with increased expression of inflammatory factors such as VEGF and cytokines.[40,90,91] Endothelin-1 (ET-1) is the most potent vasoconstrictor in the cardiovascular system and is a proinflammatory peptide which promotes neutrophil adhesion to the endothelium and subsequent platelet aggregation.[92,93] Pentraxin 3 is produced by RPE cells in the presence of proinflammatory cytokines, and its plasma concentration was significantly higher in the RVO group than healthy controls.[94,95] Elevated vitreous levels of fatty acid-binding protein 4, which coordinates lipid responses in cells, was also shown to be significantly elevated in patients with RVO compared with control patients.[96]

Optical coherence tomography (OCT) imaging has revealed diagnostic and prognostic biomarkers for RVO, the most established of which are central retinal thickness (CRT) and presence of macular fluid.[97–100]

Increased levels of inflammatory factors in RVO (eg, IL-6, VEGF, and intercellular adhesion molecule 1) and the presence of subretinal fluid are associated with serous retinal detachment in patients with RVO.[97] Hyperreflective foci (HRF) are dot-liked lesions that are believed to represent activated microglial cells; they are an indicator of active inflammation. HRF in RVO-associated CME has been associated with an increased CRT and the presence of subretinal fluid.[97,98] Additional prognostic biomarkers for visual outcomes include disorganizations of the inner or outer retinal layers, particularly later during the treatment course, ellipsoid zone integrity, and absence of a posterior vitreous detachment.[97,98,101,102]

Box 2 Clinical Features of RVO

Acute
- Dilated, tortuous retinal veins of affected area
- Deep and superficial retinal hemorrhages
- ± Cotton wool spots
- ± Cystoid macular edema
- ± Capillary nonperfusion

Chronic (Figure 3)
- Optic disc and retinal collateral vessels
- Telangiectatic capillary bed
- Perivenous sheathing
- Arteriolar narrowing
- Changes in macula; i.e chronic cystoid macular edema, retinal pigment epithelium mottling, exudate, epiretinal membrane, etc.

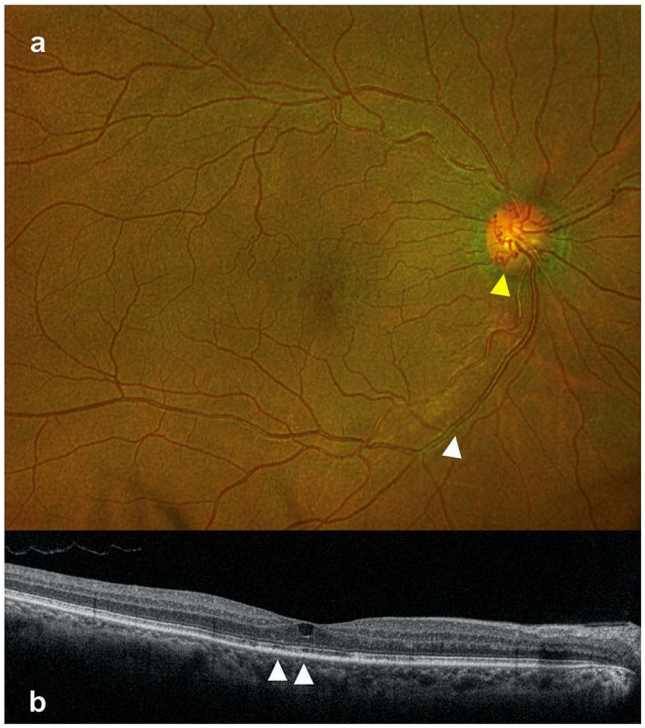

Figure 2 Chronic RVO changes including optic disc collaterals (yellow arrowhead) and perivenous sheathing (white arrowhead). RPE mottling in the macula (**a**) and associated attenuation of ellipsoid (white arrowhead in **b**) are noted. Images provided by Dr. Sivachandran.
Abbreviation: RPE, retinal pigment epithelium.

Imaging

Fundus photography remains a primary imaging tool in the diagnosis of RVO. On fundoscopic examination, CRVO typically demonstrates enlargement and tortuosity of the central retinal vein and its branches with widespread retinal hemorrhages in all 4 quadrants (Figure 3).[103]

In contrast, BRVO presents as a wedge-shaped area arising from an AV crossing, more frequently in the superotemporal quadrant.[104,105] Additionally, RVO can present with cotton wool spots, retinal hemorrhages, and preretinal/subhyaloid hemorrhage (secondary to neovascularization). These findings can be imaged on fundus photography for diagnosis and monitoring. Macular changes that can be visualized with fundus photography include CME, exudate, epiretinal membrane (ERM), and degenerative changes in the RPE. Recent advances in deep learning and artificial intelligence to interpret fundus photographs have resulted in highly accurate diagnostic models for RVO.[106–108]

Fluorescein angiography (FA) is used to identify the extent of vascular occlusion, degree of ischemia and leakage, and extent of CME.[109,110] Ultra-widefield (UWF) imaging up to an angle of 200° is helpful to visualize the peripheral retina and assess retinal capillary nonperfusion,[111] which is of particular importance in RVO to identify peripheral nonperfusion and ischemia (Figure 4).[112] UWF FA is also used to identify abnormalities associated with CME, including area and extent of retinal nonperfusion.[113]

OCT remains the most commonly used imaging device for the diagnosis and assessment of RVO-associated CME, including CRT and measurement of treatment effect (Figure 3).[32] The introduction of spectral-domain OCT allows imaging of the macula with a much faster scan rate and at a higher scan resolution.[114] OCT angiography (OCT-A) visualizes the microvasculature of the retina and choroid.[115] OCT-A imaging of qualitative vascular abnormalities in RVO – such as capillary nonperfusion, enlargement of foveal avascular zone (FAZ), neovascularization, vascular tortuosity and dilatation, and microaneurysms – has been shown to be comparable with that of FA.[116–120] Swept-source OCT-A has greater definition than dye angiography and enables widefield imaging of the retina, which is particularly useful in evaluating RVO as capillary abnormalities often extend beyond the macula.[115,121,122] Quantitative imaging of metrics such as FAZ diameter and size and vessel density may contribute to prognosis of visual

https://doi.org/10.2147/OPTH.S577821

Box 3 Diagnostic Biomarkers

- Inflammatory cytokines
- Endothelin-1
- Pentraxin 3
- Fatty acid-binding protein 4
- OCT
  - Central retinal thickness
  - Macular fluid
  - Hyperreflective foci
  - Serous retinal detachment
- OCT-A
  - Capillary nonperfusion
  - Foveal avascular zone morphology
  - Neovascularization
  - Vascular tortuosity, dilatation, and telangiectasias
  - Microaneurysms
  - Intraretinal hemorrhage
  - Deep capillary plexus fractal dimension, vessel density, and lacunarity
- Fluorescein angiography
  - Capillary nonperfusion
  - Neovascularization
  - Vessel density
  - Peripheral ischemia (ischemic index)
  - Deep capillary plexus fractal dimension, vessel density, and lacunarity
- Loss of integrity of ellipsoid zone, disorganization of retinal inner layers (DRIL), absence of a posterior vitreous detachment (PVD) are associated with poorer visual outcomes
  - DRIL and ellipsoid zone integrity after first 3 loading doses with anti-VEGF are associated with long-term (1 year) visual outcomes

outcomes in patients with RVO.[123–127] Imaging of patients with RVO is also useful in the assessment of treatment responses,[121,128,129] as these techniques can identify areas of leakage and ischemia. Studies have shown that greater extent of peripheral ischemia drives persistent CME and need for ongoing anti-VEGF therapy in patients with concomitant diabetic retinopathy.[115]

Treatment – General Principles

A clear understanding of the natural history of RVO is essential to determine optimal management strategies. As described by Berger et al,[19] the CVOS Group identified either good (>20/40) or poor (<20/200) baseline visual acuity (VA), but not intermediate, as a strong predictor of 3-year VA and of the risk of neovascularization.[31] This group also found that 34% of eyes developed ischemia over 3 years. Hayreh et al reported on natural history according to RVO classification.[130] In a cohort of 667 patients with CRVO seen within 3 months of onset, the investigators found a significant difference in the proportions of patients with VA ≥20/100 between nonischemic and ischemic cases (78% versus 1%; $P<0.0001$). Visual field defects were mild to moderate in a significantly higher proportion of patients without ischemia (91% versus 8%; $P<0.0001$). In patients with BRVO seen within 3 months of onset, VA improved or remained stable in 75% and 87% of patients with major and macular BRVO, respectively, and initial VA ≥20/60 and in 69% and 53%, respectively, of patients with initial VA ≤20/70.[21]

General management of patients with RVO begins with identification and control of modifiable risk factors. Optimal risk-factor management will likely necessitate adopting a multidisciplinary approach with a primary-care provider and/or specialist. Undiagnosed or inadequately treated systemic risk factors have a negative effect on visual prognosis and associated ocular complications. Alternative strategies to rapid patient assessment may be required, including referral to a walk-in clinic for a prompt physical examination, review of vital signs, and bloodwork.

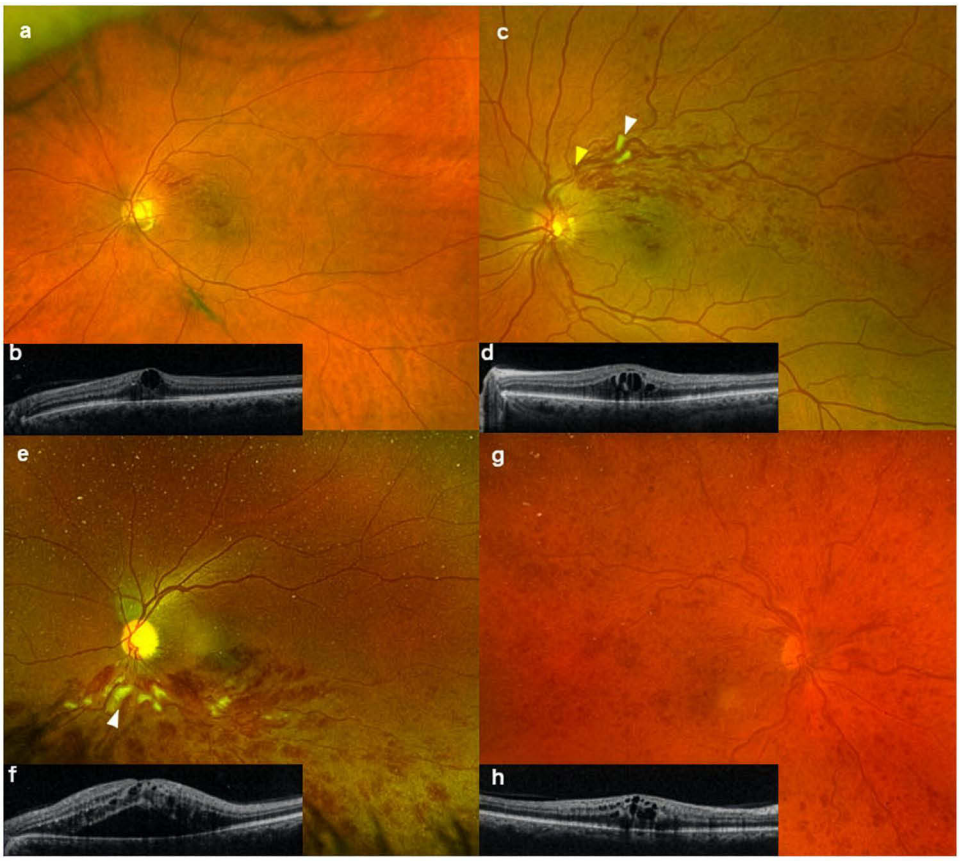

Figure 3 Representative fundus and OCT images for RVO. MRVO is shown where nerve fibre layer hemorrhages are limited to the superior macula below the arcade and does not involve the periphery (**a**) with associated CME (**b**). A dilated and tortuous superior retinal vein is noted secondary to arteriovenous nicking (yellow arrow) in superior BRVO (**c**) and associated CME (**d**). Cotton wool spots are indicated by white arrows in c and e. HRVO involving inferior nasal and temporal hemisphere (**e**) and associated CME with intra-and subretinal fluid is noted (**f**). CRVO is presented with retinal hemorrhages involving all 4 quadrants (**g**) and associated CME (**h**). Images provided by Dr. Sivachandran.

Abbreviations: BRVO, branch retinal vein occlusion; CME, cystoid macular edema; CRVO, central retinal vein occlusion; HRVO, hemiretinal vein occlusion; MRVO, macular retinal vein occlusion; OCT, optical coherence tomography.

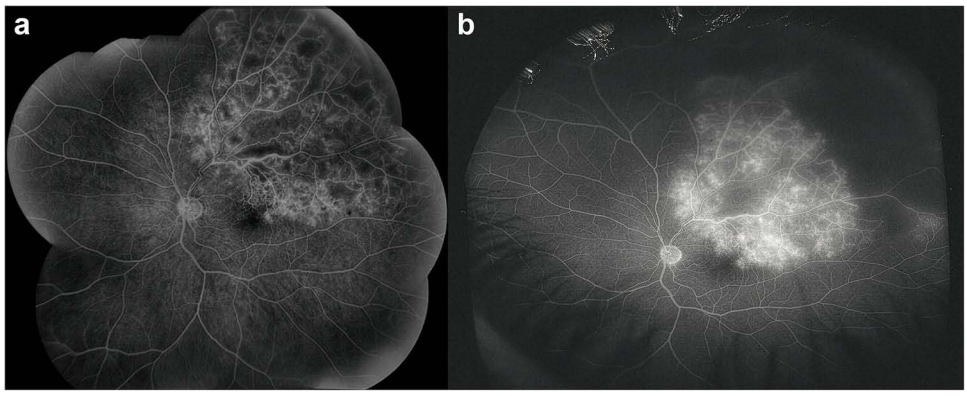

Figure 4 Fluorescein angiography of a supertemporal BRVO in the left eye. (**a**) Evidence of capillary drop out and vascular remodeling in the location of the occlusion. (**b**) Widefield angiography reveals a larger area of nonperfusion in the peripheral retina. Images provided by Dr. Hasan.

The use of antithrombotic therapy in patients with RVO is controversial and no large, randomized trials are available to assess their safety and efficacy in this patient population. A systematic review and meta-analysis of anticoagulant and antiplatelet therapy in patients with RVO (N=1422 patients from 15 studies) found that anticoagulant use was associated with a higher rate of VA improvement than antiplatelet use (64% versus 33%), and improvement by logarithm of the

https://doi.org/10.2147/OPTH.S577821

minimum angle of resolution (LogMAR) was significantly higher in patients receiving an anticoagulant than an antiplatelet (−0.20 versus 0.00; P=0.01).[131]

The role of diet in the management of patients with RVO should not be overlooked, particularly to minimize baseline inflammatory states. Plant-based diets have been associated with a reduced risk for cardiovascular disease, including ischemic heart disease and cerebrovascular disease,[132–134] as well as anti-inflammatory properties.[135] Dietary considerations should also account for providing adequate levels of key minerals and vitamins that have been implicated in RVO, including iron, magnesium, folic acid, and vitamins B12 and D.[136–140]

Updated treatment algorithms from Berger et al for patients with BRVO or CRVO are presented in Figures 5 and 6. Recommendations for general treatment principles are presented in Box 4.

Pharmacotherapy

Anti-VEGF Agents

Berger et al[19] presented the details of the Phase 3 trials involving ranibizumab[141–145] and aflibercept[146,147] (Table 2) and the small-scale clinical trials with bevacizumab[148–151] that demonstrated their safety and efficacy versus sham injection in patients with CME secondary to BRVO or CRVO. Maintenance of visual and anatomic benefits was observed with ranibizumab and aflibercept in follow-up treat-and-extend studies up to 9 years,[152–156] and meta-analyses confirmed their superiority to steroids, laser therapy, or observation.[157–161] Based on these results, international guidelines support anti-VEGF agents as first-line therapy in patients with RVO-associated CME.[10,32,110]

Real-world outcomes supported the safety and effectiveness of anti-VEGF agents.[164–170] Evaluation of 3-year outcomes in treatment-naïve patients with CRVO from the international Fight Retinal Blindness Registry found a mean (95% CI) VA improvement of 12 (9, 15) letters and a mean reduction in central subfield thickness (CST) of 324 µm (291, 358 µm).[171] No significant differences in VA improvement were identified between aflibercept, ranibizumab, and bevacizumab; however, the differences in CST reductions between aflibercept (−310 mm) versus ranibizumab (−258 mm) versus bevacizumab (−216 mm) were significant (P<0.001). It should be noted that nearly 50% of the original cohort was lost to follow-up. In the international, prospective, observational AURIGA study, 554 treatment-naïve and 65 previously treated patients who received aflibercept for RVO experienced improvements in their VA from baseline of 12.5 (10.8, 14.3) and 7.9 (3.3, 12.6) letters, respectively, at 12 months and 11.4 (9.4, 13.3) and 4.4 (- 0.6, 9.5) letters, respectively, at 24 months.[164] A treatment interval of Q≥12W at 12 months was achieved by 34.9% (187/536) of treatment-naïve and 39.3% (24/61) of treatment-experienced patients; at 24 months, 41.0% (220/536) and 41.0% (25/61), respectively, had achieved a Q≥12W treatment interval.

The exclusion of patients with a positive relative afferent pupillary defect in BRAVO and CRUISE likely prevented the participation in these trials of patients with ischemic RVO. The prospective, open-label Rubeosis Anti-VEGF (RAVE) trial enrolled 20 patients with CRVO who were at high risk of ischemia.[172] Patients received monthly doses to 8 months, were observed for 3 months, and then examined monthly on *pro re nata* (PRN) injection to 36 months. At 8 months, mean best-corrected VA (BCVA) was improved by 21.1 letters and mean central macular thickness (CMT) was reduced by 294 µm from baseline. During the 3-month observation, mean CMT increased by 203 µm and decreased by 191 µm during PRN dosing to 36 months. BCVA was +21.4 letters from baseline to 36 months. Neovascular complications were observed in 9 of the 18 patients completing the study at a mean of 24 months of follow-up. Thus, anti-VEGF therapy delayed but did not prevent neovascularization in 50% of patients.

Faricimab

Faricimab is a bispecific agent that provides dual inhibition of the Ang/Tie-2 and VEGF signalling pathways in patients with retinal diseases.[56,173] Inhibition of VEGF and Ang-2 demonstrated greater reductions in vessel lesion number, vascular permeability, retinal edema, and neuron loss than either component alone.[55] Synergistic activity of anti-inflammation and reduction of choroidal neovascularization leakage points to greater durability than with VEGF inhibition alone.[56] In an analysis of the vitreous of patients with newly diagnosed nAMD, DR, proliferative DR, or

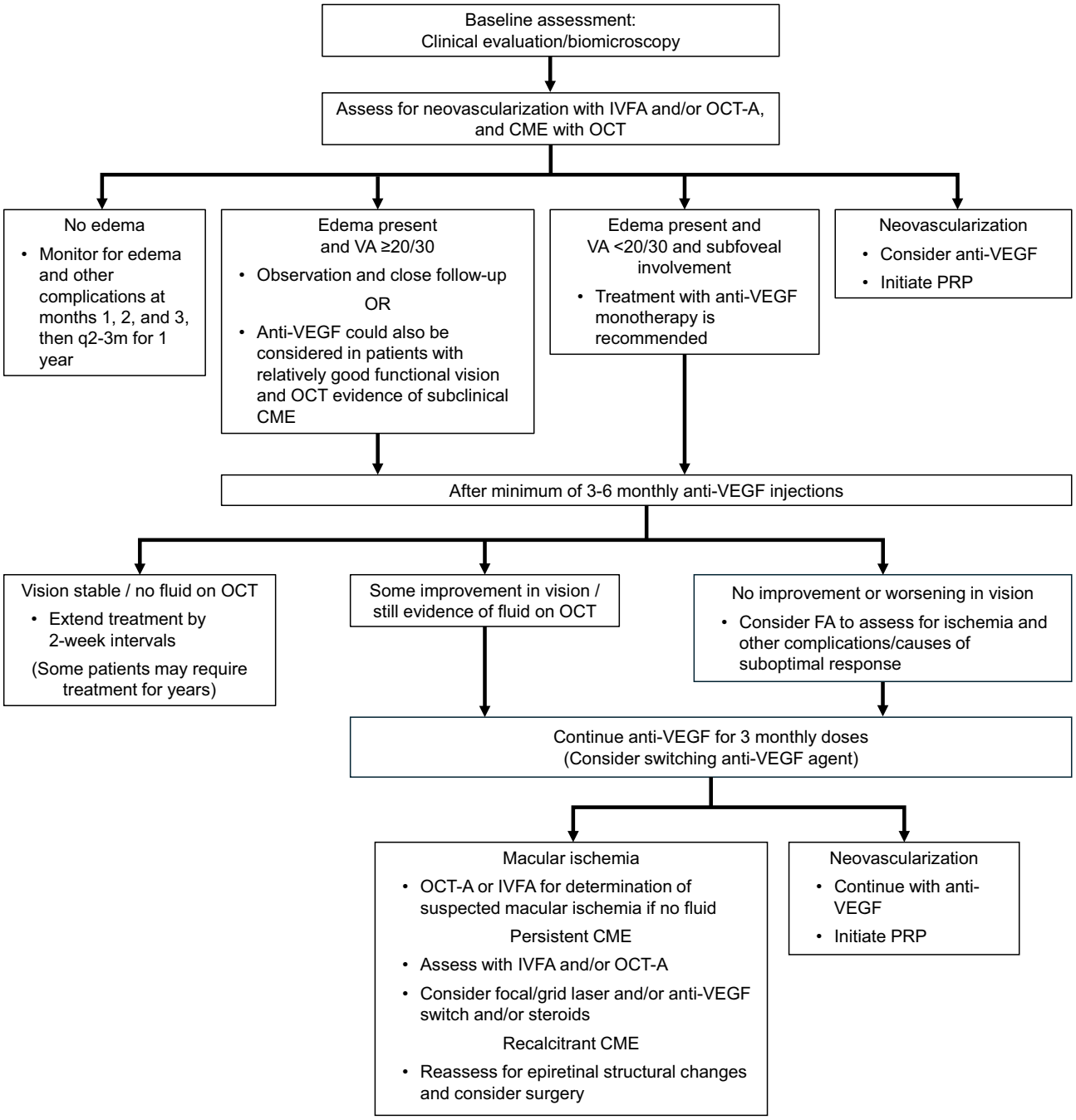

Figure 5 BRVO treatment algorithm. Bulleted text is subordinate to the text above it.
Abbreviations: CME, cystoid macular edema; IVFA, intravenous fluorescein angiography; OCT, optical coherence tomography; OCT-A, optical coherence tomography angiography; PRP, panretinal laser photocoagulation; VA, visual acuity; VEGF, vascular endothelial growth factor.

RVO; increases in Ang-2 levels were significant in all 4 subgroups and second highest (behind proliferative DR) in patients with RVO.[174]

Faricimab was approved by Health Canada in July 2024 for the treatment of patients with CME secondary to RVO.[175] Approval was based on the results of the double-masked, multicentre, randomized, parallel-group, registrational phase 3 BALATON and COMINO trials, which showed that faricimab 6.0 mg was noninferior to aflibercept 2.0 mg for adjusted mean changes in BCVA (primary endpoint) or reductions in CST from baseline to week 24 (Table 2).[162] Significantly more patients who received faricimab versus aflibercept experienced resolution of macular leakage at week 24 in

https://doi.org/10.2147/OPTH.S577821

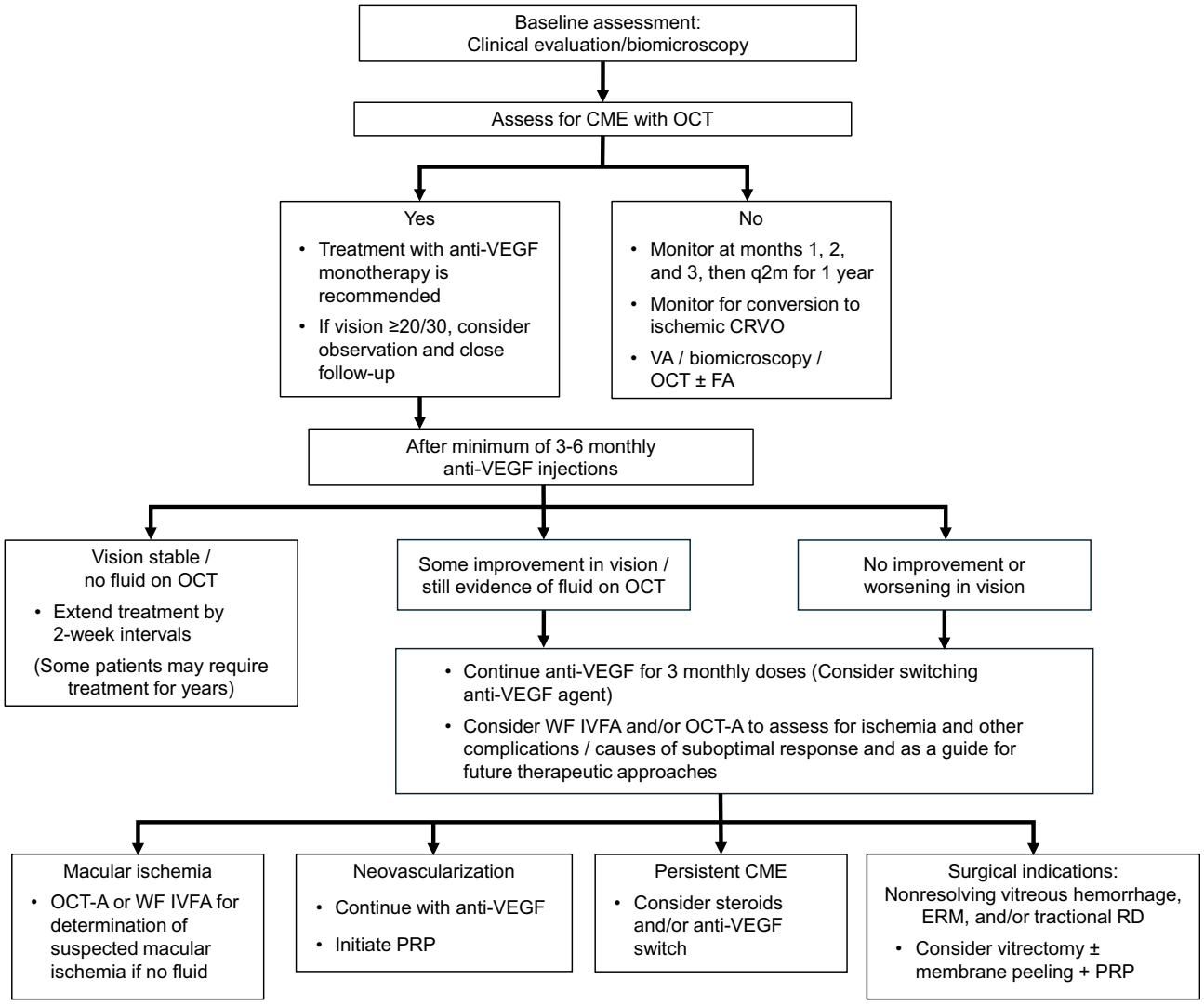

Figure 6 CRVO treatment algorithm. Bulleted text is subordinate to the text above it.
Abbreviations: CME, cystoid macular edema; CRVO, central retinal vein occlusion; ERM, epiretinal membrane; IVFA, intravenous fluorescein angiography; OCT, optical coherence tomography; OCT-A, optical coherence tomography angiography; PRP, panretinal laser photocoagulation; RD, retinal detachment; VEGF, vascular endothelial growth factor; WF, wide-field.

BALATON (33.6% versus 21.0%; nominal P=0.0023) and COMINO (44.4% versus 30.0%; nominal P=0.0002). The incidence of ocular adverse events was similar between patients receiving faricimab and aflibercept in both studies. Longer-term data for BALATON and COMINO employing a modified treat-and-extend regimen found that the VA and anatomic gains achieved at 24 weeks were maintained at 72 weeks (Table 2).[163] Dosing intervals of Q≥12W were achieved by 64% (BALATON) and 45% (COMINO) of treatment-naïve patients and by 57% (BALATON) and 50% (COMINO) of treatment-experienced patients.

Recommendations for the use of anti-VEGF agents are presented in Box 5.

Box 4 Recommendations – General Treatment Principles

- Creation of a Canadian national RVO registry is desirable to inform clinical and regulatory decision-making.
- A multidisciplinary approach is important to achieve optimal control of modifiable risk factors of RVO.

Table 2 Visual and Anatomical Outcomes in RVO Patients Treated with Ranibizumab, Aflibercept, and Faricimab

Outcome	Mean Change in BCVA from Baseline, ETDRS Letters			Mean Change in CRT from Baseline, μm		
	6 Months	12 Months	24 Months	6 Months	12 Months	24 Months
RANIBIZUMAB						
BRAVO (397 eyes with BRVO)[141,142,145]						
Ranibizumab 0.3 mg[a]	+16.6	+16.4	+15.6	–337.3	–313.6	–291.4
Ranibizumab 0.5 mg	+18.3	+18.3	+17.5	–345.2	–347.4	–330.6
Sham[b]	+7.3	+12.1	+14.9	–157.7	–273.7	–304.2
CRUISE (392 eyes with CRVO)[143,144]						
Ranibizumab 0.3 mg[a]	+12.7	+13.9	+8.2	–452.3	–452.8	–370.9
Ranibizumab 0.5 mg	+14.9	+13.9	+12.0	–433.7	–462.1	–412.2
Sham[b]	+0.8	+7.3	+7.6	–167.7	–427.2	–418.7
Aflibercept						
GALILEO (177 eyes with BRVO)[146]						
Aflibercept 2.0 mg[c]	+18.0	+16.9	–	–448.6	–423.5	–
Sham[c]	+3.3	+3.8	–	–169.3	–219.3	–
COPERNICUS (189 eyes with CRVO)[147]						
Aflibercept 2.0 mg[c]	+17.3	+16.2	–	–457.2	–413.0	–
Sham[c]	–4.0	+3.8	–	–144.8	–381.8	–
Faricimab						
BALATON (553 eyes with BRVO)[162,163]						
Faricimab 6.0 mg[d]	+16.9	+18.1[e]	–	–311.4	–310.9[e]	–
Aflibercept 2.0 mg[d]	+17.5	+18.8[e]	–	–304.4	–307.0[e]	–
COMINO (729 eyes with CRVO)[162]						
Faricimab 6.0 mg[d]	+16.9	+16.9[e]	–	–461.6	–465.9[e]	–
Aflibercept 2.0 mg[d]	+17.3	+17.1[e]	–	–448.8	–460.6[e]	–

Notes: [a]Switched to ranibizumab 0.5 mg after 12 months. [b]Switched to ranibizumab 0.5 mg after 6 months. [c]Patients received aflibercept or sham q4w for 20 weeks; from weeks 24–48, all patients received aflibercept on an as-needed basis, and patients who did not require injection at monthly evaluation received a sham injection. [d]Patients received faricimab or aflibercept q4w for 20 weeks; from weeks 24–72, all patients received faricimab up to q16w on a modified treat-and-extend regimen. [e]Outcomes were averages of measurements over weeks 64, 68, and 72.

Abbreviations: BCVA, best-corrected visual acuity; BRVO, branch retinal vein occlusion; CRT, central retinal thickness; CRVO, central retinal vein occlusion.

Box 5 Recommendations – Anti-VEGF Agents

- Anti-VEGF agents remain the first-line treatment for patients with CME secondary to RVO.
- Anti-VEGF monotherapy such as aflibercept has been used extensively due its effectiveness in a treat & extend regimen.
- In this heterogeneous RVO population, different drugs may work differently in different patients so individualized treatment selection may be warranted or beneficial.
- Long-term and real-world studies with faricimab are warranted to confirm the added benefit of Ang-2 blockade as well as the Phase 3 trial results showing comparable visual outcomes, improved macular drying, and extensions of the treatment interval.

https://doi.org/10.2147/OPTH.S577821

Box 6 Recommendations – Biosimilars

- Real-world study evidence will be beneficial to confirm the safety and effectiveness of biosimilar anti-VEGF agents in patients with RVO.

Biosimilars

Biosimilar anti-VEGF agents have been approved for the treatment of patients with nAMD and DME, and all provinces and territories have adopted switching requirements as cost-saving equivalents to brand-name agents.[176] Studies have demonstrated the equivalence of ranibizumab biosimilars with the originator agent in patients with nAMD;[177–181] however, there is a paucity of biosimilar data in patients with RVO. A subgroup analysis of the RE-ENACT 2 study involving 101 patients with RVO confirmed similar results for BCVA, CST, and presence of macular fluid, and no new safety signals; however, this study did not include a control group.[182]

At present, 2 ranibizumab biosimilars and 7 aflibercept biosimilars are approved in Canada for RVO.[183–191] Biosimilar usage in patients with RVO is expected to be primarily guided by provincial regulations as per those adopted for the anti-VEGF treatment of patients with nAMD or DME.

Recommendations for the use of anti-VEGF agents are presented in Box 6.

Steroids

As described by Berger et al,[19] steroids continue to have a second-line role in the management of patients with RVO; however, they are limited by the risk of adverse events such as cataract formation or increased intraocular pressure (IOP). Although steroids have been shown to inhibit VEGF expression,[192,193] they may be most effective in VEGF-independent pathways promoting CME in RVO.[10,32] Steroids reduce levels of inflammatory cytokines such as IL-6, IL-10, IL-17, and platelet-derived growth factor AA, stabilize the blood retinal barrier, inhibit leukostasis, and modulate downstream effectors of VEGF.[194,195]

Intravitreal triamcinolone acetonide was more efficacious in improving VA versus observation in the treatment of patients with CRVO in the Standard Care versus Corticosteroid for Retinal Vein Occlusion (SCORE) Study Report 5.[196] Incidence of cataract and increased IOP were higher in the 4-mg group than the 1-mg group. The SCORE Study Report 6 in patients with BRVO found similar rates of VA improvement between triamcinolone acetonide and grid photocoagulation (standard of care).[197] Given the higher incidence of adverse events, triamcinolone acetonide was not recommended as standard of care in this patient population. Use of the sustained-release dexamethasone intravitreal implant was shown in the GENEVA trial to be associated with significantly higher proportions of eyes with CME secondary to RVO that achieved improvement in BCVA of ≥15 letters compared with sham implant.[198] IOP-lowering medication was required in 35% of patients who received the dexamethasone implant during the 12 months of study. Subsequent real-world studies found that the mean interval for dexamethasone implant reinjection was 4.5–5.9 months.[199–202] The SOLO study found that dexamethasone implant retreatment prior to the labelled 6-month interval was performed in 22 of 54 eyes (40.7%) with BRVO and 24 of 48 eyes (50.0%) with CRVO.[203] Other studies determined a mean of 1.9–2.2 implants during the first 12 months of treatment.[200,204]

Although combination therapy with anti-VEGF and steroid was found in a systematic review and meta-analysis (10 studies) to be significantly superior to either agent alone in improving BCVA and CMT among patients with CME secondary to RVO,[30] the included studies were heterogeneous, using different anti-VEGF agents, steroids, and delivery methods. While combination therapy can be helpful in certain cases, there are insufficient data to support generalized usage to reduce the number of anti-VEGF injections.

Recommendations for the use of steroids are presented in Box 7.

Laser and Surgical Therapy

Before the advent of anti-VEGF agents, lasers were the mainstay of treatment in patients with RVO. Treatment protocols were based on the Branch Vein Occlusion and Central Vein Occlusion studies (BVOS and CVOS).[205–207]

Box 7 Recommendations – Steroids

- Intravitreal steroids should remain as a second-line option in patients with CME associated with RVO who experience an inadequate response to anti-VEGF agents and in subpopulations in whom biologic therapy should be avoided (eg, pregnant patients).
- The choice among available steroid options–triamcinolone acetonide, dexamethasone, and fluocinolone acetonide–is at the discretion on the treating physician's preference.
- Close monitoring for cataracts or increased IOP of patients receiving intravitreal steroids is required.
- There are insufficient data to support the use of steroids to reduce the number of anti-VEGF injections.

The BVOS found that grid laser photocoagulation was associated with a significantly higher proportion of eyes with CME secondary to BRVO (in eyes with baseline VA of ≤20/40) gaining ≥2 lines of VA; however, patients with baseline VA of ≤20/200 or who did not receive treatment for more than 1 year did not derive significant benefit.[205] Conversely, the CVOS determined that, while grid laser photocoagulation reduced angiographic evidence of CME, it did not improve VA relative to no treatment.[206] Laser scars expand and with excessive laser or treatment too close to the central fovea these scars may eventually grow to involve the fovea. Caution should be exercised when performing macular laser. Complications of laser therapy include foveal burns, scotomas, and rupture of Brüch's membrane and the subsequent development of choroidal neovascular membranes.

Panretinal laser photocoagulation (PRP) was also shown in the BVOS to prevent vitreous hemorrhage. The investigators also found that prophylactic PRP only partially prevented neovascularization and therefore recommended careful observation of patients with ischemic CRVO and prompt PRP in the event of signs of neovascularization.[207] When neovascularization is present, prompt PRP should be considered to prevent further sequelae of ischemia-driven cascade.

Although laser photocoagulation has been shown to confer benefits such as promotion of collateral vessel formation,[208] additional value in combination with anti-VEGF therapy in patients with RVO has been variable.[209–211] Two meta-analyses found no significant difference between combination retinal laser photocoagulation and anti-VEGF therapy versus anti-VEGF alone in the treatment of patients with CME secondary to RVO.[212,213]

Since its introduction by McAllister et al in 1995,[214] laser-induced chorioretinal venous anastomosis (CVA) has been shown to effectively bypass venous obstruction in eyes with ischemic and nonischemic CRVO, allowing the venous system to drain directly into the choroidal circulation.[215,216] This procedure was considered for nonischemic CRVOs with progressive vision loss; however, its use has dwindled due to complications including vitreous and retinal hemorrhage, rubeosis, scar tissue, traction, and choroidal neovascularization at the site of treatment.

Over the past 25 years, surgery has been performed in patients with RVO to target anatomic sites implicated in the pathoetiology. Limited benefits have been demonstrated for many surgical procedures. Surgery has become uncommon with the development of pharmacotherapies. Some surgical techniques that have been used at one time include adventitial sheathotomy for BRVO, surgical CVA, radial optic neurotomy, and vitrectomy with and without internal limiting membrane peeling for recalcitrant CME. The objective of adventitial sheathotomy is lysis of the adventitial sheath that binds vessels. It is optimally performed in patients with BRVO and VA of ≤20/200.[217,218] Vitrectomy was introduced for the management of patients with CME secondary to RVO in 1994 and has been shown to be effective with or without intraoperative combined procedures such as internal limiting membrane peeling and intravitreal triamcinolone acetonide at the completion of surgery.[219] This procedure is currently performed primarily in eyes with CRVO and nonclearing vitreous hemorrhage, ERM formation, and tractional retinal detachment. Some studies have supported the benefit of pars plana vitrectomy in patients with CME secondary to BRVO[220] and for resolution of vitreous hemorrhage in both BRVO and CRVO.[221]

Surgical complications may occur, including elevated risks of cataract development or progression,[217,222–224] retinal detachment,[217,222,223,225,226] hypotony,[223,226–228] and vitreous hemorrhage.[215,222,223,226,227] Endophthalmitis is rare.[229,230]

Recommendations for laser and surgical procedures are presented in Box 8.

https://doi.org/10.2147/OPTH.S577821

Box 8 Recommendations – Laser and Surgery

- Consider focal or grid laser in patients with BRVO and persistent CME and inadequate response to anti-VEGFs and/or steroids.
- PRP should be used in patients with CRVO and neovascularization, and sectoral PRP in patients with BRVO and neovascularization.
- Vitrectomy with adjunctive PRP laser should be recommended as first-line therapy in patients with nonclearing vitreous hemorrhage with documented previous RVO from screening or referral.
- For neovascular RVO, PRP should be more robust than in other retinal conditions to minimize the risk of progression to neovascular glaucoma and preferably be completed in a single session.
- Patients with concurrent neovascularization and macular edema can be treated with anti-VEGF or a steroid in conjunction with scatter PRP laser.
- Widefield FA or OCT-A can help to identify ischemic areas or large microaneurysms.

Future Treatments and Delivery Routes

Emerging therapies are generally directed towards increasing treatment durability and the reduction of treatment burden of current anti-VEGF agents.

Early results of the Phase 3 QUASAR trial indicate that patients receiving aflibercept 8 mg q8w experienced noninferior gains in VA versus aflibercept 2 mg q4w (primary endpoint).[231] From baseline to 36 weeks, the mean observed BCVA improvements were 17.4 and 18.3 letters in treatment-naïve patients receiving aflibercept 8 mg q8w after 3 and 5 initial monthly doses, respectively, and 17.5 letters in patients receiving aflibercept 2 mg q4w. Mean reductions in CRT from baseline to 36 weeks were −371 μm, −370 μm, and −371 μm, respectively, and mean numbers of injections were 6.1, 6.9, and 8.8, respectively. There were no new safety signals with aflibercept 8 mg compared with 2 mg. Aflibercept 8 mg is not approved in Canada for the treatment of RVO.

Other potential therapeutic classes and molecules being studied include caspase-9 inhibitors, minocycline, rho-kinase inhibitors, and CD 34+ stem cells.[232] Caspase is active in initiation of the apoptotic pathway in inflammatory and degenerative pathologies, leading to neuromuscular dysfunction, edema, and gliosis.[233,234] Caspase-9 inhibition has been shown in murine models to increase the rate of reperfusion and reduction of hyperreflective foci compared to anti-VEGF.[235]

Gene therapies such as ixoberogene soroparvovec (a single-dose gene therapy encoding for aflibercept) and ABBV-RGX-314 (an adeno-associated virus serotype 8 vector that expresses an anti-VEGF-A antigen-binding fragment) have been shown to be safe and efficacious in Phase 1 studies of patients with nAMD,[236,237] and there is potential to expand study of the role of these agents in patients with RVO. The requirement of a single dose for these agents would represent a considerable reduction in patient treatment burden.

Conclusion

As the second most common cause of vision loss related to retinal vascular disease, the disease burden of RVOs to patients, caregivers, and the healthcare system remains high. This update to the 2015 Canadian Expert Consensus highlights advances in the diagnostic tools and therapeutic options for patients with RVO.

Acknowledgments

The authors wish to thank the following expert reviewers for their contributions to this article:

Kevin M. Colleaux, MD, FRCSC, Department of Ophthalmology, Saskatoon City Hospital and the University of Saskatchewan, Saskatoon, Saskatchewan, Canada. Alan Cruess, MD, FRCSC, Department of Ophthalmology, QEII Hospital, Dalhousie University, Halifax, Nova Scotia, Canada. Peter J. Kertes, MD, CM, FRCSC, Department of Ophthalmology and Vision Sciences, University of Toronto, Toronto, ON, Canada; John and Liz Tory Eye Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada. Wai-Ching Lam, MD, FRCSC, Department of Ophthalmology and Visual Sciences, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong; Vancouver General Hospital, University of British Columbia, Vancouver, British Columbia, Canada. Ravi K Nrusimhadevara, MD, Department of Ophthalmology, University of Saskatchewan, Saskatoon, Saskatchewan, Canada. Tom Sheidow, MD, FRCSC, Ivey Eye Institute, St. Joseph's Hospital, London, Ontario, Canada. Eric

Tourville, MD, FRCSC, Department of Ophthalmology, Hospital Saint-Sacrement, Laval University, Quebec, Quebec, Canada. The authors also thank Lindsay Craik and Jeff Alexander (SNELL Medical Communication) for their editorial assistance.

Funding

Honoraria, meeting organization, and writing support were provided to the authors by SNELL Medical Communication, who received an educational grant from Hoffmann-La Roche Canada. No Roche personnel were present in the expert meeting. Authors had completed editorial independence in the preparation of their presentations and this manuscript.

Disclosure

Dr. Sivachandran has been an Advisory Board member for Amgen, Apotex, Astellas, Bayer, Innova, and Roche; received research grants from Bayer, Roche, and Sentrex; and participated in an educational consortium for Apellis. Dr. Altomare has personal financial interest in Tracery Ophthalmics Inc. and Translatum Medicus Inc. Dr. Dookeran has been a consultant and/or speaker for Roche, Bayer, Bausch + Lomb and Apotex. Dr. Hasan has been an Advisory Board member for Novartis, Bayer, Apellis, Roche, AbbVie, and Biogen, received clinical trial support from Bayer and Roche, and received conference support from Bayer. Dr. Whelan has been an Advisory Board member for Apotex, Bayer, Novartis, and Roche; and received research grants from Novartis. The authors report no other conflicts of interest in this work.

References

1. Ip M, Hendrick A. Retinal vein occlusion review. *Asia-Pac J Ophthalmol*. 2018;7(1):40–45.
2. Rogers SL, McIntosh RL, Lim L, et al. Natural history of branch retinal vein occlusion: an evidence-based systematic review. *Ophthalmology*. 2010;117(6):1094–1101. doi:10.1016/j.ophtha.2010.01.058
3. Song P, Xu Y, Zha M, Zhang Y, Rudan I. Global epidemiology of retinal vein occlusion: a systematic review and meta-analysis of prevalence, incidence, and risk factors. *J Glob Health*. 2019;9(1):010427. doi:10.7189/jogh.09.010427
4. Petrella RJ, Blouin J, Davies B, Barbeau M. Incidence and characteristics of patients with visual impairment due to macular edema secondary to retinal vein occlusion in a representative Canadian cohort. *J Ophthalmol*. 2012;2012:723169. doi:10.1155/2012/723169
5. Kalva P, Akram R, Zuberi HZ, Kooner KS. Prevalence and risk factors of retinal vein occlusion in the United States: the National Health and Nutrition Examination Survey, 2005 to 2008. *Proc*. 2023;36(3):335–340. doi:10.1080/08998280.2023.2173938
6. Park KH, Byun SJ, Woo SJ, Park SJ, Park KH. Twelve-year incidence of retinal vein occlusion and its trend in Korea. *Graefes Arch Clin Exp Ophthalmol*. 2020;258(10):2095–2104. doi:10.1007/s00417-020-04811-8
7. Zhou JQ, Xu L, Wang S, et al. The 10–year incidence and risk factors of retinal vein occlusion: the Beijing Eye Study. *Ophthalmology*. 2013;120(4):803–808. doi:10.1016/j.ophtha.2012.09.033
8. Ponto KA, Elbaz H, Peto T, et al. Prevalence and risk factors of retinal vein occlusion: the Gutenberg Health Study. *J Thromb Haemost*. 2015;13(7):1254–1263. doi:10.1111/jth.12982
9. Yasuda M, Kiyohara Y, Arakawa S, et al. Prevalence and systemic risk factors for retinal vein occlusion in a general Japanese population: the Hisayama study. *Invest Ophthalmol Vis Sci*. 2010;51(6):3205–3209. doi:10.1167/iovs.09-4453
10. Royal College of Ophthalmologists. Clinical Guidelines: retinal Vein Occlusion (RVO); 2022. Available from: https://www.rcophth.ac.uk/wp-content/uploads/2015/07/Retinal-Vein-Occlusion-Guidelines-2022.pdf. Accessed October 29, 2025.
11. Bradshaw SE, Gala S, Nanavaty M, Shah A, Mwamburi M, Kefalas P. Systematic literature review of treatments for management of complications of ischemic central retinal vein occlusion. *BMC Ophthalmol*. 2016;16:104. doi:10.1186/s12886-016-0282-5
12. Braithwaite T, Nanji AA, Lindsley K, Greenberg PB. Anti-vascular endothelial growth factor for macular oedema secondary to central retinal vein occlusion. *Cochrane Database Syst Rev*. 2014;2014(5):CD007325. doi:10.1002/14651858.CD007325.pub3
13. Mitry D, Bunce C, Charteris D. Anti-vascular endothelial growth factor for macular oedema secondary to branch retinal vein occlusion. *Cochrane Database Syst Rev*. 2013;2013(1):CD009510.
14. Brown G, Yoo J, Brown M, Turpcu A, Rajput Y, Wills Eye Hospital Retina Service Vein Occlusion Study Group. The burden of retinal venous occlusion: an assessment of fellow eyes in 1000 cases. *Ophthalmol Retina*. 2017;1(5):404–412. doi:10.1016/j.oret.2017.01.018
15. Chatzirallis A, Varaklioti A, Sergentanis TN, Theodossiadis P, Chatziralli I. Quality of life among patients with retinal vein occlusion: a case-control study. *Semin Ophthalmol*. 2021;36(8):658–664. doi:10.1080/08820538.2021.1896750
16. Ramin S, Rostami F, Ahmadieh H, et al. Vision-related quality of life in patients with retinal vein occlusion. *Int Ophthalmol*. 2024;44(1):114. doi:10.1007/s10792-024-02916-1
17. Senthil MP, Khadka J, Gilhotra JS, et al. Understanding quality of life impact in people with retinal vein occlusion: a qualitative inquiry. *Clin Exp Optom*. 2019;102(4):406–411. doi:10.1111/cxo.12875
18. Canadian Agency for Drugs and Technologies in Health. CADTH reimbursement review: patient and Clinician Group Input: faricimab (Vabysmo); 2024. Available from: https://www.cda-amc.ca/sites/default/files/DRR/2024/SR0832_Patient_and_Clinician_Input.pdf. Accessed October 29, 2025.
19. Berger AR, Cruess AF, Altomare F, et al. Optimal treatment of retinal vein occlusion: canadian expert consensus. *Ophthalmologica*. 2015;234(1):6–25. doi:10.1159/000381357

20. Wan C, Hua R, Li K, Hong X, Fang D, Yang W. Automatic diagnosis of different types of retinal vein occlusion based on fundus images. *Int J Intell Syst*. 2023;2023:1587410. doi:10.1155/2023/1587410
21. Hayreh SS. Ocular vascular occlusive disorders: natural history of visual outcome. *Prog Retin Eye Res*. 2014;41:1–25. doi:10.1016/j.preteyeres.2014.04.001
22. SCORE Study Research Group, Scott IU, Ip MS, VanVeldhuisen PC, et al. A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with standard care to treat vision loss associated with macular edema secondary to branch retinal vein occlusion: the Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) study report 6. *Arch Ophthalmol*. 2009;127(9):1115–1128. doi:10.1001/archophthalmol.2009.233.
23. Rogers S, McIntosh RL, Cheung N, et al; International Eye Disease Consortium. The prevalence of retinal vein occlusion: pooled data from population studies from the United States, Europe, Asia, and Australia. *Ophthalmology*. 2010;117(2):313–319. doi:10.1016/j.ophtha.2009.07.017
24. Cugati S, Wang JJ, Rochtchina E, Mitchell P. Ten-year incidence of retinal vein occlusion in an older population: the Blue Mountains Eye Study. *Arch Ophthalmol*. 2006;124(5):726–732. doi:10.1001/archopht.124.5.726
25. Klein R, Moss SE, Meuer SM, Klein BE. The 15–year cumulative incidence of retinal vein occlusion: the Beaver Dam Eye Study. *Arch Ophthalmol*. 2008;126(4):513–518. doi:10.1001/archopht.126.4.513
26. SCORE2 Investigator Group, Scott IU, VanVeldhuisen PC, Ip MS, et al. Effect of bevacizumab vs aflibercept on visual acuity among patients with macular edema due to central retinal vein occlusion: the SCORE2 randomized clinical trial. *JAMA*. 2017;317(20):2072–2087. doi:10.1001/jama.2017.4568.
27. Hayreh SS, Zimmerman MB, Podhajsky P. Incidence of various types of retinal vein occlusion and their recurrence and demographic characteristics. *Am J Ophthalmol*. 1994;117(4):429–441. doi:10.1016/S0002-9394(14)70001-7
28. Hayreh SS, Zimmerman MB. Branch retinal vein occlusion: natural history of visual outcome. *JAMA Ophthalmol*. 2014;132(1):13–22. doi:10.1001/jamaophthalmol.2013.5515
29. Hayreh SS, Rojas P, Podhajsky P, Montague P, Woolson RF. Ocular neovascularization with retinal vascular occlusion-III: incidence of ocular neovascularization with retinal vein occlusion. *Ophthalmology*. 1983;90(5):488–506. doi:10.1016/S0161-6420(83)34542-5
30. Zhang W, Liu Y, Sang A. Efficacy and effectiveness of anti-VEGF or steroids monotherapy versus combination treatment for macular edema secondary to retinal vein occlusion: a systematic review and meta-analysis. *BMC Ophthalmol*. 2022;22(1):472. doi:10.1186/s12886-022-02682-7
31. Central Vein Occlusion Study Group. Natural history and clinical management of central retinal vein occlusion. The Central Vein Occlusion Study Group. *Arch Ophthalmol*. 1997;115(4):486–491. doi:10.1001/archopht.1997.01100150488006
32. Schmidt-Erfurth U, Garcia-Arumi J, Gerendas BS, et al. Guidelines for the management of retinal vein occlusion by the european society of retina specialists (EURETINA). *Ophthalmologica*. 2019;242(3):123–162. doi:10.1159/000502041
33. Arsene S, Vierron E, Le Lez ML, et al. Conversion from nonischemic to ischemic retinal vein occlusion: prediction by venous velocity on color Doppler imaging. *Eur J Ophthalmol*. 2009;19(6):1009–1016. doi:10.1177/112067210901900618
34. McIntosh RL, Rogers SL, Lim L, et al. Natural history of central retinal vein occlusion: an evidence-based systematic review. *Ophthalmology*. 2010;117(6):1113–1123. doi:10.1016/j.ophtha.2010.01.060
35. Hayreh SS. Prevalent misconceptions about acute retinal vascular occlusive disorders. *Prog Retin Eye Res*. 2005;24(4):493–519. doi:10.1016/j.preteyeres.2004.12.001
36. Prisco D, Marcucci R. Retinal vein thrombosis: risk factors, pathogenesis and therapeutic approach. *Pathophysiol Haemost Thromb*. 2002;32(5–6):308–311. doi:10.1159/000073587
37. Rehak M, Krcova V, Slavik L, et al. The role of thrombophilia in patients with retinal vein occlusion and no systemic risk factors. *Can J Ophthalmol*. 2010;45(2):171–175. doi:10.3129/i09-273
38. Christoffersen NLB, Larsen M. Pathophysiology and hemodynamics of branch retinal vein occlusion. *Ophthalmology*. 1999;106(11):2054–2062. doi:10.1016/S0161-6420(99)90483-9
39. Li J, Paulus YM, Shuai Y, Fang W, Liu Q, Yuan S. New developments in the classification, pathogenesis, risk factors, natural history, and treatment of branch retinal vein occlusion. *J Ophthalmol*. 2017;2017:4936924. doi:10.1155/2017/4936924
40. Noma H, Yasuda K, Shimura M. Cytokines and pathogenesis of central retinal vein occlusion. *J Clin Med*. 2020;9(11):3457. doi:10.3390/jcm9113457
41. Dvorak HF, Brown LF, Detmar M, Dvorak AM. Vascular permeability factor/vascular endothelial growth factor, microvascular hyperpermeability, and angiogenesis. *Am J Pathol*. 1995;146(5):1029–1039.
42. Tang Y, Cheng Y, Wang S, Wang Y, Lui P, Wu H. Review: the development of risk factors and cytokines in retinal vein occlusion. *Front Med*. 2022;9:910600. doi:10.3389/fmed.2022.910600
43. Campochiaro PA, Bhisitkul RB, Shapiro H, Rubio RG. Vascular endothelial growth factor promotes progressive retinal nonperfusion in patients with retinal vein occlusion. *Ophthalmology*. 2013;120(4):795–802. doi:10.1016/j.ophtha.2012.09.032
44. Autiero M, Waltenberger J, Communi D, et al. Role of PlGF in the intra- and intermolecular cross talk between the VEGF receptors Flt1 and Flk1. *Nat Med*. 2003;9(7):936–943. doi:10.1038/nm884
45. Dewerchin M, Carmeliet P. PlGF: a multitasking cytokine with disease-restricted activity. *Cold Spring Harb Perspect Med*. 2012;2(8):a011056. doi:10.1101/cshperspect.a011056
46. Hollborn M, Tenckhoff S, Seifert M, et al. Human retinal epithelium produces and responds to placenta growth factor. *Graefes Arch Clin Exp Ophthalmol*. 2006;244(6):732–741. doi:10.1007/s00417-005-0154-9
47. Klettner A, Kaya L, Flach J, Lassen J, Treumer F, Roider J. Basal and apical regulation of VEGF-A and placenta growth factor in the RPE/choroid and primary RPE. *Mol Vis*. 2015;21:736–748.
48. Noma H, Mimura T, Yasuda K, Shimura M. Role of soluble vascular endothelial growth factor receptors-1 and −2, their ligands, and other factors in branch retinal vein occlusion with macular edema. *Invest Ophthalmol Vis Sci*. 2014;55(6):3878–3885. doi:10.1167/iovs.14-13961
49. Yamashita H, Eguchi S, Watanabe K, Takeuchi S, Yamashita T, Miura M. Expression of placenta growth factor (PIGF) in ischaemic retinal diseases. *Eye*. 1999;13(Pt 3a):372–374. doi:10.1038/eye.1999.95
50. Jonas JB, Jonas RA, Neumaier M, Findeisen P. Cytokine concentration in aqueous humor of eyes with diabetic macular edema. *Retina*. 2012;32(10):2150–2157. doi:10.1097/IAE.0b013e3182576d07

51. Noma H, Mimura T, Yasuda K, Motohashi R, Kotake O, Shimura M. Aqueous humor levels of soluble vascular endothelial growth factor receptor and inflammatory factors in diabetic macular edema. *Ophthalmologica*. 2017;238(1–2):81–88. doi:10.1159/000475603
52. Campochiaro PA. Molecular pathogenesis of retinal and choroidal vascular diseases. *Prog Retin Eye Res*. 2015;49:67–81. doi:10.1016/j.preteyeres.2015.06.002
53. Saharinen P, Eklund L, Alitalo K. Therapeutic targeting of the angiopoietin-TIE pathway. *Nat Rev Drug Discov*. 2017;16(9):635–661. doi:10.1038/nrd.2016.278
54. Felcht M, Luck R, Schering A, et al. Angiopoietin-2 differentially regulates angiogenesis through TIE2 and integrin signaling. *J Clin Invest*. 2012;122(6):1991–2005. doi:10.1172/JCI58832
55. Hakanpaa L, Sipila T, Leppanen VM, et al. Endothelial destabilization by angiopoietin-2 via integrin β1 activation. *Nat Commun*. 2015;6:5962. doi:10.1038/ncomms6962
56. Regula JT, von Leithner PL, Foxton R, et al. Targeting key angiogenic pathways with a bispecific CrossMAb optimized for neovascular eye disease. *EMBO Mol Med*. 2016;8(11):1265–1288. [2019;11(5)e10666]. doi:10.15252/emmm.201505889
57. Li Y, Hall NE, Pershing S, et al. Age, gender, and laterality of retinal vascular occlusion: a retrospective study from the IRIS® Registry. *Ophthalmol Retina*. 2022;6(2):161–171. doi:10.1016/j.oret.2021.05.004
58. Pacella F, Bongiovanni G, Malvasi M, et al. Impact of cardiovascular risk factors on incidence and severity of retinal vein occlusion. *Clin Ter*. 2020;171(6):e534–8. doi:10.7417/CT.2020.2269
59. Hashimoto Y, Kaneko H, Okada A, et al. Association between retinal vein occlusion and Life's Simple 7 cardiovascular health metrics: a large claims database study. *Ophthalmol Retina*. 2022;6(8):684–692. doi:10.1016/j.oret.2022.03.012
60. Liu J, Liu M. Associations of retinal vein and artery occlusions with mortality, stroke and cerebral small vessel disease: a systematic review and meta-analysis. *J Neurol Sci*. 2019;405S:116541.
61. Ponto KA, Scharrer I, Binder H, et al. Hypertension and multiple cardiovascular risk factors increase the risk for retinal vein occlusions: results from the Gutenberg Retinal Vein Occlusion Study. *J Hypertens*. 2019;37(7):1372–1383. doi:10.1097/HJH.0000000000002057
62. Woo SC, Lip GY, Lip PL. Associations of retinal artery occlusion and retinal vein occlusion to mortality, stroke, and myocardial infarction: a systematic review. *Eye*. 2016;30(8):1031–1038. doi:10.1038/eye.2016.111
63. Bucciarelli P, Passamonti SM, Gianniello F, Artoni A, Martinelli I. Thrombophilic and cardiovascular risk factors for retinal vein occlusion. *Eur J Intern Med*. 2017;44:44–48. doi:10.1016/j.ejim.2017.06.022
64. Martinez F, Furió E, Fabiá J, et al. Risk factors associated with retinal vein occlusion. *Int J Clin Pract*. 2014;68(7):871–881. doi:10.1111/ijcp.12390
65. Agard E, El Chehab H, Vie AL, Voirin N, Coste O, Dot C. Retinal vein occlusion and obstructive sleep apnea: a series of 114 patients. *Acta Ophthalmol*. 2018;96(8):e919–e925. doi:10.1111/aos.13798
66. Chou KT, Huang CC, Tsai DC, et al. Sleep apnea and risk of retinal vein occlusion: a nationwide population-based study of Taiwanese. *Am J Ophthalmol*. 2012;154(1):200–205.e1. doi:10.1016/j.ajo.2012.01.011
67. Glaçet-Bernard A, Leroux Les Jardins G, Lasry S, et al. Obstructive sleep apnea among patients with retinal vein occlusion. *Arch Ophthalmol*. 2010;128(12):1533–1538. doi:10.1001/archophthalmol.2010.272
68. Felfeli T, Alon R, Al Adel F, Shapiro CM, Mandelcorn ED, Brent MH. Screening for obstructive sleep apnea amongst patients with retinal vein occlusion. *Can J Ophthalmol*. 2020;55(4):310–316. doi:10.1016/j.jcjo.2020.03.004
69. Berguig J, Abdelmassih Y, Azar G, et al. Central retinal vein occlusion in young population: risk factors and outcomes. *Front Med*. 2023;10:1180234. doi:10.3389/fmed.2023.1180234
70. Yin X, Li J, Zhang B, Lu P. Association of glaucoma with risk of retinal vein occlusion: a meta-analysis. *Acta Ophthalmol*. 2019;97(7):652–659. doi:10.1111/aos.14141
71. Kolar P. Risk factors for central and branch retinal vein occlusion: a meta-analysis of published clinical data. *J Ophthalmol*. 2014;2014:724780. doi:10.1155/2014/724780
72. Na KI, Jeoung JW, Kim YK, Lee WJ, Park KH. Incidence of open-angle glaucoma in newly diagnosed retinal vein occlusion: a nationwide population-based study. *J Glaucoma*. 2019;28(2):111–118. doi:10.1097/IJG.0000000000001134
73. Jeganathan VSE, Wang JJ, Wong TY. Ocular associations of diabetes other than diabetic retinopathy. *Diabetes Care*. 2008;31(9):1905–1912. doi:10.2337/dc08-0342
74. Vieira MJ, Campos A, Do Carmo A, Arruda H, Martins J, Sousa JP. Thrombophilic risk factors for retinal vein occlusion. *Sci Rep*. 2019;9(1):18972. doi:10.1038/s41598-019-55456-5
75. Di Capua M, Coppola A, Albisinni R, et al. Cardiovascular risk factors and outcome in patients with retinal vein occlusion. *J Thromb Thrombolysis*. 2010;30(1):16–22. doi:10.1007/s11239-009-0388-1
76. Taki K, Kida T, Fukumoto M, Sato T, Oku H, Ikeda T. Central retinal vein occlusion in 2 patients using antipsychotic drugs. *Case Rep Ophthalmol*. 2017;8(2):410–415. doi:10.1159/000479219
77. Nowrouzi A, Kafiabasabadi S, Rodriguez-Calzadilla M, et al. Central retinal vein occlusion in a patient using the antipsychotic drug olanzapine: a case report. *J Med Case Rep*. 2021;15(1):307. doi:10.1186/s13256-021-02865-8
78. Francis JH, Diamond EL, Chi P, Jaben K, Hyman DM, Abramson DH. MEK inhibitor-associated central retinal vein occlusion associated with hyperhomocysteinemia and MTHFR variants. *Ocul Oncol Pathol*. 2020;6(3):159–163. doi:10.1159/000501155
79. Luo M, Sun L, Dai R, Chen Y, Wu C. Central retinal vein occlusion in patients with metastatic solid tumors on tyrosine kinase inhibitors: a report of case series and literature review. *Front Med*. 2024;11:1362108. doi:10.3389/fmed.2024.1362108
80. Torkashvand A, Anvari P, Ketabi S, Khameneh EA. Central retinal vein and artery occlusion associated with sildenafil: a case report and review of the literature. *J Med Case Rep*. 2023;17(1):399. doi:10.1186/s13256-023-04104-8
81. Pickel L, Ji PX, Abdelazim A, Sivachandran N. From hair loss to vision loss: minoxidil-associated CRVO in a young female. *Case Rep Ophthalmol*. 2024;15(1):220–224. doi:10.1159/000537911
82. Somisetty S, Santina A, Sarraf D, Mieler WF. The impact of systemic medications on retinal function. *Asia Pac J Ophthalmol*. 2023;12(2):115–157. doi:10.1097/APO.0000000000000605
83. Campbell JP, Burkholder BM, Dunn JP. Catastrophic antiphospholipid antibody syndrome and cocaine abuse associated with bilateral retinal vascular occlusions. *Retin Cases Brief Rep*. 2011;5(4):318–322. doi:10.1097/ICB.0b013e3181f66d3b

84. Sleiman I, Mangili R, Semeraro F, Mazzilli S, Spandrio S, Balestrieri GP. Cocaine-associated retinal vascular occlusion: report of two cases. *Am J Med*. 1994;97(2):198–199. doi:10.1016/0002-9343(94)90033-7
85. Hwang S, Kang SW, Choi KJ, et al. Early menopause is associated with increased risk of retinal vascular occlusions: a nationwide cohort study. *Sci Rep*. 2022;12(1):6068. doi:10.1038/s41598-022-10088-0
86. Lam HD, Lahey JM, Kearney JJ, Ng RR, Lehmer JM, Tanaka SC. Young patients with branch retinal vein occlusion: a review of 60 cases. *Retina*. 2010;30(9):1520–1523. doi:10.1097/IAE.0b013e3181e79872
87. Schreiberova Z, Rehak J, Babkova B, et al. Hypertension, hyperlipidaemia and thrombophilia as the most common risk factors for retinal vein occlusion in patients under 50 years. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*. 2024;168(1):44–49. doi:10.5507/bp.2022.036
88. Sinawat S, Bunyavee C, Ratanapakorn T, Sinawat S, Laovirojjanakul W, Yospaiboon Y. Systemic abnormalities associated with retinal vein occlusion in young patients. *Clin Ophthalmol*. 2017;11:441–447. doi:10.2147/OPTH.S128341
89. Kirwan JF, Tsaloumas MD, Vinall H, Prior P, Kritzinger EE, Dodson PM. Sex hormone preparations and retinal vein occlusion. *Eye*. 1997;11(Pt 1):53–56. doi:10.1038/eye.1997.11
90. Noma H, Yasuda K, Mimura T, Ofusa A, Shimura M. Relationship between retinal blood flow and cytokines in central retinal vein occlusion. *BMC Ophthalmol*. 2020;20(1):215. doi:10.1186/s12886-020-01486-x
91. Noma H, Yasuda K, Shimura M. Cytokines and the pathogenesis of macular edema in branch retinal vein occlusion. *J Ophthalmol*. 2019;2019:5185128. doi:10.1155/2019/5185128
92. List W, Weger M, Pinter-Hausberger S, et al. Endothelin-1 as a risk factor in retinal vein occlusion. *Retina*. 2022;42(4):738–743. doi:10.1097/IAE.0000000000003374
93. Kang HM, Hasanuzzaman M, Kim SW, Koh HJ, Lee SC. Significant elevation of aqueous endothelin-1 in central retinal vein occlusion. *PLoS One*. 2021;16(6):e0252530. doi:10.1371/journal.pone.0252530
94. Woo JM, Kwon MY, Shin DY, Kang YH, Hwang N, Chung SW. Human retinal pigment epithelial cells express the long pentraxin PTX3. *Mol Vis*. 2013;19:303–310.
95. Park KS, Kim JW, An JH, Woo JM. Elevated plasma pentraxin 3 and its association with retinal vein occlusion. *Korean J Ophthalmol*. 2014;28(6):460–465. doi:10.3341/kjo.2014.28.6.460
96. Hikage F, Furuhashi M, Ida Y, et al. Fatty acid-binding protein 4 is an independent factor in the pathogenesis of retinal vein occlusion. *PLoS One*. 2021;16(1):e0245763. doi:10.1371/journal.pone.0245763
97. Munk MR, Ceklic L, Stillenmunkes R, et al. Integrated assessment of OCT, multimodal imaging, and cytokine markers for predicting treatment responses in retinal vein occlusion associated macular edema: a comparative review of anti-VEGF and steroid therapies. *Diagnostics*. 2024;14(17):1983. doi:10.3390/diagnostics14171983
98. Chatziralli I, Kazantzis D, Kroupis C, et al. The impact of laboratory findings and optical coherence tomography biomarkers on response to intravitreal anti-VEGF treatment in patients with retinal vein occlusion. *Int Ophthalmol*. 2022;42(11):3449–3457. doi:10.1007/s10792-022-02344-z
99. Ciulla TA, Kapik B, Hu A, Harris A, Ip MS, Blodi B. Anatomic biomarkers of macular edema associated with retinal vein occlusion. *Ophthalmol Retina*. 2022;6(12):1206–1220. doi:10.1016/j.oret.2022.06.016
100. Siedlecki J, Hattenbach LO, Feltgen N, Priglinger SG. Biomarkers in the treatment of retinal vein occlusion. *Ophthalmologie*. 2022;119(11):1111–1120. doi:10.1007/s00347-022-01732-1
101. Tao Y, Ge L, Su N, et al. Exploration on OCT biomarker candidate related to macular edema caused by diabetic retinopathy and retinal vein occlusion in SD-OCT images. *Sci Rep*. 2024;14(1):14317. doi:10.1038/s41598-024-63144-2
102. Zheng Y, Woodward R, Feng HL, et al. Implications of complete posterior vitreous detachment in eyes with central retinal vein occlusion. *Retina*. 2024;44(1):159–165. doi:10.1097/IAE.0000000000003932
103. Parodi MB, Bandello F. Branch retinal vein occlusion: classification and treatment. *Ophthalmologica*. 2009;223(5):298–305. doi:10.1159/000213640
104. Wong TY, Scott IU. Retinal vein occlusion. *N Engl J Med*. 2010;363(22):2135–2144. doi:10.1056/NEJMcp1003934
105. Powers JH, Thomas AS, Mir TA, et al. Impact and implication of fovea-involving intraretinal hemorrhage after acute branch retinal vein occlusion. *Ophthalmol Retina*. 2019;3(9):760–766. doi:10.1016/j.oret.2019.04.005
106. Ji YK, Hua RR, Liu S, Xie CJ, Zhang SC, Yang WH. Intelligent diagnosis of retinal vein occlusion based on color fundus photographs. *Int J Ophthalmol*. 2024;17(1):1–6. doi:10.18240/ijo.2024.01.01
107. Beeche C, Gezer NS, Iyer K, et al. Assessing retinal vein occlusion based on color fundus photographs using neural understanding network (NUN). *Med Phys*. 2023;50(1):449–464. doi:10.1002/mp.16012
108. Ren X, Feng W, Ran R, et al. Artificial intelligence to distinguish retinal vein occlusion patients using color fundus photographs. *Eye*. 2023;37(10):2026–2032. doi:10.1038/s41433-022-02239-4
109. Thomas AS, Thomas MK, Finn AP, Fekrat S. Use of the ischemic index on widefield fluorescein angiography to characterize a central retinal vein occlusion as ischemic or nonischemic. *Retina*. 2019;39(6):1033–1038. doi:10.1097/IAE.0000000000002126
110. American Academy of Ophthalmology. Retinal vein occlusion. Preferred practice pattern®. 2019. doi:10.1016/j.ophtha.2019.09.029
111. Tan CS, Li KZ, Sadda SR. Wide-field angiography in retinal vein occlusions. *Int J Retina Vitreous*. 2019;5(suppl 1):18. doi:10.1186/s40942-019-0163-1
112. Turczyńska MJ, Krajewski P, Brydak-Godowska JE. Wide-field fluorescein angiography in the diagnosis and management of retinal vein occlusion: a retrospective single-center study. *Med Sci Monit*. 2021;27:e927782. doi:10.12659/MSM.927782
113. Prasad PS, Oliver SCN, Coffee RE, Hubschman JP, Schwartz SD. Ultra wide-field angiographic characteristics of branch retinal and hemicentral retinal vein occlusion. *Ophthalmology*. 2010;117(4):780–784. doi:10.1016/j.ophtha.2009.09.019
114. Sharma S, Sayanagi K, Kaiser PK. Pathology detection rate of spectral domain optical coherence tomography devices. *Br J Ophthalmol*. 2014;98(Suppl 1):i3–6. doi:10.1136/bjophthalmol-2013-303846
115. Cheng BT, Mishra S, Bryan JM, et al. Retinal vessel density and treatment intensity among adults with retinal vein occlusion: a swept-source optical coherence tomography angiography study. *J Clin Med*. 2022;11(10):2892. doi:10.3390/jcm11102892
116. Cardoso JN, Keane PA, Sim DA, et al. Systematic evaluation of optical coherence tomography angiography in retinal vein occlusion. *Am J Ophthalmol*. 2016;163:93–107.e6. doi:10.1016/j.ajo.2015.11.025

117. Cavalleri M, Sacconi R, Parravano M, et al. Optical coherence tomography angiography in central retinal vein occlusion: macular changes and their correlation with peripheral nonperfusion at ultra-widefield fluorescein angiography. *Ophthalmologica*. 2022;245(3):275–284. doi:10.1159/000522503
118. Glaçet-Bernard A, Miere A, Houmane B, Tilleul J, Souied E. Nonperfusion assessment in retinal vein occlusion: comparison between ultra-widefield fluorescein angiography and widefield optical coherence tomography angiography. *Retina*. 2021;41(6):1202–1209. doi:10.1097/IAE.0000000000002993
119. Siying L, Qiaozhu Z, Xinyao H, Linqi Z, Mingwei Z, Jinfeng Q. Comparison of widefield swept-source optical coherence tomography angiography with ultra-widefield fluorescein angiography for the evaluation of lesions in retinal vein occlusion. *BMC Ophthalmol*. 2022;22(1):422. doi:10.1186/s12886-022-02642-1
120. Suzuki N, Hirano Y, Yoshida M, et al. Microvascular abnormalities on optical coherence tomography angiography in macular edema associated with branch retinal vein occlusion. *Am J Ophthalmol*. 2016;161:126–32.e1. doi:10.1016/j.ajo.2015.09.038
121. Nissen AHK, Vergmann AS. Clinical utilisation of wide-field optical coherence tomography and angiography: a narrative review. *Ophthalmol Ther*. 2024;13(4):903–915. doi:10.1007/s40123-024-00905-2
122. Moussa M, Leila M, Saad Bessa A, et al. Grading of macular perfusion in retinal vein occlusion using en-face swept-source optical coherence tomography angiography: a retrospective observational case series. *BMC Ophthalmol*. 2019;19(1):127. doi:10.1186/s12886-019-1134-x
123. Finn MJ, Baldwin G, Lains I, et al. Widefield, swept-source optical coherence tomography angiography metrics as predictors of anti-VEGF treatment in retinal vein occlusions. *Ophthalmic Surg Lasers Imaging Retina*. 2024;55(7):374–382. doi:10.3928/23258160-20240208-02
124. Tan TE, Ibrahim F, Chandrasekaran PR, Chong Teo KY. Clinical utility of ultra-widefield fluorescein angiography and optical coherence tomography angiography for retinal vein occlusions. *Front Med*. 2023;10:1110166. doi:10.3389/fmed.2023.1110166
125. Ouederni M, Sassi H, Nefaa F, Kharroubi A, Kellil N, Cheour M. Anatomo-functional study in branch retinal vein occlusion using swept source optical coherence tomography angiography. *J Fr Ophtalmol*. 2019;42(3):255–261. doi:10.1016/j.jfo.2018.09.010
126. Wons J, Pfau M, Wirth MA, Freiberg FJ, Becker MD, Michels S. Optical coherence tomography angiography of the foveal avascular zone in retinal vein occlusion. *Ophthalmologica*. 2016;235(4):195–202. doi:10.1159/000445482
127. Chung CY, Tang HHY, Li SH, Li KKW. Differential microvascular assessment of retinal vein occlusion with coherence tomography angiography and fluorescein angiography: a blinded comparative study. *Int Ophthalmol*. 2018;38(3):1119–1128. doi:10.1007/s10792-017-0570-y
128. Spiewak D, Witek K, Drzyzga L, Mrukwa-Kominek E. An analysis of optical coherence tomography angiography (OCT-A) perfusion density maps in patients treated for retinal vein occlusion with intravitreal aflibercept. *Diagnostics*. 2023;13(19):3100. doi:10.3390/diagnostics13193100
129. Matsunaga DR, Yi JJ, De Koo LO, Ameri H, Puliafito CA, Kashani AH. Optical coherence tomography angiography of diabetic retinopathy in human subjects. *Ophthalmic Surg Lasers Imaging Retina*. 2015;46(8):796–805. doi:10.3928/23258160-20150909-03
130. Hayreh SS, Podhajsky PA, Zimmerman MB. Natural history of visual outcome in central retinal vein occlusion. *Ophthalmology*. 2011;118(1):119–33.e2. doi:10.1016/j.ophtha.2010.04.019
131. Valeriani E, Paciullo F, Porfidia A, et al. Antithrombotic treatment for retinal vein occlusion: a systematic review and meta-analysis. *J Thromb Haemost*. 2023;21(2):284–293. doi:10.1016/j.jtha.2022.10.003
132. Kwok CS, Umar S, Myint PK, Mamas MA, Loke YK. Vegetarian diet, Seventh Day Adventists and risk of cardiovascular mortality: a systematic review and meta-analysis. *Int J Cardiol*. 2014;176(3):680–686. doi:10.1016/j.ijcard.2014.07.080
133. Crowe FL, Appleby PN, Travis RC, Key TJ. Risk of hospitalization or death from ischemic heart disease among British vegetarians and nonvegetarians: results from the EPIC-Oxford cohort study. *Am J Clin Nutr*. 2013;97(3):597–603. doi:10.3945/ajcn.112.044073
134. Orlich MJ, Singh PN, Sabaté J, et al. Vegetarian dietary patterns and mortality in Adventist Health Study 2. *JAMA Intern Med*. 2013;173(13):1230–1238. doi:10.1001/jamainternmed.2013.6473
135. Othman RA, Moghadasian MH. Beyond cholesterol-lowering effects of plant sterols: clinical and experimental evidence of anti-inflammatory properties. *Nutr Rev*. 2011;69(7):371–382. doi:10.1111/j.1753-4887.2011.00399.x
136. Kim J, Kim M, Lee CS, Choi EY. Sufficient magnesium intake reduces retinal vein occlusion risk: National health and nutrition examination survey analysis. *Nutrients*. 2025;17(7):1285. doi:10.3390/nu17071285
137. Yang V, Turner LD, Imrie F. Central retinal vein occlusion secondary to severe iron-deficiency anaemia resulting from a plant-based diet and menorrhagia: a case presentation. *BMC Ophthalmol*. 2020;20(1):112. doi:10.1186/s12886-020-01372-6
138. Kacer B, Hattenbach LO, Hörle S, Scharrer I, Kroll P, Koch F. Central retinal vein occlusion and nonarteritic ischemic optic neuropathy in 2 patients with mild iron deficiency anemia. *Ophthalmologica*. 2001;215(2):128–131. doi:10.1159/000050843
139. Kazantzis D, Theodossiadis P, Kroupis C, Theodossiadis G, Chatziralli I. Vitamin B12 and folate as risk factors for retinal vein occlusion: a meta-analysis. *Klin Monbl Augenheilkd*. 2022;239(5):709–716. doi:10.1055/a-1473-5897
140. Daneshvar K, Akhlaghi M, Iranpour S, Irajpour M, Pourazizi M. Vitamin D deficiency in patients with retinal vein occlusion: a systematic review and meta-analysis. *Int J Retina Vitreous*. 2024;10(1):52. doi:10.1186/s40942-024-00571-3
141. Campochiaro PA, Heier JS, Feiner L, et al; BRAVO Investigators. Ranibizumab for macular edema following branch retinal vein occlusion: six-month primary end point results of a Phase III study. *Ophthalmology*. 2010;117(6):1102–1112.e1. doi:10.1016/j.ophtha.2010.02.021
142. Brown DM, Campochiaro PA, Bhisitkul RB, et al. Sustained benefits from ranibizumab for macular edema following branch retinal vein occlusion: 12–month outcomes of a phase III study. *Ophthalmology*. 2011;118:1594–1602. doi:10.1016/j.ophtha.2011.02.022
143. Brown DM, Campochiaro PA, Singh RP, et al; CRUISE Investigators. Ranibizumab for macular edema following central retinal vein occlusion: six-month primary end point results of a phase III study. *Ophthalmology*. 2010;117(6):1124–1133.e1121. doi:10.1016/j.ophtha.2010.02.022
144. Campochiaro PA, Brown DM, Awh CC, et al. Sustained benefits from ranibizumab for macular edema following central retinal vein occlusion: twelve-month outcomes of a phase III study. *Ophthalmology*. 2011;118(10):2041–2049. doi:10.1016/j.ophtha.2011.02.038
145. Heier JS, Campochiaro PA, Yau L, et al. Ranibizumab for macular edema due to retinal vein occlusion: long-term follow-up in the HORIZON trial. *Ophthalmology*. 2012;119(4):802–809. doi:10.1016/j.ophtha.2011.12.005
146. GALILEO Study Group, Korobelnik JF, Holz FG, Roider J, et al. Intravitreal aflibercept injection for macular edema resulting from central retinal vein occlusion: one-year results of the Phase 3 GALILEO study. *Ophthalmology*. 2014;121(1):202–208. doi:10.1016/j.ophtha.2013.08.012.

147. Brown DM, Heier JS, Clark WL, et al. Intravitreal aflibercept injection for macular edema secondary to central retinal vein occlusion: 1–year results from the phase 3 COPERNICUS study. *Am. J Ophthalmol*. 2013;155(3):429–437.
148. Epstein DL, Algvere PV, von Wendt G, Seregard S, Kvanta A. Benefit from bevacizumab for macular edema in central retinal vein occlusion: twelve-month results of a prospective, randomized study. *Ophthalmology*. 2012;119(12):2587–2591. doi:10.1016/j.ophtha.2012.06.037
149. Epstein DL, Algvere PV, von Wendt G, Seregard S, Kvanta A. Bevacizumab for macular edema in central retinal vein occlusion: a prospective, randomized, double-masked clinical study. *Ophthalmology*. 2012;119(6):1184–1189. doi:10.1016/j.ophtha.2012.01.022
150. Ramezani A, Esfandiari H, Entezari M, et al. Three intravitreal bevacizumab versus two intravitreal triamcinolone injections in recent-onset branch retinal vein occlusion. *Graefes Arch Clin Exp Ophthalmol*. 2012;250(8):1149–1160. doi:10.1007/s00417-012-1941-8
151. Russo V, Barone A, Conte E, Prascina F, Stella A, Noci ND. Bevacizumab compared with macular laser grid photocoagulation for cystoid macular edema in branch retinal vein occlusion. *Retina*. 2009;29(4):511–515. doi:10.1097/IAE.0b013e318195ca65
152. Park DG, Jeong WJ, Park JM, Kim JY, Ji YS, Sagong M. Prospective trial of treat-and-extend regimen with aflibercept for branch retinal vein occlusion: 1–year results of the PLATON trial. *Graefes Arch Clin Exp Ophthalmol*. 2021;259(10):2879–2886. doi:10.1007/s00417-021-05150-y
153. RETAIN Study Group, Campochiaro PA, Sophie R, Pearlman J, et al. Long-term outcomes in patients with retinal vein occlusion treated with ranibizumab: the RETAIN study. *Ophthalmology*. 2014;121(1):209–219. doi:10.1016/j.ophtha.2013.08.038.
154. Larsen M, Waldstein SM, Priglinger S, et al; CRYSTAL Study Group. Sustained benefits from ranibizumab for central retinal vein occlusion with macular edema: 24–month results of the CRYSTAL study. *Ophthalmol Retina*. 2018;2(2):134–142. doi:10.1016/j.oret.2017.05.016.
155. Korobelnik JF, Larsen M, Eter N, et al. Efficacy and safety of intravitreal aflibercept treat-and-extend for macular edema in central retinal vein occlusion: the CENTERA study. *Am J Ophthalmol*. 2021;227(227):106–115. doi:10.1016/j.ajo.2021.01.027
156. Jaggi D, Nagamany T, Wolf S, Zinkernagel MS, Heussen FM. Aflibercept for central retinal vein occlusions: long-term outcomes of a 'Treat-and-Extend' regimen. *BMJ Open Ophthalmol*. 2024;9(1):e001659. doi:10.1136/bmjophth-2024-001659
157. Patil NS, Hatamnejad A, Mihalache A, Popovic MM, Kertes PJ, Muni RH. Anti-vascular endothelial growth factor treatment compared with steroid treatment for retinal vein occlusion: a meta-analysis. *Ophthalmologica*. 2022;245(6):500–515. doi:10.1159/000527626
158. Lashay A, Riazi-Esfahani H, Mirghorbani M, Yaseri M. Intravitreal medications for retinal vein occlusion: systematic review and meta-analysis. *J Ophthalmic Vis Res*. 2019;14(3):336–366. doi:10.18502/jovr.v14i3.4791
159. Spooner K, Hong T, Fraser-Bell S, Chang A. Current outcomes of anti-VEGF therapy in the treatment of macular edema secondary to central retinal vein occlusions: a systematic review and meta-analysis. *Asia-Pac J Ophthalmol*. 2019;8(3):236–246.
160. Sangroongruangsri S, Ratanapakorn T, Wu O, Anothaisintawee T, Chaikledkaew U. Comparative efficacy of bevacizumab, ranibizumab, and aflibercept for treatment of macular edema secondary to retinal vein occlusion: a systematic review and network meta-analysis. *Expert Rev Clin Pharmacol*. 2018;11(9):903–916. doi:10.1080/17512433.2018.1507735
161. Qian T, Zhao M, Xu X. Comparison between anti-VEGF therapy and corticosteroid or laser therapy for macular oedema secondary to retinal vein occlusion: a meta-analysis. *J Clin Pharm Ther*. 2017;42(5):519–529. doi:10.1111/jcpt.12551
162. Tadayoni R, Paris LP, Danzig CJ, et al; BALATON and COMINO Investigators. Efficacy and safety of faricimab for macular edema due to retinal vein occlusion: 24–week results from the BALATON and COMINO trials. *Ophthalmology*. 2024;131(8):950–960. doi:10.1016/j.ophtha.2024.01.029
163. Danzig CJ, Dinah C, Ghanchi F, et al; BALATON and COMINO Investigators. Faricimab treat-and-extend dosing for macular edema due to retinal vein occlusion: 72–week results from the BALATON and COMINO trials. *Ophthalmol Retina*. 2025;9(9):848–859. doi:10.1016/j.oret.2025.03.005
164. Giocanti-Aurégan A, Donati S, Hoerauf H, et al; AURIGA Study Investigators. Real-world management of macular edema secondary to retinal vein occlusion with intravitreal aflibercept: 24–month results from the AURIGA observational study. *Ophthalmol Ther*. 2024;13(1):179–203. doi:10.1007/s40123-023-00830-w
165. Rodríguez-Fernández CA, Campo-Gesto A, López-López A, Gayoso-Rey M. Real-world evidence for treat-and-extend regimen of ranibizumab therapy for macular oedema secondary to branch retinal vein occlusion. *Pharmaceuticals*. 2022;15(1):59. doi:10.3390/ph15010059
166. Shimura M, Fukumatsu M, Tsujimura J, Hirano K, Sunaya T. Real-world data on intravitreal aflibercept for macular edema secondary to central retinal vein occlusion: 24–month outcomes. *Clin Ophthalmol*. 2022;16:579–592. doi:10.2147/OPTH.S344194
167. Hogg HJ, Talks SJ, Pearce M, Di simplicio S. Real-world visual and neovascularisation outcomes from anti-VEGF in central retinal vein occlusion. *Ophthalmic Epidemiol*. 2021;28(1):70–76. doi:10.1080/09286586.2020.1792937
168. Pearce I, Clemens A, Brent MH, et al; LUMINOUS™ study investigators. Real-world outcomes with ranibizumab in branch retinal vein occlusion: the prospective, global, LUMINOUS study. *PLoS One*. 2020;15(6):e0234739. doi:10.1371/journal.pone.0234739
169. Bhisitkul RB, Blotner S, Steffen V, Haskova Z. Clinical trial versus real-world outcomes with anti-VEGF therapy for central retinal vein occlusion. *Invest Ophthalmol Vis Sci*. 2020;1(7):1304.
170. Callizo J, Ziemssen F, Bertelmann T, et al. Real-world data: ranibizumab treatment for retinal vein occlusion in the OCEAN study. *Clin Ophthalmol*. 2019;13:2167–2179. doi:10.2147/OPTH.S209253
171. Hunt A, Nguyen V, Bhandari S, et al. Central retinal vein occlusion 36–month outcomes with anti-VEGF: the Fight Retinal Blindness! Registry. *Ophthalmol Retina*. 2023;7(4):338–345. doi:10.1016/j.oret.2022.11.001
172. Brown DM, Wykoff CC, Wong TP, et al. Ranibizumab in preproliferative (ischemic) central retinal vein occlusion: the Rubeosis Anti-VEGF (RAVE) trial. *Retina*. 2014;34(9):1728–1735. doi:10.1097/IAE.0000000000000191
173. Surowka M, Schaefer W, Klein C. Ten years in the making: application of CrossMAb technology for the development of therapeutic bispecific antibodies and antibody fusion proteins. *Mabs*. 2021;13:197714. doi:10.1080/19420862.2021.1967714
174. Koss MJ, Pfister M, Koch FH. Inflammatory and angiogenic protein detection in the human vitreous: cytometric bead assay. *J Ophthalmol*. 2011;2011:459251. doi:10.1155/2011/459251
175. Vabysmo® (faricimab injection) [product monograph]. Mississauga (ON): Hoffmann-La Roche Ltd. 2024.
176. Zhang Y. Biosimilars in Canada: policies to promote switching and what it means for payers. Presented at the Canadian Association for Health Service and Policy Research Annual Conference; Montreal (QC); May 29–31; 2023.
177. Holz FG, Olesky P, Ricci F, Kaiser PK, Kiefer J, Schmitz-Valckenberg S, COLUMBUS-AMD Study Group. Efficacy and safety of biosimilar FYB201 compared with ranibizumab in neovascular age-related macular degeneration. *Ophthalmology*. 2022;129(1):54–63. doi:10.1016/j.ophtha.2021.04.031

178. Yoon CK, Oh J, Bae K, Park UC, Yu KS, Yu HG. Efficacy and safety of a new ranibizumab biosimilar CKD-701 using a pro re nata treatment regimen in neovascular age-related macular degeneration: a phase 3 randomized clinical trial. *PLoS One*. 2022;17(11):e0275611. doi:10.1371/journal.pone.0275611
179. Apsangikar P, Ghadge P, Naik M, Nair S, Payghan R. Randomised, double-blind, comparative clinical study of new ranibizumab biosimilar in neovascular (Wet) age-related macular degeneration. *Clin Ophthalmol*. 2021;15:3087–3095. doi:10.2147/OPTH.S307746
180. Woo SJ, Veith M, Hamouz J, et al. Efficacy and safety of a proposed ranibizumab biosimilar product vs a reference ranibizumab product for patients with neovascular age-related macular degeneration: a randomized clinical trial. *JAMA Ophthalmol*. 2021;139(1):68. doi:10.1001/jamaophthalmol.2020.5053
181. Sharma S, Khan M, Chaturvedi A, RE-ENACT 2 Study Investigators Group. A Multicenter, Retrospective Study (RE-ENACT 2) on the use of Razumab™ (world's first biosimilar ranibizumab) in wet age-related macular degeneration. *Ophthalmol Ther*. 2020;9(1):103–114. doi:10.1007/s40123-019-00228-7
182. Sharma S, Khan M, Chaturvedi A. A multicenter, retrospective study (RE-ENACT 2) on Razumab™ (world's first biosimilar ranibizumab) in retinal vein occlusion. *Ophthalmol Ther*. 2020;9(3):625–639. doi:10.1007/s40123-020-00277-3
183. Byooviz® (ranibizumab injection) [product monograph]. Toronto (ON): Biogen Canada. 2025.
184. Ranopto® (ranibizumab injection) [product monograph]. Montreal (QC): Teva Canada. 2023.
185. Aflivu™ (aflibercept injection) [product monograph]. Toronto (ON): Apotex Inc. 2025.
186. Yesafili™ (aflibercept injection) [product monograph]. Dublin: Biosimilar Collaborations Ireland Ltd. 2025.
187. Pavblu™ (aflibercept injection) [product monograph]. Mississauga (ON). 2025.
188. Opuviz™(aflibercept injection) [product monograph]. Toronto (ON). *Biogen Canada*. 2025.
189. Enzeevu™ (aflibercept injection) [product monograph]. Saint-Hubert (QC): Sandoz Canada; 2025.
190. Eydenzelt™ (aflibercept injection) [product monograph]. Toronto (ON): Celltrion Healthcare Canada; 2025.
191. Ahzantive™ (aflibercept injection) [product monograph]. New Y (NY): Valorum Biologics. 2025.
192. Zhang X, Bao S, Lai D, Rapkins RW, Gillies MC. Intravitreal triamcinolone acetonide inhibits breakdown of the blood-retinal barrier through differential regulation of VEGF-A and its receptors in early diabetic rat retinas. *Diabetes*. 2008;57(4):1026–1033. doi:10.2337/db07-0982
193. Wang K, Wang Y, Gao L, Li X, Li M, Guo J. Dexamethasone inhibits leukocyte accumulation and vascular permeability in retina of streptozotocin-induced diabetic rats via reducing vascular endothelial growth factor and intercellular adhesion molecule-1 expression. *Biol Pharm Bull*. 2008;31(8):1541–1546. doi:10.1248/bpb.31.1541
194. Jeanneteau F, Garabedian MJ, Chao MV. Activation of Trk neurotrophin receptors by glucocorticoids provides a neuroprotective effect. *Proc Natl Acad Sci USA*. 2008;105(12):4862–4867. doi:10.1073/pnas.0709102105
195. Ip MS, Scott IU, VanVeldhuisen PC, et al; SCORE Study Research Group. A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with observation to treat vision loss associated with macular edema secondary to central retinal vein occlusion: the Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) study report 5. *Arch Ophthalmol*. 2009;127(9):1101–1114. doi:10.1001/archophthalmol.2009.234.
196. Flynn HW Jr, Scott IU. Intravitreal triamcinolone acetonide for macular edema associated with diabetic retinopathy and venous occlusive disease: it's time for clinical trials. *Arch Ophthalmol*. 2005;123(2):258–259. doi:10.1001/archopht.123.2.258
197. Scott IU, Blodi BA, Ip MS, et al; SCORE Study Investigator Group. SCORE Study Report 2: interobserver agreement between investigator and reading center classification of retinal vein occlusion type. *Ophthalmology*. 2009;116(4):756–761. doi:10.1016/j.ophtha.2008.11.015.
198. Haller JA, Bandello F, Belfort R, et al; Ozurdex GENEVA Study Group. Dexamethasone intravitreal implant in patients with macular edema related to branch or central retinal vein occlusion twelve-month study results. *Ophthalmology*. 2011;118(12):2453–2460. doi:10.1016/j.ophtha.2011.05.014.
199. Pina JP, Turki K, Labreuche J, Duhamel A, Tran THC. Efficacy and safety in retinal vein occlusion treated with at least three consecutive intravitreal dexamethasone implants. *J Ophthalmol*. 2016;2016(2016):6016491. doi:10.1155/2016/6016491
200. Bandello F, Parravano M, Cavallero E, et al. Prospective evaluation of morphological and functional changes after repeated intravitreal dexamethasone implant (Ozurdex®) for retinal vein occlusion. *Ophthalmic Res*. 2015;53(4):207–216. doi:10.1159/000381187
201. Augustin AJ, Holz FG, Haritoglou C, et al. Retrospective, observational study in patients receiving a dexamethasone intravitreal implant 0.7 mg for macular oedema secondary to retinal vein occlusion. *Ophthalmologica*. 2015;233(1):18–26. doi:10.1159/000368840
202. Coscas G, Augustin A, Bandello F, et al. Retreatment with Ozurdex for macular edema secondary to retinal vein occlusion. *Eur J Ophthalmol*. 2014;24(1):1–9. doi:10.5301/ejo.5000376
203. Bezatis A, Spital G, Höhn F, et al. Functional and anatomical results after a single Intravitreal ozurdex injection in retinale vein occlusion: a 6–month follow-up- the SOLO study. *Acta Opthalmol*. 2013;91(5):e340–e347. doi:10.1111/aos.12020
204. Joshi L, Yaganti S, Gemenetzi M, et al. Dexamethasone implants in retinal vein occlusion: 12–month clinical effectiveness using repeat injections as-needed. *Br J Ophthalmol*. 2013;97(8):1040–1044. doi:10.1136/bjophthalmol-2013-303207
205. BVOS Study Group. Argon laser photocoagulation for macular edema in branch vein occlusion. The Branch Vein Occlusion Study Group. *Am J Ophthalmol*. 1984;98(3):271–282. doi:10.1016/0002-9394(84)90316-7
206. Central Vein Occlusion Study Group. Evaluation of grid pattern photocoagulation for macular edema in central vein occlusion. The Central Vein Occlusion Study Group M report. *Ophthalmology*. 1995;102(10):1425–1433. doi:10.1016/S0161-6420(95)30849-4
207. Central Vein Occlusion Study Group. A randomized clinical trial of early panretinal photocoagulation for ischemic central vein occlusion. The Central Vein Occlusion Study Group N report. *Ophthalmology*. 1995;102(10):1434–1444. doi:10.1016/S0161-6420(95)30848-2
208. An SH, Jeong WJ. Early-scatter laser photocoagulation promotes the formation of collateral vessels in branch retinal vein occlusion. *Eur J Ophthalmol*. 2020;30(2):370–375. doi:10.1177/1120672119827857
209. Feng XX, Li C, Shao WW, et al. Intravitreal anti-VEGF agents, oral glucocorticoids, and laser photocoagulation combination therapy for macular edema secondary to retinal vein occlusion: preliminary report. *Int J Ophthalmol*. 2018;11(3):429–437. doi:10.18240/ijo.2018.03.13
210. Murata T, Kondo M, Inoue M, et al. The randomized ZIPANGU trial of ranibizumab and adjunct laser for macular edema following branch retinal vein occlusion in treatment-naïve patients. *Sci Rep*. 2021;11(1):551. doi:10.1038/s41598-020-79051-1
211. Campochiaro PA, Hafiz G, Mir TA, et al. Scatter photocoagulation does not reduce macular edema or treatment burden in patients with retinal vein occlusion: the RELATE Trial. *Ophthalmology*. 2015;122(7):1426–1437. doi:10.1016/j.ophtha.2015.04.006

212. Zou W, Du Y, Ji X, et al. Comparison of the efficiency of anti-VEGF drugs intravitreal injections treatment with or without retinal laser photocoagulation for macular edema secondary to retinal vein occlusion: a systematic review and meta-analysis. *Front Pharmacol*. 2022;13:948852. doi:10.3389/fphar.2022.948852
213. Bhambra N, Sayal AP, Popovic MM, Muni RH, Kertes PJ. Combination intravitreal anti-vascular endothelial growth factor inhibitors and macular laser photocoagulation relative to intravitreal injection monotherapy in macular oedema secondary to retinal vein occlusion: a meta-analysis of randomized controlled trials. *Eye*. 2022;36(12):2271–2278. doi:10.1038/s41433-021-01833-2
214. McAllister IL, Constable IJ. Laser-induced chorioretinal venous anastomosis for treatment of nonischemic central retinal vein occlusion. *Arch Ophthalmol*. 1995;113(4):456–462. doi:10.1001/archopht.1995.01100040072030
215. McAllister IL, Gillies ME, Smithies LA, et al. The Central Retinal Vein Bypass Study: a trial of laser-induced chorioretinal venous anastomosis for central retinal vein occlusion. *Ophthalmology*. 2010;117(5):954–965. doi:10.1016/j.ophtha.2009.10.026
216. Mirshahi A, Roohipoor R, Lashay A, Mohammadi SF, Mansouri MR. Surgical induction of chorioretinal venous anastomosis in ischaemic central retinal vein occlusion: a non-randomised controlled clinical trial. *Br J Ophthalmol*. 2005;89(1):64–69. doi:10.1136/bjo.2004.045278
217. Shah GK, Sharma S, Fineman MS, Federman J, Brown MM, Brown GC. Arteriovenous adventitial sheathotomy for the treatment of macular edema associated with branch retinal vein occlusion. *Am J Ophthalmol*. 2000;129(1):104–106. doi:10.1016/S0002-9394(99)00287-1
218. Mason JIII, Feist R, White MJ, Swanner J, McGwin G, Emond T. Sheathotomy to decompress branch retinal vein occlusion: a matched control study. *Ophthalmology*. 2005;111(3):540–545. doi:10.1016/j.ophtha.2003.05.032
219. Kumagai K, Ogino N, Fukami M, Furukawa M. Vitrectomy for macular edema due to retinal vein occlusion. *Clin Ophthalmol*. 2019;Volume 13 (13):969–984. doi:10.2147/OPTH.S203212
220. Nishida A, Kojima H, Kameda T, Mandai M, Kurimoto Y. Five-year outcomes of pars plana vitrectomy for macular edema associated with branch retinal vein occlusion. *Clin Ophthalmol*. 2017;11:369–375. doi:10.2147/OPTH.S123419
221. Wakabayashi T, Patel N, Bough M, et al. Vitrectomy for hemorrhage associated with retinal vein occlusion: visual outcomes, prognostic factors, and sequelae. *Retina*. 2023;43(9):1506–1513. doi:10.1097/IAE.0000000000003839
222. Karunatilake M, Fijardo B, Michael E, Somani R. Outcomes of pars plana vitrectomy for visually significant floaters in Northern Alberta. *Int J Retina Vitreous*. 2025;11(1):54. doi:10.1186/s40942-025-00676-3
223. Shaik S, Ho S, Richmond PP, Olson JC, Barnes CD. Untoward outcomes in 25–gauge versus 20–gauge vitreoretinal surgery. *Retina*. 2007;27 (8):1048–1053. doi:10.1097/IAE.0b013e3180592bb7
224. Cheng L, Azen SP, El-Bradey MH, et al. Duration of vitrectomy and postoperative cataract in the vitrectomy for macular hole study. *Am J Ophthalmol*. 2001;132(6):881–887. doi:10.1016/S0002-9394(01)01263-6
225. Chung YR, Mainguy A, Chatziralli I, et al. Anatomical, functional, and prognostic results of vitrectomy in epiretinal membranes secondary to retinal vein occlusions. *Ophthalmologica*. 2024;248(1):29–39. doi:10.1159/000542770
226. Parolini B, Prigione G, Romanelli F, Cereda MG, Sartore M, Pertile G. Postoperative complications and intraocular pressure in 943 consecutive cases of 23–gauge transconjunctival pars plana vitrectomy with 1–year follow-up. *Retina*. 2010;30(1):107–111. doi:10.1097/IAE.0b013e3181b21082
227. Khan CD, Berrocal MH, Lakhanpal RR, et al. Long-term visual outcomes and safety profile of 27–gauge pars plana vitrectomy for posterior segment disease. *Ophthalmology*. 2018;125(3):423–431. doi:10.1016/j.ophtha.2017.09.013
228. Yoneda K, Morikawa K, Oshima Y, Kinoshita S, Sotozono C, Japan Microincision Vitrectomy Surgery Study Group. Surgical outcomes of 27–gauge vitrectomy for a consecutive series of 163 eyes with various vitreous diseases. *Retina*. 2017;37(11):2130–2137. doi:10.1097/IAE.0000000000001442
229. Weiss SJ, Adam MK, Gao X, et al. Endophthalmitis after pars plana vitrectomy: efficacy of intraoperative subconjunctival antibiotics. *Retina*. 2018;38(9):1848–1855. doi:10.1097/IAE.0000000000002175
230. Sankara Nethralaya Vitreoretinal Study Group (SNVR-Study Group), Bhende M, Raman R, Jain M, et al. Incidence, microbiology, and outcomes of endophthalmitis after 111,876 pars plana vitrectomies at a single, tertiary eye care hospital. *PLoS One*. 2018;13(1):e0191173. doi:10.1371/journal.pone.0191173.
231. Chaudhary V. Results from the QUASAR study: comparable vision gains with aflibercept 8 mg and 2 mg in treatment-naïve macular edema secondary to retinal vein occlusion. Presented at the 25th Euretina meeting; Paris (France); September 4–7, 2025.
232. Park SS. Clinical Trial of Autologous Intravitreal Bone-marrow CD34+ Stem Cells for Retinopathy. ClinicalTrials.gov ID NCT01736059. 2025.
233. Colón Ortiz C, Neal AM, Avrutsky MI, et al. Neurovascular injury associated non-apoptotic endothelial caspase-9 and astroglial caspase-9 mediate inflammation and contrast sensitivity decline. *Cell Death Dis*. 2022;13(11):937. doi:10.1038/s41419-022-05387-3
234. Avrutsky MI, Troy CM. Caspase-9: a multimodal therapeutic target with diverse cellular expression in human disease. *Front Pharmacol*. 2021;12:701301. doi:10.3389/fphar.2021.701301
235. Avrutsky MI, Chen CW, Lawson JM, Snipas SJ, Salvesen GS. Caspase-9 inhibition confers stronger neuronal and vascular protection compared to VEGF neutralization in a mouse model of retinal vein occlusion. *Front Neurosci*. 2023;17:120927. doi:10.3389/fnins.2023.1209527
236. Khanani AM, Boyer DS, Wykoff CC, et al. Safety and efficacy of ixoberogene soroparvovec in neovascular age-related macular degeneration in the United States (OPTIC): a prospective, two-year, multicentre phase 1 study. *EClinicalMedicine*. 2023;67:102394. doi:10.1016/j.eclinm.2023.102394
237. Campochiaro PA, Avery R, Brown DM, et al. Gene therapy for neovascular age-related macular degeneration by subretinal delivery of RGX-314: a phase 1/2a dose-escalation study. *Lancet*. 2024;403(10436):1563–1573. doi:10.1016/S0140-6736(24)00310-6