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Retinal Vein Occlusions Preferred Practice Pattern®

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We would like to acknowledge the role of Andre Ambrus, MLIS, in the initial revisions of the Retina/Vitreous PPPs and the first meeting of the Retina/Vitreous PPP Committee.

Medical Editor: Susan Garratt

Approved by: Board of Trustees
September 13, 2024

Preferred Practice Pattern guidelines are developed by the Academy's H. Dunbar Hoskins Jr., MD Center for Quality Eye Care without any external financial support. Authors and reviewers of the guidelines are volunteers and do not receive any financial compensation for their contributions to the documents. The guidelines are externally reviewed by experts and stakeholders before publication.

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RETINA/VITREOUS PREFERRED PRACTICE PATTERN® DEVELOPMENT PROCESS AND PARTICIPANTS

The Retina/Vitreous Preferred Practice Pattern Committee members wrote the Retinal Vein Occlusions Preferred Practice Pattern (PPP) guidelines. The Retina/Vitreous PPP Committee members discussed and reviewed successive drafts of the document, meeting in person twice and conducting other review by e-mail discussion, to develop a consensus over the final version of the document.

Retina/Vitreous Preferred Practice Pattern Committee 2023–2024
Jaclyn L, Kovach, MD, Retina Society Representative
Steven T. Bailey, MD, Macula Society Representative
Stephen J. Kim, MD
Jennifer I. Lim, MD
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Christina J. Flaxel, MD, Chair

We thank our partners, the Cochrane Eyes and Vision US Satellite (CEV@US), for identifying reliable systematic reviews that we cite and discuss in support of the PPP recommendations.

The **Preferred Practice Patterns Committee** members reviewed and discussed the document during a meeting in June 2024. The document was edited in response to the discussion and comments.

Preferred Practice Patterns Committee 2024
David K. Wallace, MD, MPH, Chair
Christina J. Flaxel, MD
Steven J. Gedde, MD
Deborah S. Jacobs, MD
Francis S. Mah, MD
Kevin M. Miller, MD
Thomas A. Oetting, MD
Divya M. Varu, MD
David C. Musch, PhD, MPH, Methodologist

The Retinal Vein Occlusions PPP was sent for review in July 2024 to improve the quality of the guideline, to gather feedback on the draft recommendations and to assess feasibility for and applicability to the target audience, including assessing the facilitators and barriers to implementing recommendations (e.g., U.S. ophthalmologists and other important groups, including patients, other physicians, international ophthalmologists, research organizations, ophthalmological organizations, and experts in the field). The PPP was sent for review to the following patient organizations to solicit the views and preferences of patients and the public: Consumers United for Evidence-Based Healthcare, American Foundation for the Blind, Foundation Fighting Blindness, Lighthouse Guild, National Federation of the Blind, and Prevent Blindness. All those returning comments were required to provide disclosure of relevant relationships with industry to have their comments considered (indicated with an asterisk below). Members of the Retina/Vitreous PPP Committee reviewed these comments and determined revisions to the document.

<u>Academy Reviewers</u>
Board of Trustees and Committee of Secretaries*
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Ophthalmic Technology Assessment Committee Retina/Vitreous Panel
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American Society of Retina Specialists*
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North American Neuro-Ophthalmology Society*
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This guideline will be formally re-evaluated and updated on a 5-year cycle in 2029. A Summary Benchmark is a resource to facilitate application of the guideline and to provide criteria that could be used to measure the application of recommendations, which will be available to all at www.aao.org/ppp.

FINANCIAL DISCLOSURES

There is no external funding, including industry/commercial support, for the development of this PPP or for the distribution of the guidelines. The Academy has fully funded the development of this PPP, and the views or interests of the Academy have not influenced the final recommendations, which are based on evidence from systematic reviews. All those individuals significantly involved in the guideline development process, including Retina/Vitreous PPP Committee members, PPP Committee members, Secretary for Quality of Care, and Academy staff, have declared competing/financial interests through a financial interest disclosure process as well as an assessment of the Open Payments website (available at https://openpaymentsdata.cms.gov/). The interests of the Retina/Vitreous PPP Committee members are provided at the beginning of each meeting and those with competing interests in a guideline topic do not participate in voting on areas of disagreement. In compliance with the Council of Medical Specialty Societies' Code for Interactions with Companies (available at https://cmss.org/code-for-interactions-with-companies/), relevant relationships with industry are listed. As per CMSS code, direct financial relationships with industry do not include food and beverage, research funds paid to the institution and relationships outside of the topic of the PPP. The Academy has Relationship with Industry Procedures to comply with the Code (available at www.aao.org/about-preferred-practice-patterns). A majority (71%) of the members of the Retina/Vitreous PPP Committee 2023–2024 had no financial relationship to disclose.

Retina/Vitreous Preferred Practice Pattern Committee 2023–2024
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The disclosures of relevant relationships to industry of other reviewers of the document from January to October 2024 are available online at www.aao.org/ppp.

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OBJECTIVES OF PREFERRED PRACTICE PATTERN® GUIDELINES

As a service to its members and the public, the American Academy of Ophthalmology has developed a series of Preferred Practice Pattern guidelines that **identify characteristics and components of quality eye care.** Appendix 1 describes the core criteria of quality eye care.

The Preferred Practice Pattern guidelines are based on the best available scientific data as interpreted by committees of knowledgeable health professionals. In some instances, such as when results of carefully conducted clinical trials are available, the data are particularly persuasive and provide clear guidance. In other instances, the committees have to rely on their collective judgment and evaluation of available evidence.

These documents provide guidance for the pattern of practice, not for the care of a particular individual. While they should generally meet the needs of most patients, they cannot possibly best meet the needs of all patients. Adherence to these PPPs will not ensure a successful outcome in every situation. These practice patterns should not be deemed inclusive of all proper methods of care or exclusive of other methods of care reasonably directed at obtaining the best results. It may be necessary to approach different patients' needs in different ways. The physician must make the ultimate judgment about the propriety of the care of a particular patient in light of all of the circumstances presented by that patient. The American Academy of Ophthalmology is available to assist members in resolving ethical dilemmas that arise in the course of ophthalmic practice.

Preferred Practice Pattern guidelines are not medical standards to be adhered to in all individual situations. The Academy specifically disclaims any and all liability for injury or other damages of any kind, from negligence or otherwise, for any and all claims that may arise out of the use of any recommendations or other information contained herein.

References to certain drugs, instruments, and other products are made for illustrative purposes only and are not intended to constitute an endorsement of such. Such material may include information on applications that are not considered community standard, that reflect indications not included in approved US Food and Drug Administration (FDA) labeling, or that are approved for use only in restricted research settings. The FDA has stated that it is the responsibility of the physician to determine the FDA status of each drug or device he or she wishes to use, and to use them with appropriate patient consent in compliance with applicable law.

Innovation in medicine is essential to ensure the future health of the American public, and the Academy encourages the development of new diagnostic and therapeutic methods that will improve eye care. It is essential to recognize that true medical excellence is achieved only when the patients' needs are the foremost consideration.

All Preferred Practice Pattern guidelines are reviewed by their parent committee annually or earlier if developments warrant and updated accordingly. To ensure that all PPPs are current, each is valid for 5 years from the approved by date unless superseded by a revision. Preferred Practice Pattern guidelines are funded by the Academy without commercial support. Authors and reviewers of PPPs are volunteers and do not receive any financial compensation for their contributions to the documents. The PPPs are externally reviewed by experts and stakeholders, including consumer representatives, before publication. The PPPs are developed in compliance with the Council of Medical Specialty Societies' Code for Interactions with Companies. The Academy has Relationship with Industry Procedures (available at www.aao.org/about-preferred-practice-patterns) to comply with the Code.

Appendix 2 contains the International Statistical Classification of Diseases and Related Health Problems (ICD) codes for the disease entities that this PPP covers. The intended users of the Retinal Vein Occlusions PPP are ophthalmologists

METHODS AND KEY TO RATINGS

Preferred Practice Pattern® guidelines should be clinically relevant and specific enough to provide useful information to practitioners. Where evidence exists to support a recommendation for care, the recommendation should be given an explicit rating that shows the strength of evidence. To accomplish these aims, methods from the Scottish Intercollegiate Guideline Network[1] (SIGN) and the Grading of Recommendations Assessment, Development and Evaluation[2] (GRADE) group are used. GRADE is a systematic approach to grading the strength of the total body of evidence that is available to support recommendations on a specific clinical management issue. Organizations that have adopted GRADE include SIGN, the World Health Organization, the Agency for Healthcare Research and Policy, and the American College of Physicians.[3]

- All studies used to form a recommendation for care are graded for strength of evidence individually, and that grade is listed with the study citation.
- To rate individual studies, a scale based on SIGN[1] is used. The definitions and levels of evidence to rate individual studies are as follows:

I++	High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias
I+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
I-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
II++	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
II+	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
II-	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
III	Nonanalytic studies (e.g., case reports, case series)

- Recommendations for care are formed based on the body of the evidence. The body of evidence quality ratings are defined by GRADE[2] as follows:

Good quality	Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Insufficient quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate Any estimate of effect is very uncertain

- Key recommendations for care are defined by GRADE[2] as follows:

Strong recommendation	Used when the desirable effects of an intervention clearly outweigh the undesirable effects or clearly do not
Discretionary recommendation	Used when the trade-offs are less certain—either because of low-quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced

- The Highlighted Findings and Recommendations for Care section lists points determined by the Retina/Vitreous PPP Committee to be of particular importance to vision and quality of life outcomes.
- All recommendations for care in this PPP were rated using the system described above. Ratings are embedded throughout the PPP main text in italics.
- Literature searches to update the PPP were undertaken on March 6, 2023, January 23, 2024, and August 8, 2024 in PubMed. Complete details of the literature searches are available online at www.aao.org/ppp.
- Relevant systematic reviews were identified by the Cochrane Eyes and Vision US Satellite (CEV@US). These systematic reviews were screened by the committee and rated using the system described above by the committee methodologist.

- Recommendations are based on systematic reviews, as per the Institute of Medicine (Clinical Practice Guidelines We Can Trust, 2011). In formulating the recommendations, the health benefits, side effects/harms/risks, and the balance of benefits and risks are reviewed and considered. Final decisions are arrived at through informal consensus techniques. If there are areas of disagreement, a vote will be conducted among the members of the Retina/Vitreous PPP Committee. If there are individuals with direct financial relationships in the area of disagreement, these individuals will refrain from the vote.

HIGHLIGHTED FINDINGS AND RECOMMENDATIONS FOR CARE

The prognosis of retinal vein occlusions (RVOs) varies according to the site of the occlusion and the type of occlusion (ischemic or nonischemic). In general, more-distal RVOs with less occlusion have a better prognosis than more-proximal RVOs with greater ischemia.

Central retinal vein occlusions (CRVOs) and hemi-CRVOs have clinically similar courses. They are associated with glaucoma and have a higher risk of anterior segment neovascularization and neovascular glaucoma than branch retinal vein occlusion has. It is important to control intraocular pressure (IOP) for glaucoma management in conjunction with the ophthalmologist's care process for the patient's glaucoma condition.

Macular edema may complicate both CRVOs and branch retinal vein occlusions (BRVOs). The first line of treatment for associated macular edema is intravitreal anti-vascular endothelial growth factor agents (anti-VEGFs). Intravitreal corticosteroids have demonstrated efficacy but have the associated risks of glaucoma and cataract formation. Laser photocoagulation surgery is sometimes used in BRVO.

The choice of biologic product—reference, biosimilar, or interchangeable—should be that of the treating ophthalmologist and the patient because the patient may respond more favorably to one biologic over another.

In partnership with the primary care physician, it is important to control systemic arterial hypertension, diabetes, and serum lipid levels because these are all important modifiable risk factors.

Patients with any RVO have an increased risk of cardiovascular events and all-cause mortality.

INTRODUCTION

DISEASE DEFINITION

Retinal vein occlusion (RVO) is the second most common retinal vascular disorder following diabetic retinopathy and is often associated with vision loss.[4] Retinal vein occlusion occurs when there is a partial or complete obstruction of a retinal vein, and it is classified by the location of the occlusion. An obstruction of the retinal vein at or posterior to the optic nerve head is referred to as a central retinal vein occlusion (CRVO), and a complete or partial obstruction at a branch or tributary of the central retinal vein is referred to as a branch retinal vein occlusion (BRVO). An RVO involves either a complete or partial decrease in venous outflow within the retinal circulation with varying degrees of retinal vascular leakage, leading to both macular edema and an increase of intravenous pressure that results in intraretinal hemorrhages.[4] Branch retinal vein occlusions typically occur at an arteriovenous crossing point, where there is a common adventitial sheath, and are more commonly detected in the superior temporal quadrant.[5] The major risk factors for RVO include systemic arterial hypertension, arteriosclerosis, and diabetes.[6]

A hemiretinal vein occlusion (HRVO) is an occlusion occurring at the disc that commonly involves half of the neurosensory retinal venous drainage, either the superior or inferior hemifield. This pattern occurs in 90% of HRVOs.[7] Some patients with HRVO may have two distinctive central retinal veins referred to as hemicentral retinal veins; one drains the superior and the other drains the inferior retinal hemisphere. Occlusion of one trunk is referred to as a hemi-CRVO.[8] In general, HRVOs are clinically similar to BRVOs and have a visible occlusion near a branch point. However, hemi-CRVOs are clinically similar to CRVOs—no crossing point is visible and there is increased risk of late-developing iris and angle neovascularization and secondary elevated intraocular pressures (IOPs). Differentiation between an HRVO and a hemi-CRVO is not always possible.

The loss of vision that is associated with a vein occlusion usually occurs from macular ischemia or edema, retinal hemorrhages, vitreous hemorrhage, epiretinal membrane formation, rubeosis iridis, and neovascular glaucoma.[4] Other findings associated with RVOs include retinal arterial macroaneurysm formation and cilioretinal artery occlusions.

All vein occlusions are ischemic to varying degrees. The retina drained by the occluded vessels releases hypoxia-related factors such as vascular endothelial growth factor (VEGF), and thus there is a spectrum of nonperfusion.[9]

PATIENT POPULATION

The patient population includes people over 40 years of age, but RVOs most commonly occur in the 6th to 7th decade of life.[10, 11] Retinal vein occlusions are relatively uncommon in individuals under age 40.

CLINICAL OBJECTIVES

- Identify patients at risk for developing RVO
- Encourage management of potential risk factors for both CRVO and BRVO, including optimizing systemic blood pressure and diabetes as well as control of glaucoma and ocular hypertension
- Increase awareness of both ophthalmologists and primary care physicians of the higher risk of cardiovascular and stroke complications in patients presenting with RVO
- Monitor for signs of posterior or anterior segment neovascularization and neovascular glaucoma in all eyes with most RVOs, because a nonischemic can become an ischemic RVO
- Treat or follow patients who have vision loss or those at risk for vision loss after RVO and consider a systemic workup for patients under 50 years of age
- Minimize treatment side effects that might adversely impact vision and/or vision-related quality of life
- Provide or refer the patient for visual rehabilitation services when permanent visual impairment results from the disease

BACKGROUND

PREVALENCE AND INCIDENCE

In 2015, the global prevalence of RVOs was about 0.77% and was estimated to affect 28 million adults (ages 30–89 years) worldwide.[12] Branch retinal vein occlusions are six to seven times more common than CRVOs. There is no sex predilection, and there may be some variation depending on race and geographic location. The incidence in East Asia is similar to that in the United States, and people in India have a lower risk of an RVO and people in Korea might have a higher risk.[11, 13-17]

RISK FACTORS

The main risk factor for both CRVO and BRVO is older age. A prior RVO is a risk factor for an RVO in the fellow eye.[16] The chance of a patient with a pre-existing CRVO developing a CRVO in the fellow eye is 1% per year.[18] Patients with a BRVO in one eye have a 10% risk of developing an RVO of either type in the fellow eye over 3 years.[19, 20] The other major risk factors for BRVO differ from those for CRVO or hemi-CRVO. Risk of BRVO is more likely associated with local vascular factors (arterial-venous crossing changes) rather than local ocular factors, including retinal phlebitis.

Controversy exists regarding the contribution of other hematologic factors, such as factor V Leiden and homocysteinemia, in the development of BRVO. These hematologic factors may be more likely to contribute to the development of CRVO, although there is not uniform agreement. Risk factors for CRVO include carotid occlusive disease and sleep apnea as well as glaucoma.[21] In selected cases, elevated homocysteine levels have been associated with CRVO. Fifty-eight percent of patients with CRVO onset at an age younger than 50 were found to have a nontraditional risk factor on systemic/laboratory evaluation.[22-24] In a cohort of people with systemic lupus erythematosus, the incidence of CRVO was 3.5 times higher than in a control population.[25]

A study found that patients with depression had a higher risk for RVO.[26] Two studies suggested that low high-density lipoprotein-cholesterol is an independent risk factor for RVO.[27, 28] A claims-based study did not find an association with RVO for patients filling prescriptions for female hormone therapy.[29] Other studies have suggested higher risks associated with glaucoma, diabetes, and air pollution.[30-32] A variety of systemic disorders may be present in association with different types of RVO and in different age groups, and therefore a referral for routine medical evaluations is warranted.[33-35]

NATURAL HISTORY

A patient with a CRVO is likely to develop macular edema. Additionally, approximately 25% of patients with CRVO will develop iris neovascularization, and occasionally patients may develop retinal neovascularization. Patients with a CRVO have a higher mortality rate than controls in an age-adjusted general population due to a higher prevalence of cardiovascular disease and diabetes.[36]

An extensive study of the natural history of RVO categorized BRVOs as mild, moderate, or marked, based on the level of capillary nonperfusion seen angiographically.[19] Eyes with BRVO and significant capillary nonperfusion can develop retinal neovascularization and vitreous hemorrhage, but they are much less likely to develop neovascular glaucoma than eyes with CRVO or hemi-CRVO. Macula-involving RVOs are usually acutely symptomatic with the sudden onset of visual symptoms, including a decrease in central vision and/or a corresponding visual field defect. If a BRVO does not involve one of the major temporal branch veins or macular veins, symptoms may go unrecognized unless the occlusion is detected during a routine eye examination or unless complications develop, such as a vitreous hemorrhage from retinal neovascularization. Typically, patients will present with acute visual symptoms in one eye due to macular edema. Early clinical findings include vascular tortuosity, dilation of the affected veins, retinal edema, intraretinal hemorrhages, cotton wool spots, and occasionally hard exudates or even retinal detachment in the affected region.[37] Over time, the

acute process resolves and the hemorrhages may clear, along with the cotton wool spots. In general, the macular edema persists and is a common cause of vision loss unless appropriately treated. Collaterals may also develop between the retinal venules and the choroidal circulation at the disc following a CRVO and between the superior and inferior retinal veins in a BRVO.

The prognosis for vision loss due to BRVO depends on the amount of nonperfusion and the location of the occlusion.[38] The Branch Vein Occlusion Study (BVOS) Group found a spontaneous improvement in visual acuity by 2 or more lines in 37% of eyes, and only 17% had decreased vision. After 3 years of average follow-up, a mean increase in visual acuity of 2.3 lines occurred in the study, and 34% of eyes attained a visual acuity of 20/40 or better. However, 23% of eyes had a visual acuity of 20/200 or worse. Recovery of visual acuity usually occurs as a result of the development of collateral vessels that help with the venous drainage and subsequent resolution of retinal edema and ischemia.[38] The severity of the occlusion and extent of ischemia are important prognostic factors for the visual acuity deficit resulting from BRVO.[39]

Long-standing BRVO is usually characterized by minimal intraretinal blood and resolution of cotton wool spots with mild residual venous tortuosity and collateral vessels adjacent to the affected area. Macular edema may persist or resolve over time, leaving secondary retinal pigment epithelial atrophy and suboptimal visual acuity. Macular edema causes a substantial decrease in vision-related quality of life.[38] Epiretinal membrane often develops in eyes affected by BRVO.

A meta-analysis and systematic review suggest that patients with any RVO have an increased risk of cardiovascular events and all-cause mortality.[40] A retrospective cohort study on an electronic health record database found an increased risk of death, myocardial infarction, and stroke after RVO compared with a matched control population.[41]

RATIONALE FOR TREATMENT

For individuals who develop iris neovascularization or retinal neovascularization following a CRVO, the best long-term treatment is often dense peripheral panretinal photocoagulation surgery (PRP).[42] Although PRP does not usually improve the visual acuity, it decreases the risk of progression to iris neovascularization and may prevent neovascular glaucoma. Additionally, anti-VEGF agents that may or may not treat other targets can be used in an adjunctive manner when complete PRP is insufficient to control angiogenesis.[42, 43] Anti-vascular endothelial growth factor agents are commonly used to treat the macular edema, reduce the severity of anterior segment neovascularization, and lower the risk of ocular angiogenesis.[43] One study found the incidence of macular edema in all BRVOs to be 30%.[44]

CARE PROCESS

Patients under evaluation for RVO should undergo a thorough medical history, ocular exam, and appropriate retinal imaging as needed. An internist may be involved in the management of patients with a new RVO because of associated systemic risk factors, including diabetes, hypertension, and hyperlipidemia.[45] Comprehensive ocular examination and retinal imaging should accomplish the following: (1) distinguish RVO as either BRVO, HRVO, or CRVO; (2) evaluate for macular edema; (3) estimate the degree of retinal ischemia; and (4) evaluate for retinal and/or iris neovascularization.

In eyes with BRVO and macular edema, anti-VEGF injections,[46-50] focal laser surgery,[38] and intravitreal corticosteroids[51] all have demonstrated therapeutic benefit.[52, 53] In eyes with CRVO and macular edema, anti-VEGF[54-64] and intravitreal corticosteroids[65] have demonstrated benefit.[66] Currently, four anti-VEGF agents are used routinely for the treatment of macular edema associated with RVO; three (ranibizumab, aflibercept 2 mg, and faricimab-svoa) are approved by the U.S. Food and Drug Administration (FDA). Although bevacizumab remains off-label for ophthalmologic conditions, there is evidence demonstrating its efficacy and safety.[62-64] Intravitreal corticosteroids (triamcinolone and dexamethasone implant) are considered second line because of significant ocular side effects, such as secondary glaucoma and cataract formation.[65]

In patients with a BRVO and neovascularization of the retina, retinal laser photocoagulation surgery in the area of nonperfusion helps to decrease the risk of a vitreous hemorrhage.[67] In patients with CRVO with retinal and/or iris neovascularization, dense peripheral PRP is indicated.[18] Often, initial treatment with an anti-VEGF agent is helpful for an immediate but not a sustained benefit, and it may also improve the ability to deliver a complete laser surgery treatment.[43, 68]

PATIENT OUTCOME CRITERIA

Patient outcome criteria include the following:

- Improvement or stabilization of visual function
- Improvement or stabilization of vision-related quality of life
- Detection and treatment of all neovascular complications
- Detection and treatment of macular edema
- Optimal control of blood pressure, diabetes and blood glucose, and other risk factors through direct communication and coordination of care with the patient's primary care physician

DIAGNOSIS

The initial examination of a patient with an RVO includes all relevant aspects of the comprehensive adult medical eye evaluation,[69] with particular attention to those aspects related to retinal vascular disease.

History

An initial history should consider the following elements:

- The location and duration of vision loss
- Current medications, history of smoking, recreational drug use
- Medical history (e.g., systemic hypertension, diabetes, hyperlipidemia, cardiovascular disease, sleep apnea, coagulopathies, thrombotic disorders, pulmonary embolus)
- Ocular history (e.g., glaucoma; other ophthalmologic disorders; ocular injections; surgery, including retinal laser surgery, cataract, and refractive)

Examination

The initial examination should include the following elements:

- Visual acuity
- Pupillary assessment for a relative afferent pupillary defect, which corresponds to the level of ischemia and is also predictive for eyes at risk for neovascularization
- Slit-lamp biomicroscopy, looking carefully for fine, abnormal, new iris vessels
- IOP measurement
- Gonioscopy prior to dilation. This is important to perform, especially in cases of an ischemic CRVO, when there is an elevated IOP or when iris neovascularization risk is high.
- Binocular funduscopic evaluation of the posterior pole
- Examination of the peripheral retina and vitreous. A dilated examination is recommended to ensure an optimal view of the entire retina. Slit-lamp biomicroscopy is recommended to evaluate retinopathy of the posterior pole and midperipheral retina. Examination of the far peripheral retina is best performed using indirect ophthalmoscopy or a three-mirror contact lens. Because treatment is effective in reducing the risk of vision loss, a detailed examination is indicated to assess for the following features that often lead to visual impairment:
    - Macular edema, detected both clinically and/or by using optical coherence tomography (OCT) imaging or fluorescein angiography
    - Signs of ischemia, including neovascularization of the disc or elsewhere, presence of a relative afferent pupillary defect, extensive hemorrhages, venous dilation and tortuosity, and cotton wool spots
    - Optic nerve head neovascularization and/or neovascularization elsewhere
    - Vitreous or preretinal hemorrhage

Diagnostic Tests

If used appropriately, a number of imaging tests may enhance the clinical examination and optimize patient care. The most common tests include the following:

Color and Red-Free Fundus Photography

Fundus photography is useful for documenting the severity of the retinal findings, the presence of new vessels elsewhere in the retina (NVE), the extent of intraretinal hemorrhages, and new vessels on or near the optic disc (NVD), the response to treatment, and the need for additional treatment at future visits.

Optical Coherence Tomography

Optical coherence tomography provides high-resolution imaging of the macula and is extremely useful to detect the presence and extent of any macular edema, vitreoretinal interface changes, and subretinal fluid. It is also useful to detect or distinguish RVO from other macular diseases. Large clinical trials testing anti-VEGF treatment are based primarily on quantifiable OCT measurements rather than on the more subjective stereoscopic photographs or clinical examination to evaluate and follow macular edema. In clinical practice, treatment decisions are commonly based on OCT measurements. For example, the decision to repeat anti-VEGF injections, change therapeutic agents (e.g., intraocular corticosteroids), initiate laser surgery, or even consider vitrectomy surgery is frequently based on both visual acuity and OCT findings. Nevertheless, retinal thickness, even when measured by OCT, does not always correlate with visual acuity.[70]

Fluorescein Angiography

Fluorescein angiography (FA) is used to evaluate the extent of the vascular occlusion, the degree of ischemia (ischemic eyes as defined by the Central Vein Occlusion Study [CVOS] as eyes with 10 disc areas of capillary nonperfusion on standard FA vs. nonischemic[18]), and the extent of macular edema. Angiography can identify macular capillary nonperfusion that may explain the associated vision loss as well as the response to therapy. It is a useful technique to distinguish collateral vessels, which do not leak fluorescein in later frames, from retinal neovascularization that is associated with both early and late leakage. It can identify regions of peripheral nonperfusion, helping to guide effective laser surgery or possibly detecting areas of untreated retinal capillary nonperfusion that may explain persistent retinal or disc neovascularization that remains despite prior laser surgery. Recent advances in wide-field FA have enabled its use to evaluate peripheral nonperfusion, yet current data on the benefits of this technique are inconclusive. Some have proposed that the degree of ischemia on wide-field FA can help classify a CRVO as ischemic or nonischemic as well as determine the risk of conversion of a CRVO from nonischemic to ischemic.[71]

As the use of anti-VEGF agents and intraocular corticosteroids has increased for the treatment of macular edema, the use of macular laser surgery has decreased and is infrequent, though it can be considered in certain cases where the edema is focal and outside the central macular subfield. Therefore, the need for FA has also declined. However, FA remains a valuable tool and should be considered by ophthalmologists who diagnose and treat patients who have an RVO.

An ophthalmologist who orders an FA must obtain informed consent and be aware of both common and rare potential risks associated with the procedure, including death in about 1 of 200,000 patients.[72] Each angiography facility should have in place an emergency care plan and a clear protocol to manage known risks and complications. Fluorescein dye crosses the placenta into the fetal circulation,[73] but detrimental effects of fluorescein dye on a fetus have not been documented. Nevertheless, women of childbearing age should be questioned about the possibility of pregnancy and breastfeeding, and FA should be recommended only when absolutely necessary. Fluorescein is present in breastmilk for 72 hours.[74, 75]

Optical Coherence Tomography Angiography

Several studies have demonstrated that in eyes with RVO, noninvasive optical coherence tomography angiography (OCTA) is similar to FA in detecting capillary nonperfusion, enlarged foveal avascular zone, and vascular abnormalities.[76, 77] This promising technology is currently limited by image artifacts and insufficient field of view. Future studies are needed to determine its clinical utility and if it can replace FA in the future.

Ultrasonography

Ultrasonography enables assessment of the anatomic status of the retina in the presence of a vitreous hemorrhage or other media opacity.

Artificial Intelligence

Artificial intelligence is being evaluated as an adjunct in clinical practice to identify RVO and is demonstrating good performance in recognizing RVO from color fundus photographs with deep learning algorithms.[78, 79]

Systemic Evaluation

The extent of the systemic evaluation is dependent on the patient's age and medical history. Discussion with the primary care physician is important, because a patient who has had an RVO is at risk for developing an RVO in the fellow eye and has a higher risk of cardiovascular disease and cerebrovascular accidents.[16, 35] Clear guidelines on systemic testing are lacking.[80] Referral to hematology or internal medicine specialists should also be considered in patients under 50 years of age for a possible hypercoagulable workup.

MANAGEMENT

Prevention and Early Detection

There is a strong relationship between BRVO and systemic vascular disorders such as arterial hypertension and peripheral vascular disease. Older age and systemic vascular disorders are the strongest risk factors for RVO.[81] A meta-analysis of published studies suggests that 48% of RVO is attributable to hypertension, 20% to hyperlipidemia, and 5% to diabetes.[45] It is known that arteriovenous nicking, ocular perfusion pressure, and focal arteriolar narrowing are related to an increased risk of developing a BRVO.[35, 37] Data are inconclusive in determining whether lowering blood pressure and/or serum lipid levels improves visual acuity or the complications from RVO.[45]

Medical and Surgical Management

Consequences of untreated RVOs and vision loss include an economic burden on patients, their family, and society. Anti-VEGF agents, laser surgery, and intravitreal corticosteroids are effective and cost-effective for the management of RVOs. The choice of treatment should be individually tailored based on discussion among the patient, family, and physician.[82, 83] The current treatment strategies for RVO target the sequelae of the venous occlusion (i.e., macular edema and NVD/NVE) rather than treating the occlusion itself. The pivotal studies discussed below are summarized in Table 1.

TABLE 1 EFFECTS OF TREATMENT ON VISION IN RANDOMIZED CONTROLLED TRIALS OF RETINAL AND BRANCH VEIN OCCLUSIONS

Study	No. of Patients	Patient Characteristics			Duration and Frequency of Treatment	Years after Enrollment	Treated Eyes		Untreated Eyes	
		Mean Age	Baseline BCVA (Snellen)	Criteria			Visual Loss of ≥15 Letters	Visual Gain of ≥15 Letters	Visual Loss of ≥15 Letters	Visual Gain of ≥15 Letters
SCORE Trial (Scott et al, 2009)[51]	411	65	20/40	Patients with ME associated with BRVO (included hemiretinal vein occlusion), with best corrected EDTRS visual acuity ≤73 and ≥19	1-mg and 4-mg doses of intravitreal triamcinolone, compared with grid photocoagulation (standard care) >12 months	1 year	11.6% (1 mg) – 12% (4 mg)	25.6% (1 mg) – 27.2% (4 mg)	14.9%	28.9%
GENEVA Trial (Haller et al, 2010)[84]	1267	65	20/80	Patients with vision loss due to ME associated with BRVO or CRVO, central subfield thickness >300 µm	Single treatment with 0.7 mg or 0.35 mg DEX implant, compared with sham, >6 months	6 months	6% (0.7 mg) – 7% (0.35 mg)	41% (0.7 mg) – 40% (0.35 mg)	11%	23%
BRAVO Trial (Campochiaro et al, 2010)[48]	397	66	20/80	Patients with ME secondary to BRVO, central subfield macular thickness ≥250 µm	Ranibizumab 0.3 mg or 0.5 mg, or sham injections, every 4 weeks for 6 months	6 months	0% (0.3 mg) – 2% (0.5 mg)	55.2% (0.3 mg) – 61.1% (0.5 mg)	6%	28.8%
CRUISE Trial (Campochiaro et al, 2011)[57]	392	67	20/100	Patients with ME secondary to CRVO, central subfield macular thickness ≥250 µm	Ranibizumab 0.3 mg or 0.5 mg, or sham injections, every 4 weeks for 6 months	12 months	3.8% (0.3 mg) – 2.3 (0.5 mg)	47% (0.3 mg) – 50.8% (0.5 mg)	10%	33.1%
BALATON Trial (Tadayoni et al, 2024)[85]	1282	64	20/80	Patients with foveal center-involved ME due to BRVO	Faricimab 6 mg or aflibercept 2 mg every 4 weeks for 24 weeks	24 weeks	Not available	Faricimab 56.1% Aflibercept 60.4%	Not applicable	Not applicable

TABLE 1 EFFECTS OF TREATMENT ON VISION IN RANDOMIZED CONTROLLED TRIALS OF RETINAL AND BRANCH VEIN OCCLUSIONS

Study	No. of Patients	Patient Characteristics			Duration and Frequency of Treatment	Years after Enrollment	Treated Eyes		Untreated Eyes	
		Mean Age	Baseline BCVA (Snellen)	Criteria			Visual Loss of ≥15 Letters	Visual Gain of ≥15 Letters	Visual Loss of ≥15 Letters	Visual Gain of ≥15 Letters
VIBRANT Trial (Campochiaro et al, 2013)[46]	183	65	20/80	Patients with ME secondary to BRVO	Aflibercept 2 mg every 4 weeks through week 20 or grid laser surgery and a rescue laser surgery if needed	24 weeks	0%	48%	4%	24%
BRIGHTER Trial (Tadayoni et al, 2017)[86]	455	66	20/80	Patients with visual impairment due to ME secondary to BRVO	Ranibizumab 0.5 mg PRN with or without laser surgery for 24 months	24 weeks	Not available	Ranibizumab 45% ranibizumab + laser surgery 47.2%	Not available	27.8%
LEAVO Trial (Hykin et al, 2019)[87]	463	69	20/60	Adult patients (18+) with CRVO-related ME, BCVA ETDRS letter score of 19–78	Anti-VEGF therapy (aflibercept, bevacizumab, ranibizumab) >100 weeks	100 weeks	Ranibizumab 5% aflibercept 2% bevacizumab 6%	Ranibizumab 47% aflibercept 52% bevacizumab 45%	Not applicable	Not applicable
SCORE2 Trial (Scott et al, 2019)[88]	362	69	20/100	Patients with ME due to central retinal or hemiretinal vein occlusion	Intravitreal injection of bevacizumab (1.25 mg) or aflibercept (2 mg) every 4 weeks	24 months	Aflibercept 6.8% bevacizumab 10.9%	Aflibercept 53% bevacizumab 51%	Not applicable	Not applicable
COMINO Trial (Tadayoni et al, 2024)[85]	1282	65	20/100	Patients with foveal center-involved ME due to central/hemiretinal RVO	Faricimab 6 mg or aflibercept 2 mg every 4 weeks for 24 weeks	24 weeks	Not available	Faricimab 56.6% Aflibercept 58.8%	Not applicable	Not applicable

BCVA = best corrected visual acuity; BRVO = branch retinal vein occlusion; CRVO = central retinal vein occlusion; DEX = dexamethasone; ETDRS = Early Treatment Diabetic Retinopathy Study; ME = macular edema; PRN = pro re nata; RVO = retinal vein occlusion; VEGF = vascular endothelial growth factor.

Anti-Vascular Endothelial Growth Factor Agents

Clinical trials have evaluated the efficacy of anti-VEGF agents and/or intravitreal corticosteroid injections. Multiple randomized controlled trials (RCTs) have demonstrated the efficacy of these agents in the treatment of macular edema associated with BRVO.[47-50, 60, 81] Currently, there are four that are commonly used in these cases: off-label bevacizumab (Avastin®, Genentech, Inc., South San Francisco, CA) and FDA-approved ranibizumab (LUCENTIS®, Genentech, Inc., South San Francisco, CA),[89] aflibercept 2 mg (EYLEA®, Regeneron Pharmaceuticals, Inc., Tarrytown, NY),[90] and faricimab-svoa (VABYSMO™, Genentech, San Francisco, CA).[91] (See Appendix 3.)

The double-masked, multicenter, randomized phase 3 clinical trial BRAVO (Ranibizumab for the Treatment of Macular Edema following Branch Retinal Vein Occlusion: Evaluation of Efficacy and Safety) demonstrated efficacy of monthly intravitreal 0.3- or 0.5-mg ranibizumab compared with sham injection in 397 eyes when followed for 6 months. In this trial, monthly intravitreal ranibizumab injections resulted in a gain of 16 (0.3-mg) to 18 letters (0.5-mg) compared with a gain of 7.3 letters in the sham group at month 6; 55% (0.3-mg) to 61% (0.5-mg) of ranibizumab-treated eyes gained at least 15 letters from baseline compared with 29% in the sham group.[48] After 6 months, all eyes were eligible for injections of ranibizumab 0.5 mg as required until month 12. Eyes randomized to initial sham injection and then eligible for ranibizumab 0.5 mg after 6 months demonstrated vision improvement but did not achieve the level of vision gain compared with those eyes that were randomized to ranibizumab initially—demonstrating that delay in treatment can be deleterious.[52] The benefits of ranibizumab seen at 6 months were generally maintained by month 12.[47]

The HORIZON trial included all patients who completed the BRAVO trial and entered an open-label, multicenter, extension trial. Patients were followed quarterly for 12 months with repeat injections of 0.5-mg ranibizumab, used at the investigator's discretion.[60] Approximately half of the eyes in HORIZON achieved resolution of edema and 80% had visual acuity of better than or equal to 20/40. However, approximately half of the eyes enrolled in the HORIZON extension study received grid laser photocoagulation surgery at some point during the study period. These studies used ranibizumab, whereas other smaller studies have demonstrated the efficacy of bevacizumab for BRVO-associated macular edema.[49, 50, 81, 92] The VIBRANT trial was a randomized, double-masked, phase 3 trial that demonstrated the efficacy of aflibercept 2 mg over grid laser surgery for macular edema in BRVO.[93] Three systematic reviews between 2013 and 2020 have confirmed the efficacy of anti-VEGF injections for treatment of macular edema associated with RVO with minimal side effects.[94-96] *(I++, Good quality, Strong recommendation)*

BALATON (BRVO) and COMINO (CRVO) were two phase 3 randomized clinical trials designed to assess the efficacy, safety, and durability of faricimab-svoa, which provides dual inhibition of angiopoietin-2 and VEGF, in the treatment of retinal vein occlusion.[97] According to Hattenbach et al, "Patients were randomized to 6 monthly injections of faricimab 6 mg or aflibercept 2 mg. From weeks 24-72, all patients received faricimab 6 mg administered in up to 16-week intervals using a treat-and-extend personalized treatment interval dosing regimen." At the time of this writing, only results through week 24 (fixed monthly dosing) have been reported. More than 1200 patients were enrolled worldwide. The primary endpoint was noninferiority of faricimab to aflibercept based on mean change in best corrected visual acuity (BCVA), and this primary endpoint was achieved.

Comparable reductions in central subfield thickness were observed for both agents. The faricimab group had a greater proportion of patients without macular leakage on FA compared with the aflibercept group at week 24. A comparable safety profile was observed for both agents.[85] A faricimab single-dose, prefilled syringe was FDA approved in 2024.

Several randomized clinical trials have also shown the efficacy of anti-VEGF agents in treating CRVO with macular edema.[54, 57, 61, 98] The Ranibizumab for the Treatment of Macular Edema after Central Retinal Vein Occlusion Study: Evaluation of Efficacy and

Safety (CRUISE) showed a doubling of the number of letters read following intravitreal ranibizumab compared with sham injections and a decrease in macular edema by OCT imaging.[57] In the Vascular Endothelial Growth Factor [VEGF] Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (COPERNICUS) study, intravitreal aflibercept 2 mg was compared with sham injections; there was a 15-letter gain in 56% of the treated eyes compared with 12% of sham injections.[54] Similar findings were found in the General Assessment Limiting Infiltration of Exudates in Central Retinal Vein Occlusion with VEGF Trap-Eye (GALILEO) study.[61] Intravitreal bevacizumab was compared with sham injections in a randomized trial that found a 15-letter gain in 60% of the treated eyes compared with 20% for sham injections.[58] In the Lucentis, Eylea, Avastin in Vein Occlusion (LEAVO) study, ranibizumab, aflibercept 2 mg, and bevacizumab treatment for macular edema secondary to CRVO resulted in a mean gain of 12.5, 15.1, and 9.8 letters, respectively, at 100 weeks. Aflibercept 2 mg was found to be noninferior to ranibizumab at 100 weeks. Bevacizumab was found to not be noninferior to ranibizumab at 100 weeks; however, the results of the comparison were inconclusive.[87] Systematic reviews have also supported the efficacy of anti-VEGF for treatment of macular edema secondary to CRVO.[66, 99-101] *(I++, Good quality, Strong recommendation)*

The Study of Comparative Treatments for Retinal Vein Occlusion 2 (SCORE2) comparison of monthly aflibercept 2 mg to bevacizumab for macular edema from CRVO and HRVO showed that aflibercept was similar to bevacizumab in mean visual acuity at 6 months (primary outcome).[92] From months 6 to 12, patients in SCORE2 were then stratified based on their response to the original monthly treatment as good, poor, or marginal response. Those with a good response were then given the original treatment drug monthly or on a treat-and-extend protocol basis. Patients in the treat-and-extend protocol received about one to two fewer injections compared with the monthly regimen. However, because of the widths of the confidence intervals on visual acuity at 12 months, caution is advised before concluding that the two regimens yield similar visual outcomes.[102] For eyes classified as poor responders to aflibercept at 6 months, dexamethasone rescue was used.[102] Aflibercept was used for eyes with a marginal response to bevacizumab.[102]

After month 12, the original SCORE2 study protocol was discontinued, and patients were treated with any drug or frequency at the investigator's discretion. Overall, visual acuity worsened from month 12 to 24 in both groups. Among 65% of patients who completed the month 24 study visit, there were no differences in visual acuity or central subfield thickness between patients originally assigned to aflibercept or bevacizumab. However, interpretation of these results is limited by the high attrition rate.[88]

Approximately half of patients with a BRVO and 56% to 75% of patients with a CRVO will continue to require anti-VEGF therapy to control macular edema beyond 5 years after initiation of treatment.[103] Long-term follow-up of patients up to 60 months identified a nonlinear relationship, with a thinner retina not always associated with a better visual acuity letter score.[104]

In general, the use of topical anti-sepsis such as povidone iodine is recommended before all intravitreal injections, whereas the use of routine antibiotic eye drops is not recommended.[105] Severe adverse effects of intravitreal injections are uncommon and include infectious endophthalmitis, cataract formation, retinal detachment, and elevated IOP. Intraocular pressure elevations are particularly common with the use of intravitreal corticosteroids and the corticosteroid implants.

All anti-VEGF treatments may carry theoretical risks for systemic arterial thromboembolic events, although the results of clinical trials studying these risks remain inconclusive.[106-109] One meta-analysis of eight RCTs with 2320 patients with RVO did not find an increased risk of cardiovascular diseases, heart rate disorders, or hypertension.[110] A meta-analysis of systemic safety of anti-VEGF agents across several retinal conditions did not find an increase of major cardiovascular events.[111] *(I+, Moderate quality)* Another meta-analysis did not find an increased risk of mortality among patients with retinal conditions, including RVO, receiving anti-VEGF drugs.[112] *(I+, Moderate quality)*

A further meta-analysis demonstrated no evidence of increased arterial thromboembolic events associated with anti-VEGF treatment.[113] The atherothrombotic event rate in the two controlled RVO studies (BALATON AND COMINO) during the first 6 months was 0.8% in both the ranibizumab and control arms of the studies (4 of 525 in the combined group of patients treated with 0.3-mg or 0.5-mg ranibizumab and 2 of 260 in the control arms). The stroke rate was 0.2% (1 of 525) in the combined group of ranibizumab-treated patients compared with 0.4% (1 of 260) in the control arms. The incidence of reported atherothrombotic events in the RVO studies during the first 6 months was 1.1% (7 of 641) in patients treated with faricimab compared with 1.4% (9 of 635) in patients treated with aflibercept. Faricimab was found to have a 1.4% rate of intraocular inflammation (not counting endophthalmitis) when used for RVO.[91, 114]

In conclusion, because of the favorable risk-to-benefit profile, anti-VEGF agents are the preferred initial therapy for treatment of macular edema related to BRVO. Either corticosteroids and/or grid laser surgery should be considered when there is a failure to respond or an inadequate response.

Biosimilars

As defined by the FDA, biosimilars are large complex molecules produced by living organisms that are similar to an existing molecule.[115] To approve a biosimilar, the FDA compares the purity, molecular structure, and bioactivity of the biosimilar to the existing molecule. The FDA also examines comparative clinical studies to ensure that there are "no clinically meaningful differences between the proposed biosimilar product (also called biosimilar) and the reference product in terms of safety, purity, or potency (i.e., safety and effectiveness)."[116] This abbreviated approval process means that the usual clinical trials that involve human subjects to determine safety and efficacy of a reference molecule may not be needed. For ophthalmic biosimilars, one comparative clinical trial is required for the approval process, whereas reference products typically require two clinical trials.

A randomized clinical equivalence trial for patients with neovascular age-related macular degeneration found that a proposed ranibizumab biosimilar product met efficacy for mean changes of BVCA at 8 week and OCT central subfield thickness at week 4. Safety and immunogenicity profiles were reported to be similar in age-related macular degeneration.[117] Post hoc analysis revealed no evidence of immunogenicity affecting clinical efficacy, safety, or pharmacokinetic profiles.[118] There are several biosimilar ranibizumab molecules approved by the FDA and others are available in numerous other countries.[119] There are no prospective long-term clinical data comparing ranibizumab biosimilars to ranibizumab.

In 2021, the FDA approved the first biosimilar, ranibizumab-nuna 0.5 mg (Byooviz™, Samsung Bioepis, Incheon, South Korea; and Biogen Inc, Cambridge, MA)[120] for the treatment of macular edema following RVO, based on ranibizumab as the reference molecule. In 2022, the FDA approved ranibizumab-eqrn 0.5 mg (Cimerli®, Coherus, Redwood City, CA)[121] for treatment of macular edema following RVO, based on ranibizumab as the reference molecule.

In 2024, the FDA approved four biosimilars to aflibercept 2 mg for macular edema following RVO as of the time of writing this PPP: aflibercept-jbvf (Yesafili®, Biocon Biologics, Bridgeport, NJ),[122] aflibercept-yszy (Opuviz®, Samsung Bioepis, Incheon, South Korea; and Biogen Inc, Cambridge, MA),[123] and aflibercept-mrbb (Ahzantive®, Formycon AG, Martinsried/Planegg, Germany),[124] and aflibercept-ayyh (Pavblu™, Amgen, Inc., Thousand Oaks, CA).[125] All are injected intravitreally as a 2-mg solution, and the adverse events appear consistent with aflibercept. The recommended dose for all four agents is 2 mg every 4 weeks.

When used, the choice of biologic product (reference, biosimilar, or interchangeable) should be that of the treating ophthalmologist and the patient, because patients may respond more favorably to one biologic over another.[126]

Corticosteroids

Intravitreal corticosteroids such as triamcinolone, dexamethasone, and others have been shown to be efficacious for macular edema associated with BRVO and CRVO, yet there are known associated risks of cataracts and glaucoma.[65, 98, 127]

The SCORE study for BRVO evaluated the use of two doses of intravitreal corticosteroids (triamcinolone 1 mg and 4 mg) versus macular grid laser surgery in 411 eyes randomized to one of the three treatment arms in a 1:1:1 fashion and followed for 12 months.[51] After 1 year, approximately one third of eyes in the laser surgery group, one third of eyes in the triamcinolone 1-mg group, and one third of eyes in the triamcinolone 4-mg group gained 15 or more letters. The mean gain in BCVA was 4 to 5 letters in all groups; however, patients in either of the corticosteroid groups were more likely to develop cataract or elevated IOP than those who received laser surgery treatment. The SCORE recommendations for BRVO were to consider macular grid laser surgery in eyes with BRVO and perfused macular edema leading to vision loss because the efficacy was similar in all treatment arms.

The SCORE CRVO trial included 271 people aged 68 years on average.[65] Seventy-three percent of patients with CRVO had high blood pressure and 23% percent had diabetes. Patients in the corticosteroid medication groups received an average of two injections in the first 12 months of the study. After 1 year, 27% of patients in the 1-mg group and 26% of patients in the 4-mg group experienced a substantial visual gain of 3 or more lines of visual acuity. Only 7% of patients in the observation group experienced a similar visual gain. Therefore, patients in the corticosteroid treatment groups were much more likely to have a substantial visual gain at 1 year. These results persisted up to 2 years. However, participants who received the 4-mg dose had the highest rates of cataract formation, cataract surgery, and elevated IOP, indicating a preference for the 1-mg dose.[65]

The GENEVA study evaluated the use of the intravitreal dexamethasone implant (Ozurdex®, Allergan, Inc., Irvine, CA) in two doses compared with sham injection in eyes with either a CRVO or a BRVO.[84] The study included pooled data from 1131 patients, 34% with CRVO and 66% with BRVO, and showed treatment with either the 0.35-mg or the 0.7-mg dose implant led to significant visual acuity gain by day 30 that peaked at 90 days and was lost at 6 months. Results from an open-label extension beyond 6 months were similar to the initial study, showing visual acuity gains up to 90 days, then loss of a treatment effect at 1 year.[98] Cataract formation and elevated IOP were seen more frequently at 1 year than at 6 months (16% had an elevated IOP of 25 mmHg or greater). The dexamethasone implant was FDA approved in 2009 for the treatment of macular edema due to CRVO and BRVO.

The COBALT study has shown that with retreatment using the dexamethasone implant as often as every 4 months, significant visual acuity gains can be achieved for eyes with macular edema secondary to a BRVO.[128] In fact, mean visual acuity improvement was 18.6 ± 12.9 and 15.3 ± 15.0 letters at 6 and 12 months, respectively. There was a rapid response, with approximately 70% of maximum treatment response seen at 1 week. Incidence of IOP elevation was 18% and cataract incidence was 16% at one year.

A Cochrane systematic review questioned the results of SCORE because of incomplete outcome data and the GENEVA study because of selective reporting and found that there was insufficient evidence to determine if corticosteroids are beneficial or not.[129] *(I+, Good quality, Strong recommendation)* A 2014 meta-analysis found no difference in visual improvement for treatment of macular edema from CRVO with bevacizumab, ranibizumab, aflibercept 2 mg, and triamcinolone.[127] *(I+, Good quality, Strong recommendation)* However, a meta-analysis of 11 RCTs with 879 eyes found that anti-VEGF agents were associated with better outcomes in terms of safety, anatomic measures, and visual acuity compared with intravitreal corticosteroids.[130] *(I+, Moderate quality, Discretionary recommendation)* A 2023 meta-analysis of five RCTs including 1041 eyes found high-dose intravitreal triamcinolone acetonide had greater visual acuity improvement and greater reductions in retinal thickness than a low-dose regimen but had more safety concerns.[131]

(I-, Insufficient quality, Discretionary recommendation) Altogether, the risks of IOP increases and cataract associated with corticosteroids make anti-VEGF agents more favorable as initial therapy.

Laser Photocoagulation Surgery

The BVOS first demonstrated the efficacy of grid laser photocoagulation surgery for macular edema due to BRVO. Patients with BRVO who presented with a visual acuity of 20/40 or worse due to perfused BRVO (retained macular perfusion on FA) with macular edema were randomized to either grid-pattern laser photocoagulation surgery or no treatment. There were more patients who gained at least 2 lines of visual acuity from baseline in the laser photocoagulation surgery group than in the untreated group (65% vs. 37%). Nearly twice as many treated eyes had visual acuity outcomes greater than 20/40 when compared with untreated eyes. This finding led to the recommendation that grid laser surgery should be considered for eyes with BRVO, macular perfusion, and macular edema with a visual acuity of 20/40 or worse.[38] However, anti-VEGF therapy results in more improvement in visual acuity (see above) than laser surgery and should be the preferred treatment unless there are contraindications to its use. Additionally, treatment for macular edema should not be delayed. Patients for whom monthly follow-up is difficult may also be managed more easily with laser photocoagulation surgery, with follow-up 3 months after laser surgery. Sectoral PRP is still recommended for neovascularization when complications such as vitreous hemorrhage or iris neovascularization occur.[67] Clinical trials have shown no added benefit for macular grid or peripheral scatter laser photocoagulation surgery for BRVO. A systematic review did not find that combination therapies provided benefit in terms of BCVA or structural outcomes compared with intravitreal anti-VEGF therapy.[132] *(I-, Moderate quality)* The 2-year BRIGHTER[86] and the 4-year RETAIN[133] studies demonstrated that adding laser surgery to ranibizumab did not result in a better visual outcome or reduce the need for treatment. In the RELATE study, scatter laser surgery for peripheral ischemic areas did not decrease the macular edema.[134]

The Central Vein Occlusion Study (CVOS) did not show any value of focal photocoagulation for macular edema in patients with CRVO.[18] For patients with iris or angle neovascularization, the CVOS recommended complete peripheral PRP.[18] Currently, anti-VEGF agents are being used as an adjunct to treat iris or angle neovascularization. There is no phase 3 clinical trial evidence on anti-VEGF therapy for this usage.

Real-world treatment tends to fall short of clinical trial guidelines. A single institution study found that one in four patients did not return for a year or longer after receiving intravitreal injections.[135] A systematic review of intravitreal injection therapy found that worse vision at baseline, worsening of vision, age, and distance from the treatment center were associated with nonadherence.[136]

Follow-up Evaluation

The follow-up evaluation includes a history and examination.[18, 38, 46, 48, 51, 54, 57, 60, 61, 65, 84, 86, 87, 92, 97, 128, 133, 134]

History

A follow-up history should include changes in the following:

- Symptoms
- Systemic status (pregnancy, blood pressure, serum cholesterol, blood glucose)

Examination

- Visual acuity
- Undilated slit-lamp biomicroscopy and gonioscopy with careful iris examination for early iris or angle neovascularization[137] as often as monthly for 6 months in eyes with CRVO and in eyes with ischemic CRVO after discontinuing anti-VEGF to detect neovascularization[18]

- Pupillary assessment for a relative afferent pupillary defect
- IOP measurement
- Stereoscopic examination of the posterior pole after dilation of the pupils
- OCT imaging
- Peripheral retina and vitreous examination, when indicated
- FA (should be considered)

PROVIDER AND SETTING

Although the ophthalmologist will perform the examination and any associated surgery, certain aspects of data collection may be performed by trained individuals under the ophthalmologist's supervision and review. Because of the complexities of the diagnosis and treatment for RVO, the ophthalmologist caring for patients with these conditions should be familiar with the specific recommendations of relevant clinical trials.[18, 38, 46, 48, 51, 54, 57, 60, 61, 65, 84, 86, 87, 92, 97, 128, 133, 134] The American Academy of Ophthalmology has a stated position and a policy statement on the role of the ophthalmologist in the delivery of intravitreal agents.[138] Outside of the United States, there are varying practice patterns.[139-141]

COUNSELING AND REFERRAL

The ophthalmologist should refer patients with an RVO to a primary care physician for appropriate management of their systemic condition and should communicate examination results to the physician managing the patient's ongoing medical care.[45] The risk to the fellow eye should also be communicated to both the primary care provider and the patient.[16, 35] An Eye MD Examination Report Form is available from the American Academy of Ophthalmology.[142] Some patients with RVO will lose substantial vision despite being treated according to the recommendations in this document. Patients whose conditions fail to respond to therapy and those for whom further treatment is unavailable should be provided with proper professional support and offered referral for treatment, counseling, vision rehabilitation, or social services as appropriate.[143, 144] Empathic communication and questioning by the provider is helpful to elicit patient concerns. Referrals for counseling, vocational rehabilitation, and or peer support groups for patients with depression, anxiety, and loss of independence or employment should be considered.[145] Vision rehabilitation helps to restore some functional ability,[146] and patients with functionally limiting postoperative visual impairment should be referred for vision rehabilitation and social services.[144] More information on vision rehabilitation, including materials for patients, is available at www.aao.org/low-vision-and-vision-rehab.

SOCIOECONOMIC CONSIDERATIONS

Very few studies have evaluated the cost/benefit ratio of the various treatment types for RVO but applying commonly used metrics, anti-VEGF therapy, focal laser surgery, and intraocular corticosteroids all appear to be cost-effective. One 2011 study evaluated the cost/benefit ratio of treatment methods for macular edema due to various etiologies. The dollars per quality-adjusted life years (QALY) for treatment of BRVO with macular edema ranges between approximately $800 and $26,000, and for CRVO with macular edema it ranges between approximately $1,400 and $16,000. These are considered cost-effective treatments.[82] The same study also concluded that the benefit conveyed by pharmacologic therapy for visual acuity, although statistically significant, may only be modestly beneficial (i.e., 1 line or less of visual acuity gained). This study demonstrates the wide range of cost parameters for macular edema treatment, ranging from a low of $1,326 for laser surgery to $23,119 for a 1-year course of ranibizumab treatment, a 17-fold difference. In a 2011 study, costs per visual acuity line-year ranged from $25 to $754.[82] In this analysis, the natural history of BRVO was calculated as 0.23 lines (1.15 letters) of spontaneous improvement and was used for the natural history adjustment. The index study for laser surgery yielded a 1.33-line (6.65 letters) improvement for laser surgery that yielded 1.1 lines (5.5 letters) saved when reduced by the natural history adjustment. Calculations, including similar adjustments for corticosteroids (with triamcinolone), yielded 1.4 lines saved. Lines-saved values calculated for bevacizumab (4.9) and ranibizumab (2.2) had higher values. When looking at the dollars per QALY, this was $824 for bevacizumab versus $1,572 for grid laser surgery, $5,536 for the dexamethasone implant, and $25,566 for ranibizumab.

The dollars per line-year saved followed along similar lines, with bevacizumab at $25, grid laser surgery $68, the dexamethasone implant $162, and ranibizumab $754.

A 2014 study reported on the direct medical costs for treating CRVO and BRVO in working-age and Medicare populations.[83] The authors found that overall health care utilization and expenditures for patients with BRVO or CRVO were significantly greater than those for control subjects without these diseases at both 1 and 3 years postdiagnosis. Utilization and expenditures were greater in the first year following diagnosis and continued to exceed those of control subjects at 3 years postdiagnosis. The authors felt that the development of RVO is a marker for poorer overall systemic vascular health and increased utilization of medical resources. One study evaluated quality of life in patients with RVO and found a significantly lower composite Visual Function Questionnaire-25 score compared with controls.[147]

APPENDIX 1. QUALITY OF OPHTHALMIC CARE CORE CRITERIA

Providing quality care
is the physician's foremost ethical obligation and is
the basis of public trust in physicians.
AMA Board of Trustees, 1986

Quality ophthalmic care is provided in a manner and with the skill that is consistent with the best interests of the patient. The discussion that follows characterizes the core elements of such care.

The ophthalmologist is first and foremost a physician. As such, the ophthalmologist demonstrates compassion and concern for the individual and utilizes the science and art of medicine to help alleviate patient fear and suffering. The ophthalmologist strives to develop and maintain clinical skills at the highest feasible level, consistent with the needs of patients, through training and continuing education. The ophthalmologist evaluates those skills and medical knowledge in relation to the needs of the patient and responds accordingly. The ophthalmologist also ensures that needy patients receive necessary care directly or through referral to appropriate persons and facilities that will provide such care, and he or she supports activities that promote health and prevent disease and disability.

The ophthalmologist recognizes that disease places patients in a disadvantaged, dependent state. The ophthalmologist respects the dignity and integrity of his or her patients and does not exploit their vulnerability.

Quality ophthalmic care has the following optimal attributes, among others.

- The essence of quality care is a meaningful partnership relationship between patient and physician. The ophthalmologist strives to communicate effectively with his or her patients, listening carefully to their needs and concerns. In turn, the ophthalmologist educates his or her patients about the nature and prognosis of their condition and about proper and appropriate therapeutic modalities. This is to ensure their meaningful participation (appropriate to their unique physical, intellectual and emotional state) in decisions affecting their management and care, to improve their motivation and compliance with the agreed plan of treatment, and to help alleviate their fears and concerns.
- The ophthalmologist uses his or her best judgment in choosing and timing appropriate diagnostic and therapeutic modalities as well as the frequency of evaluation and follow-up, with due regard to the urgency and nature of the patient's condition and unique needs and desires.
- The ophthalmologist carries out only those procedures for which he or she is adequately trained, experienced and competent, or, when necessary, is assisted by someone who is, depending on the urgency of the problem and availability and accessibility of alternative providers.
- Patients are assured access to, and continuity of, needed and appropriate ophthalmic care, which can be described as follows.
  - The ophthalmologist treats patients with due regard to timeliness, appropriateness, and his or her own ability to provide such care.
  - The operating ophthalmologist makes adequate provision for appropriate pre- and postoperative patient care.
  - When the ophthalmologist is unavailable for his or her patient, he or she provides appropriate alternate ophthalmic care, with adequate mechanisms for informing patients of the existence of such care and procedures for obtaining it.
  - The ophthalmologist refers patients to other ophthalmologists and eye care providers based on the timeliness and appropriateness of such referral, the patient's needs, the competence and qualifications of the person to whom the referral is made, and access and availability.

- The ophthalmologist seeks appropriate consultation with due regard to the nature of the ocular or other medical or surgical problem. Consultants are suggested for their skill, competence, and accessibility. They receive as complete and accurate an accounting of the problem as necessary to provide efficient and effective advice or intervention, and in turn respond in an adequate and timely manner.
- The ophthalmologist maintains complete and accurate medical records.
- On appropriate request, the ophthalmologist provides a full and accurate rendering of the patient's records in his or her possession.
- The ophthalmologist reviews the results of consultations and laboratory tests in a timely and effective manner and takes appropriate actions.
- The ophthalmologist and those who assist in providing care identify themselves and their profession.
- For patients whose conditions fail to respond to treatment and for whom further treatment is unavailable, the ophthalmologist provides proper professional support, counseling, rehabilitative and social services, and referral as appropriate and accessible.

- Prior to therapeutic or invasive diagnostic procedures, the ophthalmologist becomes appropriately conversant with the patient's condition by collecting pertinent historical information and performing relevant preoperative examinations. Additionally, he or she enables the patient to reach a fully informed decision by providing an accurate and truthful explanation of the diagnosis; the nature, purpose, risks, benefits, and probability of success of the proposed treatment and of alternative treatment; and the risks and benefits of no treatment.
- The ophthalmologist adopts new technology (e.g., drugs, devices, surgical techniques) in judicious fashion, appropriate to the cost and potential benefit relative to existing alternatives and to its demonstrated safety and efficacy.
- The ophthalmologist enhances the quality of care he or she provides by periodically reviewing and assessing his or her personal performance in relation to established standards, and by revising or altering his or her practices and techniques appropriately.
- The ophthalmologist improves ophthalmic care by communicating to colleagues, through appropriate professional channels, knowledge gained through clinical research and practice. This includes alerting colleagues of instances of unusual or unexpected rates of complications and problems related to new drugs, devices or procedures.
- The ophthalmologist provides care in suitably staffed and equipped facilities adequate to deal with potential ocular and systemic complications requiring immediate attention.
- The ophthalmologist also provides ophthalmic care in a manner that is cost effective without unacceptably compromising accepted standards of quality.

Reviewed by: Council
Approved by: Board of Trustees
October 12, 1988

2nd Printing: January 1991
3rd Printing: August 2001
4th Printing: July 2005

APPENDIX 2. INTERNATIONAL STATISTICAL CLASSIFICATION OF DISEASES AND RELATED HEALTH PROBLEMS (ICD) CODES

Retinal vein occlusion, which include entities with the following ICD-9 and ICD-10 classifications:

	ICD-9 CM	ICD-10 CM
Central retinal vein occlusion	362.35	H34.811- H34.812- H34.813-
Venous tributary (branch) occlusion	362.36	H34.831- H34.832- H34.833-
Venous engorgement	362.37	H34.821- H34.822- H34.823-

ICD = International Classification of Diseases; CM = Clinical Modification used in the United States

Additional information for ICD-10 codes:

- For bilateral sites, the final character of the codes in the ICD-10 CM indicates laterality. If no bilateral code is provided and the condition is bilateral, separate codes for both the left and right side should be assigned. Unspecified codes should be used only when there is no other code option available.
- When the diagnosis code specifies laterality, regardless of which digit it is found in (i.e., 4th digit, 5th digit, or 6th digit):
    - Right is always 1
    - Left is always 2
    - Bilateral is always 3

APPENDIX 3. INTRAVITREAL AGENTS FOR PATIENTS WITH MACULAR EDEMA FOLLOWING RETINAL VEIN OCCLUSIONS

The intravitreal agents used in the treatment of macular edema following retinal vein occlusions are listed in Table A3-1.

TABLE A3-1 INTRAVITREAL AGENTS FOR PATIENTS WITH MACULAR EDEMA FOLLOWING RETINAL VEIN OCCLUSIONS

Generic	Brand Name	Company
Aflibercept intravitreal injection 2.0 mg	EYLEA®	Regeneron
Aflibercept-jbvf intravitreal injection 2.0 mg	Yesafili™	Biocon Biologics
Aflibercept-yszy intravitreal injection 2.0 mg	Opuviz™	Samsung Biopeis and Biogen MA, Inc
Aflibercept-mrbb intravitreal injection 2.0 mg	Ahzantive®	Formycon AG
Aflibercept-ayyh intravitreal injection 2.0 mg	Pavblu™	Amgen, Inc
Bevacizumab intravitreal injection 1.25 mg (off-label)	Avastin®	Genentech
Brolucizumab intravitreal injection 6.0 mg	Beovu®	Novartis
Dexamethasone intravitreal implant 0.7 mg	Ozurdex®	AbbVie
Faricimab-svoa intravitreal injection 6.0 mg	VABYSMO®	Genentech
Ranibizumab intravitreal injection 0.5 mg	LUCENTIS®	Genentech
Ranibizumab-eqrn intravitreal injection 0.5 mg (biosimilar)	Cimerli™	Coherus Biosciences
Ranibizumab-nuna intravitreal injection 0.5 mg (biosimilar)	Byooviz™	Samsung Bioepis and Biogen MA, Inc
Triamcinolone acetonide intravitreal injection 4.0 mg (off-label)	Triescence®	Harrow

GLOSSARY

Aflibercept: Aflibercept is an anti-VEGF agent that acts as a soluble decoy receptor that binds VEGF-A and placental growth factor and inhibits the binding and activation of these VEGF receptors.

Anti-VEGF (Anti-vascular endothelial growth factor): Substances that inhibit the action of vascular endothelial growth factor protein.

BALATON: A phase 3 randomized clinical trial designed to assess the efficacy, safety, and durability of faricimab, which provides dual inhibition of angiopoietin-2 and VEGF, in the treatment of branch retinal vein occlusion.

Bevacizumab: Bevacizumab is a full-length monoclonal antibody that binds all isoforms of VEGF and has FDA approval for intravenous use in the treatment of metastatic colorectal, metastatic breast, and non-small cell lung cancer.

BRVO (Branch retinal vein occlusion): BRVO is an occlusion of any branch of the central retinal vein.

BVOS (Branch Vein Occlusion Study): BVOS first demonstrated the efficacy of grid laser photocoagulation surgery for macular edema and sectoral PRP for retinal neovascularization due to BRVO.

BRAVO: The BRAVO study demonstrated efficacy of monthly intravitreal 0.3 or 0.5 mg ranibizumab compared with sham injection in 397 eyes when followed for 6 months.

BRIGHTER: The BRIGHTER study results confirmed the long-term efficacy and safety profile of PRN dosing driven by individualized VA stabilization criteria using ranibizumab 0.5 mg in patients with BRVO.

CRVO (Central retinal vein occlusion): In a CRVO, the vascular occlusion is at or proximal to the lamina cribrosa of the optic nerve, where the central retinal vein exits the eye. A CRVO can be further classified into perfused (nonischemic) and nonperfused (ischemic), each of the which has implications for prognosis and treatment.

COBALT: Dexamethasone Intravitreal Implant for Early Treatment and Retreatment of Macular Edema Related to Branch Retinal Vein Occlusion: The multicenter COBALT study

COMINO: A phase 3 randomized clinical trial designed to assess the efficacy, safety, and durability of faricimab, which provides dual inhibition of angiopoietin-2 and VEGF, in the treatment of central retinal vein occlusion.

COPERNICUS: In the COPERNICUS study, intravitreal aflibercept was compared with sham injections in the treatment of macular edema secondary to CRVO and there was a 15-letter gain in 56% of the treated eyes compared with 12% of sham injections.

CRUISE: The CRUISE study showed a doubling of the number of letters read following intravitreal ranibizumab compared with sham injections and a decrease in macular edema by OCT imaging.

CVOS (Central Vein Occlusion Study): CVOS concluded that macular grid laser surgery for macular edema secondary to CRVO did not yield an improvement in visual acuity and is therefore not warranted.

Faricimab: Faricimab is a humanized bispecific immunoglobulin G1 (IgG1) antibody that binds both vascular endothelial growth factor A (VEGF-A) and angiopoietin-2 (Ang-2) providing dual inhibition.

FA (Fluorescein angiography): An invasive technique in which fluorescein dye is injected intravenously into an antecubital vein that allows visualization of the retinal and choroidal vasculature.

GALILEO: GALILEO evaluated the efficacy of aflibercept vs. sham in the treatment of macular edema secondary to CRVO and concluded that patients treated with aflibercept gained more vision compared to sham.

GENEVA: The GENEVA study evaluated the use of the intravitreal dexamethasone implant in two doses compared with sham injection in eyes with either a CRVO or a BRVO.

HRVO (Hemi-retinal vein occlusion): An HRVO has been associated with a congenital variation in central vein anatomy and can involve either the superior or inferior half of the retina.

HORIZON: The HORIZON trial was an extension of the BRAVO trial in which patients were followed quarterly for 12 months with repeat injections of 0.5 mg ranibizumab, used at the investigator's discretion. Approximately half of the eyes in HORIZON achieved resolution of edema and 80% had visual acuity of better than or equal to 20/40.

NVE (New vessels elsewhere in the retina): Retinal neovascularization not on or near the optic disc.

NVD (New vessels on or near the optic disc): Retinal neovascularization on or near the optic disc.

OCT (Optical coherence tomography): A noninvasive technique to image intraocular tissues by measuring the echo time delay and intensity of back-reflected light. The resulting image provides high-resolution, cross-sectional representation of structure with near-histological detail.

OCTA (Optical coherence tomography angiography): A non-invasive imaging technique for the microvasculature of the retina and choroid.

PRP (Peripheral panretinal photocoagulation): Extensive laser surgery treatment applied to the peripheral retina often in an effort to treat retinal neovascularization secondary to retinal ischemia.

Ranibizumab: A recombinant humanized immunoglobulin G1 kappa isotype therapeutic antibody fragment that binds to and inhibits the biologic activity of a form of VEGF-A.

RELATE: In the RELATE study, scatter laser surgery to peripheral ischemic areas did not decrease macular edema in BRVO

RETAIN: The RETAIN study evaluated patients out to 5 years and found that 50% of 34 patients with BRVO and 56% of 32 patients with CRVO required ranibizumab injections 4 years after therapeutic onset.

RVO (Retinal vein occlusion): Blockage of a retinal vein.

SCORE2: The SCORE2 study was a phase 3 non-inferiority trial with study eyes randomized to intravitreal bevacizumab every 4 weeks versus intravitreal aflibercept every 4 weeks. SCORE2 aimed to determine if bevacizumab is non-inferior to aflibercept for the treatment of macular edema secondary to central retinal vein occlusion (CRVO), with the primary outcome of visual acuity measured at month 6. SCORE2 demonstrated that aflibercept treatment was associated with a more favorable OCT outcomes but not VA outcomes at month 6.

Severe visual loss: In this document, severe visual loss means quadrupling or more of the visual angle (e.g., 20/20 to 20/80 or worse, or 20/50 to 20/200 or worse).

VEGF (Vascular endothelial growth factor): A significant mediator in the process of angiogenesis and increased vascular permeability and inflammation. It has been identified in neovascularization related to both diabetic retinopathy and AMD. In animal models, the introduction of VEGF has initiated the cascade of neovascularization seen in AMD. Thus, the inhibition or antagonism of the action of VEGF is a targeted area of research, with several novel therapeutic agents being developed, and in various stages of investigation and FDA approval.

VIBRANT: The VIBRANT trial was a randomized double-masked phase 3 trial that demonstrated the efficacy of aflibercept over grid laser surgery treatment for macular edema in BRVO.

LITERATURE SEARCHES FOR THIS PPP

Literature searches of the PubMed database were conducted on March 6, 2023; the search strategies are listed below. Specific limited update searches were conducted on January 23, 2024 and August 8, 2024. The searches had added filters for human, English-language randomized controlled trials and systematic reviews and date limiters to capture literature published since June 1, 2019. The Retina/Vitreous PPP Committee analyzed 877 studies of which 38 were included in the PPP. The literature searches with the disease condition and the search terms patient values and patient preferences yielded 11 studies. The literature searches for economic evaluation and treatment cost yielded 33 studies which were provided to the Retina/Vitreous PPP Committee and 1 study merited inclusion in the PPP.

Cost: (“Retinal Vein Occlusion”[MeSH] OR “Retinal Vein Occlusion”[tiab]) AND (“Cost-Benefit Analysis”[MeSH] OR “Cost of Illness”[MeSH] OR economics[MeSH] OR cost[tiab] OR cost[MeSH])

Diagnosis: “Retinal Vein Occlusion”/diagnosis[MeSH]

Epidemiology: “Retinal Vein Occlusion/epidemiology”[MeSH]

Natural History: (“Retinal Vein Occlusion”[MeSH] OR “Retinal Vein Occlusion”[tiab]) AND “Natural History”[tiab]

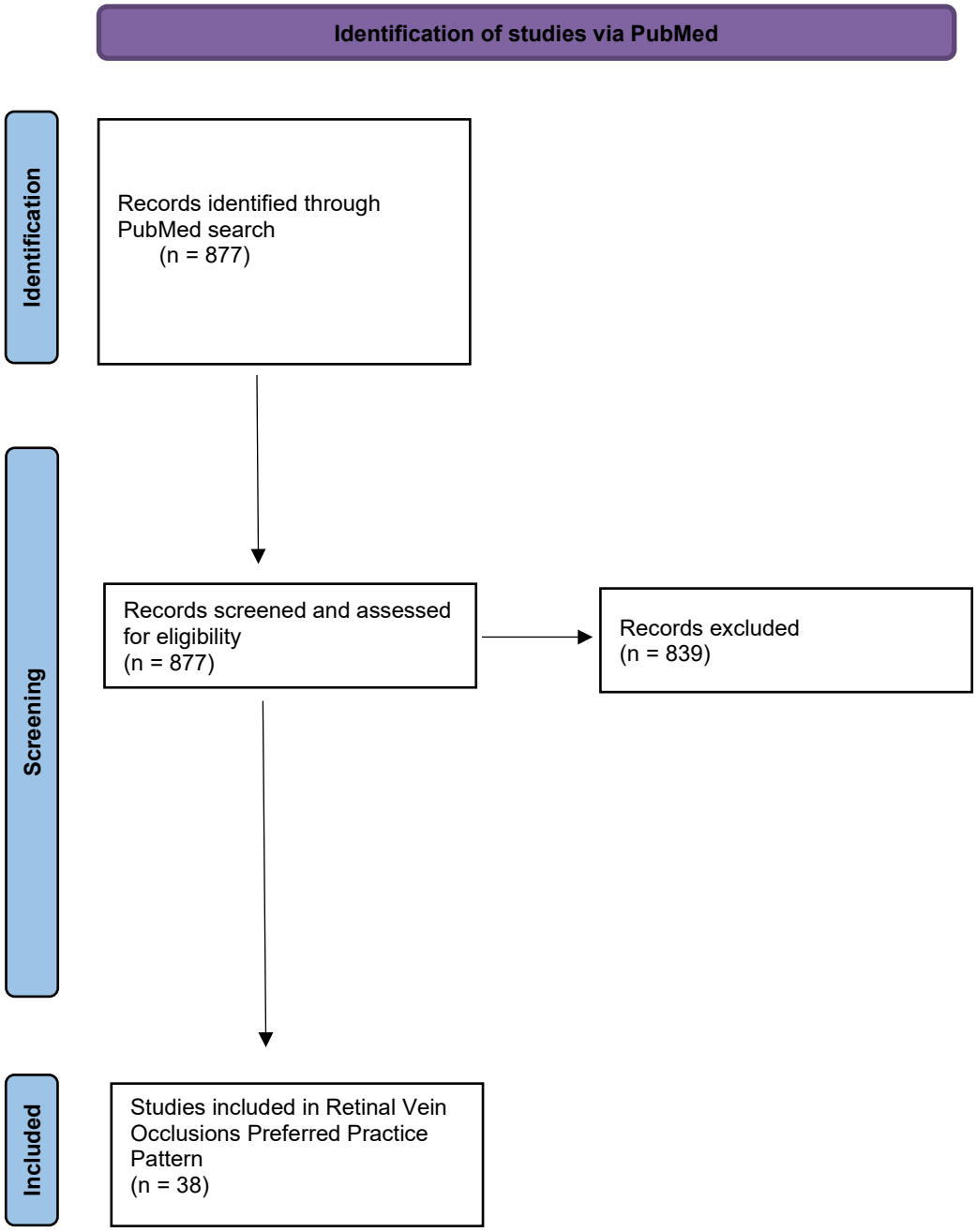
Patient Values and Preferences: (“Retinal Vein Occlusion”[MeSH] OR “Retinal Vein Occlusion”[tiab]) AND ((“Patient Values”[tiab] OR “Patient Preference”[tiab]) OR (patient[tiab] AND (values[tiab] OR preference[tiab])))

Physiology: “Retinal Vein Occlusion/pathology”[MeSH] OR “Retinal Vein Occlusion/physiology”[MeSH] OR “Retinal Vein Occlusion/physiopathology”[MeSH]

Quality of Life: (“Retinal Vein Occlusion”[MeSH] OR “Retinal Vein Occlusion”[tiab]) AND (“Quality of Life”[MeSH] OR QoL[tiab])

Risk Factors: (("Retinal Vein Occlusion"[MeSH] OR "Retinal Vein Occlusion"[tiab]) AND (risk[tiab] OR “Risk Factors”[MeSH]))

Therapy: “Retinal Vein Occlusion/surgery”[MeSH] OR “Retinal Artery Occlusion/surgery”[MeSH] OR “Retinal Vein Occlusion/therapy”[MeSH] OR “Retinal Vein Occlusion/drug therapy”[MeSH]



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

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Laser Surgery (2015)

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Therapies for Macular Edema Associated with Branch Retinal Vein Occlusion (2017)

Therapies for Macular Edema Associated with Central Retinal Vein Occlusion (2015)

Patient Education

Face-Down Recover After Retinal Surgery Brochure (2024)

Laser Eye Surgery Brochure (2024)

Retinal Vein Occlusion Brochure (2024)

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REFERENCES

1. Scottish Intercollegiate Guidelines Network (SIGN). *SIGN 50: A guideline developer's handbook.* Edinburgh: SIGN; 2015. (SIGN publication no. 50). [November 2015]. Available from url: Http://www.Sign.Ac.Uk. Accessed September 13, 2024.
2. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924-6.
3. GRADE working group. Organizations that have endorsed or that are using GRADE. Http://www.Gradeworkinggroup.Org/. Accessed September 13, 2024..
4. Buehl W, Sacu S, Schmidt-Erfurth U. Retinal vein occlusions. *Dev Ophthalmol* 2010;46:54-72.
5. Weinberg D, Dodwell DG, Fern SA. Anatomy of arteriovenous crossings in branch retinal vein occlusion. *Am J Ophthalmol* 1990;109:298-302.
6. Kumar B, Yu DY, Morgan WH, et al. The distribution of angioarchitectural changes within the vicinity of the arteriovenous crossing in branch retinal vein occlusion. *Ophthalmology* 1998;105:424-7.
7. Sanborn GE, Magargal LE. Characteristics of the hemispheric retinal vein occlusion. *Ophthalmology* 1984;91:1616-26.
8. Hayreh SS, Hayreh MS. Hemi-central retinal vein occulsion. Pathogenesis, clinical features, and natural history. *Arch Ophthalmol* 1980;98:1600-9.
9. Mir TA, Kherani S, Hafiz G, et al. Changes in retinal nonperfusion associated with suppression of vascular endothelial growth factor in retinal vein occlusion. *Ophthalmology* 2016;123:625-34 e1.
10. Central vein occlusion study group. Baseline and early natural history report: The Central Vein Occlusion Study. *Arch Ophthalmol* 1993;111:1087-95.
11. 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;117:313-9.
12. Song P, Xu Y, Zha M, et al. Global epidemiology of retinal vein occlusion: A systematic review and meta-analysis of prevalence, incidence, and risk factors. *J Glob Health* 2019;9:010427.
13. 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;120:803-8.
14. Jonas JB, Nangia V, Khare A, et al. Prevalence and associations of retinal vein occlusions: The Central India Eye and Medical Study. *Retina* 2013;33:152-9.
15. Arakawa S, Yasuda M, Nagata M, et al. Nine-year incidence and risk factors for retinal vein occlusion in a general Japanese population: The Hisayama Study. *Invest Ophthalmol Vis Sci* 2011;52:5905-9.
16. Jaulim A, Ahmed B, Khanam T, Chatziralli IP. Branch retinal vein occlusion: Epidemiology, pathogenesis, risk factors, clinical features, diagnosis, and complications: An update of the literature. *Retina* 2013;33:901-10.
17. Park SH, Kim BJ, Kim JH, et al. Incidence rates of retinal vascular occlusive diseases from 2011 to 2020 in South Korea: A nationwide cohort study. *BMC Ophthalmol* 2024;24:128.
18. Central Vein Occlusion Study Group. Natural history and clinical management of central retinal vein occlusion. *Arch Ophthalmol* 1997;115:486-91.
19. Hayreh SS, Zimmerman MB, Podhajsky P. Incidence of various types of retinal vein occlusion and their recurrence and demographic characteristics. *Am J Ophthalmol* 1994;117:429-41.
20. Michels RG, Gass JD. The natural course of retinal branch vein obstruction. *Trans Am Acad Ophthalmol Otolaryngol* 1974;78:OP166-77.
21. 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;154:200-5.
22. Fong AC, Schatz H. Central retinal vein occlusion in young adults. *Surv Ophthalmol* 1993;37:393-417.
23. Tourville E, Schachat AP. Plasma proteins - possible risk factors for retinal vascular occlusive disease. In: Joussen AM, Gardner TW, Kirchhof B, Ryan SJ, eds. Retinal vascular disease, 1st ed. Berlin; New York: Springer-Verlag, 2007.
24. Rothman AL, Thomas AS, Khan K, Fekrat S. Central retinal vein occlusion in young individuals: A comparison of risk factors and clinical outcomes. *Retina* 2018.
25. Yen YC, Weng SF, Chen HA, Lin YS. Risk of retinal vein occlusion in patients with systemic lupus erythematosus: A population-based cohort study. *Br J Ophthalmol* 2013;97:1192-6.
26. Ha M, Han K, Jung Y, et al. Is retinal vein occlusion associated with depression symptoms?: A nationwide cohort study. *Medicine (Baltimore)* 2021;100:e26937.

27. Zheng C, Lin Y, Jiang B, et al. Plasma lipid levels and risk of retinal vascular occlusion: A genetic study using Mendelian randomization. *Front Endocrinol (Lausanne)* 2022;13:954453.
28. Kim J, Lim DH, Han K, et al. Retinal vein occlusion is associated with low blood high-density lipoprotein cholesterol: A nationwide cohort study. *Am J Ophthalmol* 2019;205:35-42.
29. Song D, Nadelmann J, Yu Y, VanderBeek BL. Association of retinal vascular occlusion with women filling a prescription for female hormone therapy. *JAMA Ophthalmol* 2021;139:42-8.
30. Zhang HW, Lin CW, Kok VC, et al. Incidence of retinal vein occlusion with long-term exposure to ambient air pollution. *PLoS One* 2019;14:e0222895.
31. Yin X, Li J, Zhang B, Lu P. Association of glaucoma with risk of retinal vein occlusion: A meta-analysis. *Acta Ophthalmol* 2019;97:652-9.
32. Wang Y, Wu S, Wen F, Cao Q. Diabetes mellitus as a risk factor for retinal vein occlusion: A meta-analysis. *Medicine (Baltimore)* 2020;99:e19319.
33. Kim HR, Lee NK, Lee CS, et al. Retinal vascular occlusion risks in high blood pressure and the benefits of blood pressure control. *Am J Ophthalmol* 2023;250:111-9.
34. Eye Disease Case-Control Study Group. Risk factors for central retinal vein occlusion *Arch Ophthalmol* 1996;114:545-54.
35. Hayreh SS, Zimmerman B, McCarthy MJ, Podhajsky P. Systemic diseases associated with various types of retinal vein occlusion. *Am J Ophthalmol* 2001;131:61-77.
36. Bertelsen M, Linneberg A, Christoffersen N, et al. Mortality in patients with central retinal vein occlusion. *Ophthalmology* 2014;121:637-42.
37. Klein R, Klein BE, Moss SE, Meuer SM. The epidemiology of retinal vein occlusion: The Beaver Dam Eye Study. *Trans Am Ophthalmol Soc* 2000;98:133-41; discussion 41-3.
38. Branch Vein Occlusion Study Group. Argon laser photocoagulation for macular edema in branch vein occlusion. *Am J Ophthalmol* 1984;98:271-82.
39. Christoffersen NL, Larsen M. Pathophysiology and hemodynamics of branch retinal vein occlusion. *Ophthalmology* 1999;106:2054-62.
40. Wu CY, Riangwiwat T, Limpruttidham N, et al. Association of retinal vein occlusion with cardiovascular events and mortality: A systematic review and meta-analysis. *Retina* 2019;39:1635-45.
41. Wai KM, Ludwig CA, Koo E, et al. Risk of stroke, myocardial infarction, deep vein thrombosis, pulmonary embolism, and death after retinal vein occlusion. *Am J Ophthalmol* 2024;257:129-36.
42. A randomized clinical trial of early panretinal photocoagulation for ischemic central vein occlusion: The Central Vein Occlusion Study Group N Report. *Ophthalmology* 1995;102:1434-44.
43. Iliev ME, Domig D, Wolf-Schnurrbursch U, et al. Intravitreal bevacizumab (avastin) in the treatment of neovascular glaucoma. *Am J Ophthalmol* 2006;142:1054-6.
44. Li J, Paulus YM, Shuai Y, et al. New developments in the classification, pathogenesis, risk factors, natural history, and treatment of branch retinal vein occlusion. *J Ophthalmol* 2017;2017:4936924.
45. O'Mahoney PR, Wong DT, Ray JG. Retinal vein occlusion and traditional risk factors for atherosclerosis. *Arch Ophthalmol* 2008;126:692-9.
46. Study to assess the clinical efficacy and safety of intravitreal aflibercept injection (IAI;EYLEA®;BAY86-5321) in patients with branch retinal vein occlusion (BRVO) (VIBRANT). Available at: Https://clinicaltrials.Gov/ct2/show/study/nct01521559. Accessed September 13, 2024.
47. 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;118:1594-602.
48. 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;117:1102-12.
49. Russo V, Barone A, Conte E, et al. Bevacizumab compared with macular laser grid photocoagulation for cystoid macular edema in branch retinal vein occlusion. *Retina* 2009;29:511-5.
50. Yilmaz T, Cordero-Coma M. Use of bevacizumab for macular edema secondary to branch retinal vein occlusion: A systematic review. *Graefes Arch Clin Exp Ophthalmol* 2012;250:787-93.
51. Scott IU, Ip MS, VanVeldhuisen PC, et al. SCORE Study Research Group. 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;127:1115-28.
52. Ehlers JP, Kim SJ, Yeh S, et al. Therapies for macular edema associated with branch retinal vein occlusion: A report by the American Academy of Ophthalmology. *Ophthalmology* 2017;124:1412-23.
53. Chatziralli IP, Jaulim A, Peponis VG, et al. Branch retinal vein occlusion: Treatment modalities: An update of the literature. *Semin Ophthalmol* 2014;29:85-107.

54. Boyer D, Heier J, Brown DM, et al. Vascular endothelial growth factor Trap-Eye for macular edema secondary to central retinal vein occlusion: Six-month results of the phase 3 COPERNICUS study. *Ophthalmology* 2012;119:1024-32. Erratum in: Ophthalmology 2012;119:204.
55. Brown DM, Campochiaro PA, Singh RP, et al. Ranibizumab for macular edema following central retinal vein occlusion: Six-month primary end point results of a phase III study. *Ophthalmology* 2010;117:1124-33.
56. 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;155:429-37.
57. 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;118:2041-9.
58. Epstein DL, Algvere PV, von Wendt G, et al. Bevacizumab for macular edema in central retinal vein occlusion: A prospective, randomized, double-masked clinical study. *Ophthalmology* 2012;119:1184-9.
59. Epstein DL, Algvere PV, von Wendt G, et al. Benefit from bevacizumab for macular edema in central retinal vein occlusion: Twelve-month results of a prospective, randomized study. *Ophthalmology* 2012;119:2587-91.
60. Heier JS, Campochiaro PA, Yau L, et al. Ranibizumab for macular edema due to retinal vein occlusions: Long-term follow-up in the HORIZON trial. *Ophthalmology* 2012;119:802-9.
61. Holz FG, Roider J, Ogura Y, et al. VEGF Trap-Eye for macular oedema secondary to central retinal vein occlusion: 6-month results of the phase III GALILEO study. *Br J Ophthalmol* 2013;97:278-84.
62. Kriechbaum K, Michels S, Prager F, et al. Intravitreal avastin for macular oedema secondary to retinal vein occlusion: A prospective study. *Br J Ophthalmol* 2008;92:518-22.
63. Prager F, Michels S, Kriechbaum K, et al. Intravitreal bevacizumab (avastin) for macular oedema secondary to retinal vein occlusion: 12-month results of a prospective clinical trial. *Br J Ophthalmol* 2009;93:452-6.
64. Zhang H, Liu ZL, Sun P, Gu F. Intravitreal bevacizumab for treatment of macular edema secondary to central retinal vein occlusion: Eighteen-month results of a prospective trial. *J Ocul Pharmacol Ther* 2011;27:615-21.
65. 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;127:1101-14.
66. Yeh S, Kim SJ, Ho AC, et al. Therapies for macular edema associated with central retinal vein occlusion: A report by the American Academy of Ophthalmology. *Ophthalmology* 2015;122:769-78.
67. Branch Vein Occlusion Study Group. Argon laser scatter photocoagulation for prevention of neovascularization and vitreous hemorrhage in branch vein occlusion: A randomized clinical trial. *Arch Ophthalmol* 1986;104:34-41.
68. Mahdy RA, Nada WM, Fawzy KM, et al. Efficacy of intravitreal bevacizumab with panretinal photocoagulation followed by Ahmed valve implantation in neovascular glaucoma. *J Glaucoma* 2013;22:768-72.
69. Frank RN, Hoffman WH, Podgor MJ, et al. Retinopathy in juvenile-onset diabetes of short duration. *Ophthalmology* 1980;87:1-9.
70. Davis MD, Bressler SB, Aiello LP, et al. Diabetic Retinopathy Clinical Research Network Study Group. Comparison of time-domain OCT and fundus photographic assessments of retinal thickening in eyes with diabetic macular edema. *Invest Ophthalmol Vis Sci* 2008;49:1745-52.
71. 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;39:1033-8.
72. Yannuzzi LA, Rohrer KT, Tindel LJ, et al. Fluorescein angiography complication survey. *Ophthalmology* 1986;93:611-7.
73. Sunness JS. The pregnant woman's eye. *Surv Ophthalmol* 1988;32:219-38.
74. Halperin LS, Olk RJ, Soubrane G, Coscas G. Safety of fluorescein angiography during pregnancy. *Am J Ophthalmol* 1990;109:563-6.
75. Rosenthal JM, Johnson MW. Management of retinal diseases in pregnant patients. *J Ophthalmic Vis Res* 2018;13:62-5.
76. Rispoli M, Savastano MC, Lumbroso B. Capillary network anomalies in branch retinal vein occlusion on optical coherence tomography angiography. *Retina* 2015;35:2332-8.
77. Kashani AH, Lee SY, Moshfeghi A, et al. Optical coherence tomography angiography of retinal venous occlusion. *Retina* 2015;35:2323-31.

78. Chen Q, Yu WH, Lin S, et al. Artificial intelligence can assist with diagnosing retinal vein occlusion. *Int J Ophthalmol* 2021;14:1895-902.
79. Ren X, Feng W, Ran R, et al. Artificial intelligence to distinguish retinal vein occlusion patients using color fundus photographs. *Eye (Lond)* 2023;37:2026-32.
80. Wai KM, Ludwig CA, Koo E, et al. Risk of stroke, myocardial infarction, deep vein thrombosis, pulmonary embolism, and death after retinal vein occlusion. *Am J Ophthalmol* 2023.
81. Ehlers JP, Fekrat S. Retinal vein occlusion: Beyond the acute event. *Surv Ophthalmol* 2011;56:281-99.
82. Smiddy WE. Economic considerations of macular edema therapies. *Ophthalmology* 2011;118:1827-33.
83. Suner IJ, Margolis J, Ruiz K, et al. Direct medical costs and resource use for treating central and branch retinal vein occlusion in commercially insured working-age and medicare populations. *Retina* 2014;34:2250-8.
84. Haller JA, Bandello F, Belfort R, Jr., et al. Ozurdex Geneva Study Group. Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion. *Ophthalmology* 2010;117:1134-46.
85. Tadayoni R, Paris LP, Danzig CJ, et al. Efficacy and safety of faricimab for macular edema due to retinal vein occlusion: 24-week results from the BALATON and COMINO trials. *Ophthalmology* 2024;131:950-60.
86. Tadayoni R, Waldstein SM, Boscia F, et al. Sustained benefits of ranibizumab with or without laser in branch retinal vein occlusion: 24-month results of the BRIGHTER study. *Ophthalmology* 2017;124:1778-87.
87. Hykin P, Prevost AT, Vasconcelos JC, et al. Clinical effectiveness of intravitreal therapy with ranibizumab vs aflibercept vs bevacizumab for macular edema secondary to central retinal vein occlusion: A randomized clinical trial. *JAMA Ophthalmol* 2019;137:1256-64.
88. Scott IU, Oden NL, VanVeldhuisen PC, et al. Month 24 outcomes after treatment initiation with anti-vascular endothelial growth factor therapy for macular edema due to central retinal or hemiretinal vein occlusion: SCORE2 report 10: A secondary analysis of the SCORE2 randomized clinical trial. *JAMA Ophthalmol* 2019;137:1389-98.
89. U.S. Food and Drug Administration. Highlights of prescribing information for Lucentis. Https://www.Accessdata.Fda.Gov/drugsatfda_docs/label/2017/125156s111lbl.Pdf. Accessed September 13, 2024.
90. U.S. Food and Drug Administration. Highlights of prescribing information for EYLEA injection. Https://www.Accessdata.Fda.Gov/drugsatfda_docs/label/2011/125387lbl.Pdf. Accessed September 13, 2024.
91. U.S. Food and Drug Administration. Highlights of prescribing information for VABYSMO injection. Https://www.Accessdata.Fda.Gov/drugsatfda_docs/label/2022/761235s000lbl.Pdf. Accessed September 13, 2024.
92. 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;317:2072-87.
93. Clark WL, Boyer DS, Heier JS, et al. Intravitreal aflibercept for macular edema following branch retinal vein occlusion: 52-week results of the VIBRANT study. *Ophthalmology* 2016;123:330-6.
94. Regnier SA, Larsen M, Bezlyak V, Allen F. Comparative efficacy and safety of approved treatments for macular oedema secondary to branch retinal vein occlusion: A network meta-analysis. *BMJ Open* 2015;5:e007527.
95. Song WT, Xia XB. Ranibizumab for macular edema secondary to retinal vein occlusion: A meta-analysis of dose effects and comparison with no anti-VEGF treatment. *BMC Ophthalmol* 2015;15:31.
96. Shalchi Z, Mahroo O, Bunce C, Mitry D. Anti-vascular endothelial growth factor for macular oedema secondary to branch retinal vein occlusion. *Cochrane Database Syst Rev* 2020;7:CD009510.
97. Hattenbach LO, Abreu F, Arrisi P, et al. BALATON and COMINO: Phase III randomized clinical trials of faricimab for retinal vein occlusion: Study design and rationale. *Ophthalmol Sci* 2023;3:100302.
98. Haller JA, Bandello F, Belfort R, Jr., 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;118:2453-60.
99. 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:CD007325.
100. Ford JA, Clar C, Lois N, et al. Treatments for macular oedema following central retinal vein occlusion: Systematic review. *BMJ Open* 2014;4:e004120.
101. Zhou S, Gao J, Xu X. Antivascular endothelial growth factors in the treatment of macular oedema secondary to central retinal vein occlusion: A meta-analysis. *Clin Exp Ophthalmol* 2014;42:637-49.
102. Scott IU, VanVeldhuisen PC, Ip MS, et al. Comparison of monthly vs treat-and-extend regimens for individuals with macular edema who respond well to anti-vascular endothelial growth factor medications: Secondary outcomes from the SCORE2 randomized clinical trial. *JAMA Ophthalmol* 2018;136:337-45.

103. Scott IU, Campochiaro PA, Newman NJ, Biousse V. Retinal vascular occlusions. *Lancet* 2020;396:1927-40.
104. Scott IU, Oden NL, VanVeldhuisen PC, et al. SCORE2 report 24: Nonlinear relationship of retinal thickness and visual acuity in central retinal and hemiretinal vein occlusion. *Ophthalmology* 2023;130:1066-72.
105. Parke DW, II, Coleman AL, Rich WL, III, Lum F. Choosing wisely: Five ideas that physicians and patients can discuss. *Ophthalmology* 2013;120:443-4.
106. Virgili G, Parravano M, Menchini F, Brunetti M. Antiangiogenic therapy with anti-vascular endothelial growth factor modalities for diabetic macular oedema. *Cochrane Database Syst Rev* 2012;12:CD007419.
107. Hoang QV, Mendonca LS, Della Torre KE, et al. Effect on intraocular pressure in patients receiving unilateral intravitreal anti-vascular endothelial growth factor injections. *Ophthalmology* 2012;119:321-6.
108. Wehrli SJ, Tawse K, Levin MH, et al. A lack of delayed intraocular pressure elevation in patients treated with intravitreal injection of bevacizumab and ranibizumab. *Retina* 2012;32:1295-301.
109. Pielen A, Feltgen N, Isserstedt C, et al. Efficacy and safety of intravitreal therapy in macular edema due to branch and central retinal vein occlusion: A systematic review. *PLoS One* 2013;8:e78538.
110. Zhong P, He M, Yu H, et al. A meta-analysis of cardiovascular events associated with intravitreal anti-VEGF treatment in patients with retinal vein occlusion. *Curr Eye Res* 2020;45:615-22.
111. Ngo Ntjam N, Thulliez M, Paintaud G, et al. Cardiovascular adverse events with intravitreal anti-vascular endothelial growth factor drugs: A systematic review and meta-analysis of randomized clinical trials. *JAMA Ophthalmol* 2021;139:1-11.
112. Reibaldi M, Fallico M, Avitabile T, et al. Risk of death associated with intravitreal anti-vascular endothelial growth factor therapy: A systematic review and meta-analysis. *JAMA Ophthalmol* 2020;138:50-7.
113. Cheng JW, Cheng SW, Lu GC, Wei RL. Effect of intravitreal anti-vascular endothelial growth factor therapy on the risk of arterial thromboembolic events: A meta-analysis. *PLoS One* 2012;7:e41325.
114. Li Y, Chong R, Fung AT. Association of occlusive retinal vasculitis with intravitreal faricimab. *JAMA Ophthalmol* 2024.
115. U.S. Food and Drug Administration. What is a biosimilar? Https://www.Fda.Gov/media/108905/download Accessed September 13, 2024.
116. U.S. Food and Drug Administration. Review and approval. 2022. Https://www.Fda.Gov/drugs/biosimilars/review-and-approval Accessed September 13, 2024.
117. 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;139:68-76.
118. Bressler NM, Kim T, Oh I, et al. Immunogenicity with ranibizumab biosimilar SB11 (Byooviz) and reference product Lucentis and association with efficacy, safety, and pharmacokinetics: A post hoc analysis of a phase 3 randomized clinical trial. *JAMA Ophthalmol* 2023;141:117-27.
119. Sharma A, Kondo M, Iwahashi C, et al. Approved biosimilar ranibizumab-a global update. *Eye (Lond)* 2023;37:200-2.
120. U.S. Food and Drug Administration. Highlights of prescribing information for Byooviz injection. Https://www.Accessdata.Fda.Gov/drugsatfda_docs/label/2021/761202s000lbl.Pdf. Accessed September 13, 2024.
121. U.S. Food and Drug Administration. Highlights of prescribing information for Cimerli injection. Https://www.Accessdata.Fda.Gov/drugsatfda_docs/label/2022/761165s000lbl.Pdf. Accessed September 13, 2024.
122. U.S. Food and Drug Administration. Highlights of prescribing information for Yesafili (aflibercept-jbvf). Https://www.Accessdata.Fda.Gov/drugsatfda_docs/label/2024/761274s000lbl.Pdf. Accessed September 13, 2024.
123. U.S. Food and Drug Administration. Highlights of prescribing information for Opuviz (aflibercept-yszy). Https://www.Accessdata.Fda.Gov/drugsatfda_docs/label/2024/761350s000lbl.Pdf. Accessed September 13, 2024.
124. U.S. Food and Drug Administration. Highlights of prescribing information for Ahzantive injection. Https://www.Accessdata.Fda.Gov/drugsatfda_docs/label/2024/761378s000lbl.Pdf. Accessed September 13, 2024.
125. U.S. Food and Drug Administration. Highlights of prescribing information for Pavblu injection. Https://www.Accessdata.Fda.Gov/drugsatfda_docs/label/2024/761298s000lbl.Pdf. Accessed September 13, 2024.
126. American Academy of Ophthalmology. The use of biosimilars in ophthalmic practice. 2022. Available at: Https://www.Aao.Org/education/clinical-statement/use-of-biosimilars-in-ophthalmic-practice. Accessed September 13, 2024.

127. Ford JA, Shyangdan D, Uthman OA, et al. Drug treatment of macular oedema secondary to central retinal vein occlusion: A network meta-analysis. *BMJ Open* 2014;4:e005292.
128. Yoon YH, Kim JW, Lee JY, et al. Dexamethasone intravitreal implant for early treatment and retreatment of macular edema related to branch retinal vein occlusion: The multicenter COBALT study. *Ophthalmologica* 2018;240:81-9.
129. Gewaily D, Muthuswamy K, Greenberg PB. Intravitreal steroids versus observation for macular edema secondary to central retinal vein occlusion. *Cochrane Database Syst Rev* 2015:CD007324.
130. Patil NS, Hatamnejad A, Mihalache A, et al. Anti-vascular endothelial growth factor treatment compared with steroid treatment for retinal vein occlusion: A meta-analysis. *Ophthalmologica* 2022;245:500-15.
131. Mihalache A, Hatamnejad A, Patil NS, et al. Intravitreal triamcinolone acetonide for diabetic macular edema and macular edema secondary to retinal vein occlusion: A meta-analysis. *Ophthalmologica* 2024;247:19-29.
132. Bhambra N, Sayal AP, Popovic MM, et al. 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 (Lond)* 2022;36:2271-8.
133. 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;121:209-19.
134. 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;122:1426-37.
135. Gao X, Obeid A, Adam MK, et al. Loss to follow-up in patients with retinal vein occlusion undergoing intravitreal anti-VEGF injections. *Ophthalmic Surg Lasers Imaging Retina* 2019;50:159-66.
136. Ehlken C, Ziemssen F, Eter N, et al. Systematic review: Non-adherence and non-persistence in intravitreal treatment. *Graefes Arch Clin Exp Ophthalmol* 2020;258:2077-90.
137. Jacobson DR, Murphy RP, Rosenthal AR. The treatment of angle neovascularization with panretinal photocoagulation. *Ophthalmology* 1979;86:1270-7.
138. American Academy of Ophthalmology. Clinical statement. Intravitreal injections. San Francisco, CA: American Academy of Ophthalmology; 2015. Available at: Https://www.Aao.Org/education/clinical-statement/intravitreal-injections-statement. Accessed September 13, 2024.
139. Simcock P, Kingett B, Mann N, et al. A safety audit of the first 10 000 intravitreal ranibizumab injections performed by nurse practitioners. *Eye (Lond)* 2014;28:1161-4.
140. DaCosta J, Hamilton R, Nago J, et al. Implementation of a nurse-delivered intravitreal injection service. *Eye (Lond)* 2014;28:734-40.
141. Hasler PW, Bloch SB, Villumsen J, et al. Safety study of 38,503 intravitreal ranibizumab injections performed mainly by physicians in training and nurses in a hospital setting. *Acta Ophthalmol* 2015;93:122-5.
142. Lee PP, Feldman ZW, Ostermann J, Brown DS. Longitudinal rates of annual eye examinations of persons with diabetes and chronic eye diseases. *Ophthalmology* 2003;110:1952-9.
143. Jackson ML, Virgili G, Shepherd JD, et al. Vision rehabilitation preferred practice pattern. *Ophthalmology* 2023;130:P271-P335.
144. Leese GP, Ellis JD, Morris AD, Ellingford A. Does direct ophthalmoscopy improve retinal screening for diabetic eye disease by retinal photography? *Diabet Med* 2002;19:867-9.
145. Center for Vision and Population Health. Vision loss and mental health: Key takeaways from an interprofessional task force. Https://preventblindness.Org/wp-content/uploads/2023/05/mental-health-issue-brieff.Pdf Accessed September 13, 2024.
146. Stelmack JA, Tang XC, Reda DJ, et al. LOVIT study group. Outcomes of the veterans affairs low vision intervention trial (LOVIT). *Arch Ophthalmol* 2008;126:608-17.
147. Chatzirallis A, Varaklioti A, Sergentanis TN, et al. Quality of life among patients with retinal vein occlusion: A case-control study. *Semin Ophthalmol* 2021;36:658-64.