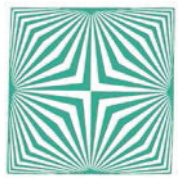
PREFERRED PRACTICE PATTERN®



# Retinal Vein Occlusions

AMERICAN ACADEMY® OF OPHTHALMOLOGY
*The Eye M.D. Association*





http://dx.doi.org/10.1016/j.ophtha.2015.10.045
ISSN 0161-6420/16

# RETINA/VITREOUS PREFERRED PRACTICE PATTERN® DEVELOPMENT PROCESS AND PARTICIPANTS

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

**Retina/Vitreous Preferred Practice Pattern Panel 2014–2015**
Jose S. Pulido, MD, MS, MPH, Macula Society Representative
Christina J. Flaxel, MD
Ron A. Adelman, MD, MPH, MBA, FACS, Retina Society Representative
Leslie Hyman, PhD, Methodologist
James C. Folk, MD, American Society of Retina Specialists Representative
Timothy W. Olsen, MD, Chair

The **Preferred Practice Patterns Committee** members conducted their review by e-mail discussion in May 2015. The document was edited in response to their comments.

**Preferred Practice Patterns Committee 2015**
Robert S. Feder, MD, Chair
Timothy W. Olsen, MD
Randall J. Olson, MD
Bruce E. Prum, Jr., MD
C. Gail Summers, MD
Ruth D. Williams, MD
David C. Musch, PhD, MPH, Methodologist

The Retinal Vein Occlusions PPP was then sent for review to additional internal and external groups and individuals in July 2015. All those who returned comments were required to provide disclosure of relevant relationships with industry to have their comments considered (indicated with an asterisk below). Members of the PPP Panel reviewed and discussed these comments and determined revisions to the document.

Academy Reviewers
Board of Trustees and Committee of Secretaries*
Council*
General Counsel*
Basic and Clinical Science Course Section 12 Subcommittee
Ophthalmic Technology Assessment Committee Retina/Vitreous Panel*
Practicing Ophthalmologists Advisory Committee for Education*

Invited Reviewers
American Society of Retina Specialists*
Canadian Ophthalmological Society
Central American Retina and Vitreous Society
Consumer Reports Health Choices
European Society of Retina Specialists
Macula Society*
National Eye Institute
National Medical Association
National Partnership of Women and Families
Retina Research Foundation
Retina Society*
Thai Retina Society*
J. Michael Jumper, MD
Wayne A. Solley, MD

# FINANCIAL DISCLOSURES

In compliance with the Council of Medical Specialty Societies' Code for Interactions with Companies (available at www.cmss.org/codeforinteractions.aspx), relevant relationships with industry are listed. The Academy has Relationship with Industry Procedures to comply with the Code (available at www.aao.org/about-preferred-practice-patterns). A majority (100%) of the members of the Retina/Vitreous Preferred Practice Pattern Panel 2014–2015 had no financial relationship to disclose.

**Retina/Vitreous Preferred Practice Pattern Panel 2014–2015**
**Ron A. Adelman, MD, MPH, MBA, FACS**: No financial relationships to disclose
**Christina J. Flaxel, MD**: No financial relationships to disclose
**James C. Folk, MD**: No financial relationships to disclose
**Leslie Hyman, PhD**: No financial relationships to disclose
**Timothy W. Olsen, MD**: No financial relationships to disclose
**Jose S. Pulido, MD, MS, MPH**: No financial relationships to disclose

**Preferred Practice Patterns Committee 2015**
**Robert S. Feder, MD**: No financial relationships to disclose
**David C. Musch, PhD, MPH**: No financial relationships to disclose
**Timothy W. Olsen, MD**: No financial relationships to disclose
**Randall J. Olson, MD:** No financial relationships to disclose
**Bruce E. Prum, Jr., MD**: No financial relationships to disclose
**C. Gail Summers, MD**: No financial relationships to disclose
**Ruth D. Williams, MD**: Allergan – Consultant/Advisor

**Secretary for Quality of Care**
Stephen D. McLeod, MD: No financial relationships to disclose

**Academy Staff**
Laurie Bagley, MLS: No financial relationships to disclose
Nicholas P. Emptage, MAE: No financial relationships to disclose
Susan Garratt: No financial relationships to disclose
Flora C. Lum, MD: No financial relationships to disclose
Doris Mizuiri: No financial relationships to disclose

The disclosures of relevant relationships to industry of other reviewers of the document from January to August 2015 are available online at www.aao.org/ppp.

# TABLE OF CONTENTS

# 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 panels 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 panels 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 U.S. 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 panel 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<br>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<br>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 PPP Panel 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 October 30, 2014 in the PubMed database. Complete details of the literature searches are available in Appendix 3.

# HIGHLIGHTED FINDINGS AND RECOMMENDATIONS FOR CARE

The prognosis of retinal vein occlusions (RVOs) varies according to the site of the occlusion and the degree 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 behave similarly. They are often associated with glaucoma and have a higher risk of anterior segment neovascularization and neovascular glaucoma. Branch retinal vein occlusions (BRVOs) and hemiretinal vein occlusions ([HRVOs], which are distinct from hemi-CRVOs) have a visible arterial-venous crossing where the occlusion occurs. They are more commonly associated with systemic hypertension, diabetes, and lipid disorders, and they are more likely to lead to retinal neovascularization.

Macular edema may complicate both CRVOs and BRVOs. The safest treatment for the associated macular edema is the use of antivascular endothelial growth factors (anti-VEGFs). Intravitreal corticosteroids, with the associated risk of glaucoma and cataract formation, have demonstrated efficacy. Also, laser photocoagulation in BRVO has a potential role in treatment.

Risk factors for vein occlusions include systemic medical conditions, such as systemic arterial hypertension, diabetes, and lipid and coagulation disorders. Thus, communication with the patient's primary care provider to help coordinate care is important.

Optimizing control of systemic arterial hypertension, diabetes, serum lipid levels, and intraocular pressure (IOP) to control glaucoma are all important in the management of systemic risk factors, as is communicating end-organ damage to the primary care provider.

# 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 BRVO 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, typically either the superior or inferior hemifield. This pattern occurs in 90% of HRVOs.[7] Some HRVO patients 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 behave like BRVOs and have a visible occlusion near a branch point. Hemi-CRVOs act like 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.

## PATIENT POPULATION

The patient population includes people over 40 years of age. The most common age range is from the 6$^{th}$ to the 7$^{th}$ decade.[9,10] 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, diabetes, as well as control of glaucoma and ocular hypertension
- Increase internist and family practice physician awareness 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 following all RVOs
- Treat patients who have vision loss or those at risk for vision loss after RVO
- 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

The prevalence of RVOs is about 0.5% in the 2008 general world population and is estimated to affect more than 16 million people worldwide.[10,11] The prevalence appears to be similar in East Asia and in the United States. Branch retinal vein occlusions occur six to seven times more commonly than CRVOs.[12] African Americans have a similar incidence of CRVO to white Americans and a gender predilection does not seem to exist.[10] The prevalence of RVOs might be lower in East Indians (0.76/100), with a similar sixfold higher prevalence of BRVO compared with CRVO.[13] In a Japanese study, the nine-year incidence was 3% for any RVO, and there was a ninefold higher rate of BRVO compared with CRVO.[14] The incidence rate is about 48/100,000 person-years in Korea.[15] In the United States, the 5-year incidence rate is 0.8 per 100, whereas the 15-year incidence is 2.3 per 100 for individuals 40 years of age or older at baseline.[14,16] In China, the 10-year incidence rate for those 40 years of age or older at baseline is 1.9 per 100.[16] In a pooled group of 68,751 subjects aged 30 to 101 years from 15 studies standardized to the 2008 world population, there were 5.2 per 100 vein occlusions (CI = 4.4–6.0), 4.2 per 1000 for BRVO (CI = 3.7–5.2) and 0.8 per 100 for CRVO (CI = 0.6–1.0).

## 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.[10,11] The chance of a person with a pre-existing CRVO developing a CRVO in the fellow eye is 1% per year.[17] 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.[10,18,19] 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. Risk factors for BRVO include arterial hypertension, hyperlipidemia, diabetes, and coronary artery disease. Controversy exists regarding the contribution of other hematologic factors, such as factor V Leiden and homocysteinemia, in the development of BRVO. Such factors may be more likely to contribute to the development of CRVO, although there is not uniform agreement. Retinal phlebitis may be associated with BRVO. Whereas the most common systemic risk factors for BRVO are hypertension and diabetes,[20,21] the most common ocular association with CRVO is glaucoma.[22] Other risk factors for CRVO include carotid occlusive disease and sleep apnea.[23] In selected cases, elevated homocysteine levels have been associated with CRVO. Younger patients, below the age of 50 years, warrant consideration of an evaluation for other hematologic risk factors; however, the cost-effectiveness of such an assessment remains controversial.[24,25] In a cohort with systemic lupus erythematosus, the incidence of CRVO was 3.5 times higher than in a control population.[16]

## NATURAL HISTORY

Patients with a CRVO have a higher mortality rate than controls in an age-adjusted general population. This additional risk is due to a higher prevalence of cardiovascular disease and diabetes.[26]

A patient with a CRVO is likely to develop macular edema. Additionally, approximately 25% of patients with CRVO will develop iris neovascularization, and occasional patients may develop retinal neovascularization. Once diagnosed with a CRVO, patients need to be evaluated every 4 to 6 weeks for approximately 6 months by means of a slit-lamp biomicroscopic examination and undilated gonioscopy to detect iris or angle neovascularization that leads to neovascular glaucoma. In addition, patients with reduced vision should also be evaluated for the development of cystoid macular edema (CME).

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.[18] 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 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, venous dilation of the affected veins, retinal edema, intraretinal hemorrhages, cotton-wool spots, and occasionally hard exudates or even retinal detachment in the affected region.[27] 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 visual dysfunction 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 degree of perfusion and the location of the occlusion.[28] The Branch Vein Occlusion Study (BVOS) Group found a spontaneous improvement in visual acuity by two or more lines in 37% of eyes, whereas 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 final 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 due to the development of collateral vessels that help with the venous drainage and subsequent resolution of retinal edema and ischemia.[28] The severity of the occlusion and extent of ischemia are important prognostic factors for the final visual acuity deficit resulting from BRVO.[29]

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 yet may also resolve over time, leaving secondary retinal pigment epithelial atrophy and suboptimal visual acuity.

### RATIONALE FOR TREATMENT

For individuals who develop iris neovascularization or retinal neovascularization following a CRVO, the best treatment is dense peripheral panretinal photocoagulation (PRP).[30] Although PRP does not usually improve the visual acuity, it decreases the risk of progression to iris neovascularization and may prevent neovascular glaucoma. Additionally, antivascular endothelial growth factor (anti-VEGF) agents can be used in an adjunctive manner when the complete PRP is insufficient to control angiogenesis.[30,31] Antivascular 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.[31]

Treatment of visual acuity loss associated with RVO-related CME should be strongly considered, using either anti-VEGF and/or intraocular corticosteroid agents.

The primary treatment for BRVO involves treatment of macular edema using anti-VEGF agents, corticosteroids, and/or laser to help to reduce vision loss and neovascular complications. Macular edema causes a substantial decrease in vision-related quality of life.[28] According to a systematic review, an estimated 5% to 15% of BRVO eyes develop macular edema.[10]

## CARE PROCESS

In 1984, the BVOS demonstrated a benefit of grid laser treatment for visual acuity outcomes in eyes with BRVO and macular edema.[28] This has been the standard of care until only recently, when the results of intravitreal corticosteroids and anti-VEGF agents in this setting were reported.[32] The BVOS also demonstrated the benefit of laser management of ischemic BRVO in reducing complications related to retinal neovascularization. More recently, the Standard Care vs. COrticosteroid for REtinal Vein Occlusion (SCORE) study and the Global Evaluation of implaNtable dExamethasone in retinal Vein occlusion with macular edemA (GENEVA) study demonstrated the benefits of intravitreal corticosteroids in reducing BRVO-associated CME.[33] However, intravitreal corticosteroid use can lead to significant ocular side effects, such as secondary glaucoma and cataract formation.[34]

In several studies, anti-VEGF agents have been shown to be both safe and effective in treating the macular edema as well as in limiting the neovascularization associated with BRVO.[35-45] Currently, three anti-VEGF agents are used routinely for the treatment of BRVOs; two are FDA-approved (ranibizumab and aflibercept), but bevacizumab remains off-label for ophthalmologic conditions. In general, an internist should be involved in the management of patients with a new RVO because of associated systemic risk factors, including diabetes, hypertension, and hyperlipidemia.[46] *(II++, good quality, strong recommendation)* Initial treatment for patients with macular edema and CRVO is similar and uses anti-VEGF agents or secondary treatments that include intravitreal corticosteroids.

In patients with a BRVO and neovascularization of the retina, grid laser photocoagulation in the area of nonperfusion helps to decrease the risk of a vitreous hemorrhage.[47] In patients with CRVO and iris neovascularization, extensive and complete peripheral PRP is indicated.[17] Occasionally, initial treatment with an anti-VEGF agent might be helpful for an immediate benefit and may also improve the ability to deliver a complete laser treatment.[31]

## 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 a RVO includes all relevant aspects of the comprehensive adult medical eye evaluation,[48] 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
- 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 treatment, cataract surgery, refractive surgery)

### Physical Examination

The initial examination should include the following elements:

- Visual acuity
- Pupillary assessment for a relative afferent pupillary defect 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
- 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 preferred to ensure an optimal view of the entire retina. Slit-lamp biomicroscopy with appropriate lenses is recommended to evaluate retinopathy of the posterior pole and midperipheral retina. Examination of the far peripheral retina is best performed using indirect ophthalmoscopy. 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
  - 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 fundus photography
- OCT
- Fluorescein angiography (FA)
- Ultrasonography

### Color and Red-free Fundus Photography

Fundus photography is also 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 fovea and is extremely useful to detect the presence and extent of any associated macular edema, vitreoretinal interface changes, neurosensory retinal detachment or subretinal fluid, and also to detect other forms of macular disease. Large clinical trials testing anti-VEGF treatment are based largely on using quantifiable OCT measurements rather than 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 treatment, or even consider vitrectomy surgery is frequently based on both visual acuity and OCT findings. Nevertheless, retinal thickness, even when measured by OCT, is not always consistently correlated with visual acuity.[49]

### Fluorescein Angiography

Fluorescein angiography is used to evaluate the extent of the vascular occlusion, the degree of ischemia and the type of macular edema (ischemic vs. nonischemic). Fluorescein angiography images are able to localize leaking microaneurysms or areas of capillary dropout, distinguish collateral vessels, and enhance effective treatment using grid laser. As the use of anti-VEGF agents and intraocular corticosteroids has increased for the treatment of macular edema, the use of grid laser treatment has decreased. Therefore, the need for FA has also declined.

Angiography can identify macular capillary nonperfusion in the areas of the macula and fovea that may explain the associated vision loss as well as the response to therapy. Fluorescein angiography may also detect areas of untreated retinal capillary nonperfusion that may explain persistent retinal or disc neovascularization that remains present after scatter treatment. Wide-field FA is being used to evaluate peripheral nonperfusion, yet

current data on the benefits of this technique are inconclusive. Thus, FA remains a valuable tool and should be considered by ophthalmologists who diagnose and treat patients with retinal vascular disease.

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 1/200,000 patients.[50] *(good quality, strong recommendation)* Each angiography facility should have in place an emergency care plan and a clear protocol to manage known risks and complications. *(good quality, strong recommendation)* Fluorescein dye crosses the placenta into the fetal circulation,[51] 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 breast-feeding, and FA should be recommended only when absolutely necessary. *(good quality, strong recommendation)*

#### Ultrasonography

Ultrasonography is an extremely valuable diagnostic tool that enables assessment of the anatomic status of the retina in the presence of a vitreous hemorrhage or other media opacity. Currently, ultrasonography is not commonly used with clear media and OCT is more appropriate.

#### Systemic Evaluation

The extent of the systemic evaluation is dependent upon the patient's age and medical history. Discussion with the internist is important, since a patient following an RVO is at risk for developing an RVO in the fellow eye and has a higher risk of cardiovascular disease and cerebrovascular accidents.[11,21] Clear guidelines on systemic testing are lacking.

## 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.[52] A recent meta-analysis of published studies suggests that 48% of RVO is attributable to hypertension, 20% to hyperlipidemia, and 5% to diabetes.[46] It is known that arteriovenous nicking, ocular perfusion pressure, and focal arteriolar narrowing are related to an increased risk of developing a BRVO.[21,27] The best prevention is to manage risk factors aggressively by optimizing control of diabetes mellitus, hypertension, and hyperlipidemia.[46] *(I+, good quality, strong recommendation)*

### Choice of Therapy

The current treatment strategies for BRVO target the sequelae of the venous occlusion (i.e., CME and NVD/NVE) rather than attempting to treat the occlusion itself. For CRVO, the risk of retinal neovascularization is less, yet there is an increased risk of iris neovascularization and neovascular glaucoma, especially in ischemic CRVOs.

### Medical and Surgical Management

#### Intravitreal Injections

Subsequent clinical trials have evaluated the efficacy of anti-VEGF agents and/or intravitreal corticosteroid injections. The SCORE study for BRVO evaluated the use of two doses of intravitreal corticosteroids (triamcinolone 1 mg and 4 mg) versus macular grid laser therapy in 411 eyes randomized to one of the three treatment arms in a 1:1:1 fashion and followed for 12 months.[33] After 1 year, approximately one-third of eyes in the laser treatment group, one-third of eyes in the triamcinolone1-mg group, and one-third of eyes in the triamcinolone 4-mg group gained greater than or equal to 15 letters. The mean gain in best-corrected visual acuity was four to five 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 treatment. The SCORE recommendations for BRVO were to consider macular grid laser treatment 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.[34] 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 three 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 within the eye, indicating a preference for the 1-mg dose.[34] *(I++, good quality, strong recommendation*)

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.[53] The study included pooled data from 1131 patients, 34% with CRVO and 66% with BRVO, and showed that in the BRVO eyes with either the 0.35-mg or the 0.7-mg dose implant had no efficacy at 6 months. However, there was significant visual acuity gain at 90 days that 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.[54] Cataract formation and elevated IOP was seen more frequently at 1 year than at 6 months. The dexamethasone implant was FDA-approved in 2009 for the treatment of macular edema due to CRVO and BRVO.

A third corticosteroid implant, fluocinolone (ILUVIEN®, pSivida Corp., Watertown, MA), has also been shown to be beneficial in the treatment of BRVO-associated macular edema up to 3 years following injection. There were improvements in both edema and visual acuity,[55] but fluocinolone is not yet approved by the FDA for this indication. Glaucoma and cataract formation remain side effects associated with intravitreal corticosteroids in this study.

Multiple studies have demonstrated the efficacy of anti-VEGF agents in the treatment of macular edema associated with BRVO.[37,52,56-59] (*I++, good quality, strong recommendation*) Currently, there are three anti-VEGF agents that are available for use in these cases: off-label use of bevacizumab, on-label use of ranibizumab, and aflibercept. 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.[56] After 6 months, all eyes were eligible for injections of ranibizumab 0.5 mg as required until month 12. The benefits of ranibizumab seen at 6 months were generally maintained by month 12.[57] 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.[37] 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 at some point during the study period. These studies used ranibizumab, whereas other smaller, level 2 studies have demonstrated the efficacy of bevacizumab for BRVO-associated macular edema.[52,58,59] The VIBRANT trial was a randomized double-masked phase 3 trial that demonstrated the efficacy of aflibercept over grid laser treatment for macular edema in BRVO.[60]

In general, the use of betadine antiseptic drops and a lid speculum is recommended during all intravitreal injections, while the use of routine antibiotic eye drops is not recommended.[61] *(III, moderate quality, discretionary recommendation)* 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. In conclusion, because of the favorable risk-to-benefit profile, the use of anti-VEGF agents is the preferred initial therapy for treatment of macular edema related to BRVO. Either corticosteroids and/or grid laser treatment should be considered when there is a failure to respond or an inadequate response.

Several randomized controlled trials have also shown the efficacy of anti-VEGF agents in treating macular edema with CRVO.[36,38,40,54] *(I++, good quality, strong recommendation)* 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.[36] In the Vascular Endothelial Growth Factor [VEGF] Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (COPERNICUS) study, intravitreal aflibercept was compared with sham injections; there was a 15-letter gain in 56% of the treated eyes compared with 12% of sham injections.[38] Similar findings were found in the General Assessment Limiting Infiltration of Exudates in central retinal vein Occlusion with VEGF Trap-Eye (GALILEO) study.[40] 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.[41]

There is a role for intravitreal triamcinolone, dexamethasone, and other corticosteroids that have been shown to be efficacious for macular edema associated with CRVO, yet there are known associated risks of cataracts and glaucoma.[34,54] *(I+, good quality, strong recommendation)*

### Laser Photocoagulation

The BVOS first demonstrated the efficacy of grid laser photocoagulation for macular edema due to BRVO. Patients with BRVO who presented with a visual acuity of 20/40 or worse due to perfused BRVO with CME were randomized to either grid-pattern laser photocoagulation or no treatment. There were more patients who gained at least two lines of visual acuity from baseline in the laser photocoagulation group than in the untreated group (65% vs. 37%). Nearly twice as many treated eyes had final visual acuity outcomes greater than 20/40 when compared with untreated eyes. This finding led to the recommendation that grid laser treatment should be considered for eyes with BRVO, macular perfusion, and CME with a visual acuity of 20/40 or worse. The study was not designed to evaluate early versus late treatment. If the duration of BRVO was less than or equal to 12 months, 78% of treated eyes gained two or more lines of visual acuity compared with 53% of eyes when the duration was greater than 12 months. Sixty percent (60%) of untreated eyes gained two or more lines of visual acuity when the duration of a BRVO was less than12 months compared with 8% of untreated eyes when the duration was more than 12 months. Laser treatment remains a viable treatment in eyes with BRVO, even if the duration of the disease is greater than 12 months.[28] *(I++, good quality, strong recommendation)* Sectoral PRP is still recommended for neovascularization when complications such as vitreous hemorrhage or iris neovascularization occur.[47] *(I+, good quality, strong recommendation)*

The Central Vein Occlusion Study (CVOS) did not show any value of focal photocoagulation for CME in patients with CRVO.[17] For patients with iris or angle neovascularization, the CVOS recommended complete peripheral PRP.[17]

### Follow-up Evaluation

The follow-up evaluation includes a history and examination.

#### History

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

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

#### Examination

- Visual acuity[62]
- Undilated slit-lamp biomicroscopy and gonioscopy with careful iris examination for early iris or angle neovascularization[63]
- Pupillary assessment for a relative afferent pupillary defect
- IOP
- Stereoscopic examination of the posterior pole after dilation of the pupils[64]
- OCT imaging, when appropriate
- Peripheral retina and vitreous examination, when indicated[65]

## PROVIDER AND SETTING

Although the ophthalmologist will perform most of 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 retinal vascular occlusion, the ophthalmologist caring for patients with this condition should be familiar with the specific recommendations of relevant clinical trials.[66-81] *(I++, good quality, strong recommendation)* 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.[82] Outside of the United States, there are varying practice patterns.[83-85]

## 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.[46] *(II++, good quality, strong recommendation)* The risk to the fellow eye should also be communicated to both the primary care provider and the patient.[11,21] *(I+, moderate quality, strong recommendation)* An Eye MD Examination Report Form is available from the American Academy of Ophthalmology.[86] 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 counseling, vision rehabilitation, or social services as appropriate.[87] *(I++, good quality, strong recommendation)* Vision rehabilitation helps to restore some functional ability,[88] and patients with functionally limiting postoperative visual impairment should be referred for vision rehabilitation and social services.[87] More information on vision rehabilitation, including materials for patients, is available at www.aao.org/smart-sight-low-vision.

## SOCIOECONOMIC CONSIDERATIONS

Very few studies have evaluated the cost/benefit ratio of the various treatment types for RVO. One study evaluated the cost/benefit ratio of treatment methods for macular edema due to various etiologies and concluded that pharmacologic treatments can be extremely expensive even for 1 year of therapy. It is also concluded that the benefit conveyed by pharmacologic therapy for visual acuity, although statistically significant, may be modestly beneficial (i.e., one 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 $1326 for laser to $23,119 for a 1-year course of ranibizumab treatment, a 17-fold difference. Costs/visual acuity line-year ranged from $25 to $754.[89] 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 treatment yielded a 1.33-line (6.65 letters) improvement for laser that when reduced by the natural history adjustment, yielded 1.1 lines (5.5 letters) saved. 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 quality-adjusted life years (QALY), this was $824 for bevacizumab versus $1572 for grid laser, $5536 for Ozurdex, and $25,566 for ranibizumab. The dollars per line-year saved followed along similar lines, with bevacizumab at $25, grid laser $68, Ozurdex $162, and ranibizumab $754.

A recent study reported on the direct medical costs for treating CRVO and BRVO in working-age and Medicare populations.[90] The authors found that 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; however, these 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.

# 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<br>H34.812<br>H34.813 |
| Venous tributary (branch) occlusion | 362.36 | H34.831<br>H34.832<br>H34.833 |
| Venous engorgement | 362.37 | H34.821<br>H34.822<br>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. LITERATURE SEARCHES FOR THIS PPP

Literature searches of the PubMed database were conducted on October 30, 2014; the search strategies were as follows. Specific limited update searches were conducted after October 30, 2014.

(retinal vein occlusion/pathology[majr] OR retinal artery occlusion/pathology[majr] OR retinal vein occlusion/physiology[majr] OR retinal artery occlusion/physiology[majr] OR retinal vein occlusion/physiopathology[majr] OR retinal artery occlusion/physiopathology[majr]) Publication Date from 2005/01/01, Humans. Retrieved 192 citations.

(retinal vein occlusion/surgery[mh] OR retinal artery occlusion/surgery[mh] OR retinal vein occlusion/therapy[mh] OR retinal artery occlusion/therapy[mh] OR retinal vein occlusion/drug therapy[mh] OR retinal artery occlusion/drug therapy[mh]) Publication Date from 2005/01/01, Humans. Retrieved 465 citations.

(retinal vein occlusion/diagnosis[MeSH Major Topic] OR retinal artery occlusion/diagnosis[MeSH Major Topic]) Publication Date from 2005/01/01, Humans. Retrieved 112 citations.

# RELATED ACADEMY MATERIALS

**Basic and Clinical Science Course**
Retina and Vitreous (Section 12, 2015–2016)

**Patient Education**
Retinal Vein Occlusion Brochure (2014)
Retina Patient Education Video Collection (2014)

**Preferred Practice Pattern® Guidelines – Free download available at www.aao.org/ppp.**
Comprehensive Adult Medical Eye Evaluation (2015)

To order any of these products, except for the free materials, please contact the Academy's Customer Service at 866.561.8558 (U.S. only) or 415.561.8540 or www.aao.org/store.

# REFERENCES


1. Scottish Intercollegiate Guidelines Network. Annex B: key to evidence statements and grades of recommendations. In: SIGN 50: A Guideline Developer's Handbook. 2008 edition, revised 2011. Edinburgh, Scotland: Scottish Intercollegiate Guidelines Network. Available at: www.sign.ac.uk/guidelines/fulltext/50/index.html. Accessed June 26, 2015.
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. Available at: www.gradeworkinggroup.org/society/index.htm. Accessed January 14, 2015.
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. Central Vein Occlusion Study Group. Baseline and early natural history report: the Central Vein Occlusion Study. Arch Ophthalmol 1993;111:1087-95.
10. 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.
11. 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.
12. 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.
13. 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.
14. 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.

15. Park SJ, Choi NK, Seo KH, et al. Nationwide incidence of clinically diagnosed central retinal artery occlusion in Korea, 2008 to 2011. Ophthalmology 2014;121:1933-8.
16. 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.
17. Central Vein Occlusion Study Group. Natural history and clinical management of central retinal vein occlusion. Arch Ophthalmol 1997;115:486-91.
18. 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.
19. Michels RG, Gass JD. The natural course of retinal branch vein obstruction. Trans Am Acad Ophthalmol Otolaryngol 1974;78:OP166-77.
20. Eye Disease Case-Control Study Group. Risk factors for central retinal vein occlusion Arch Ophthalmol 1996;114:545-54.
21. 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.
22. Hayreh SS, Zimmerman MB, Beri M, Podhajsky P. Intraocular pressure abnormalities associated with central and hemicentral retinal vein occlusion. Ophthalmology 2004;111:133-41.
23. 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.
24. Fong AC, Schatz H. Central retinal vein occlusion in young adults. Surv Ophthalmol 1993;37:393-417.
25. 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.
26. Bertelsen M, Linneberg A, Christoffersen N, et al. Mortality in patients with central retinal vein occlusion. Ophthalmology 2014;121:637-42.
27. 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 141-3.
28. Branch Vein Occlusion Study Group. Argon laser photocoagulation for macular edema in branch vein occlusion. Am J Ophthalmol 1984;98:271-82.
29. Christoffersen NL, Larsen M. Pathophysiology and hemodynamics of branch retinal vein occlusion. Ophthalmology 1999;106:2054-62.
30. 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.
31. 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.
32. 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.
33. 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.
34. 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.
35. 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.
36. 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.
37. 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.
38. 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.

39. 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.
40. 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.
41. 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.
42. 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.
43. 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.
44. 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.
45. 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.
46. O'Mahoney PR, Wong DT, Ray JG. Retinal vein occlusion and traditional risk factors for atherosclerosis. Arch Ophthalmol 2008;126:692-9.
47. 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.
48. American Academy of Ophthalmology Preferred Practice Patterns Committee. Preferred Practice Pattern® Guidelines. Comprehensive Adult Medical Eye Evaluation. San Francisco, CA: American Academy of Ophthalmology; 2015. Available at: www.aao.org/ppp.
49. 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.
50. Yannuzzi LA, Rohrer KT, Tindel LJ, et al. Fluorescein angiography complication survey. Ophthalmology 1986;93:611-7.
51. Sunness JS. The pregnant woman's eye. Surv Ophthalmol 1988;32:219-38.
52. Ehlers JP, Fekrat S. Retinal vein occlusion: beyond the acute event. Surv Ophthalmol 2011;56:281-99.
53. 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.
54. 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.
55. Jain N, Stinnett SS, Jaffe GJ. Prospective study of a fluocinolone acetonide implant for chronic macular edema from central retinal vein occlusion: thirty-six-month results. Ophthalmology 2012;119:132-7.
56. 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.
57. 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.
58. 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.
59. 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.
60. ClinicalTrials.gov. 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). November 2014. Available at: https://clinicaltrials.gov/ct2/show/study/NCT01521559. Accessed May 15, 2015.

61. 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.
62. Early Treatment Diabetic Retinopathy Study Research Group. Early photocoagulation for diabetic retinopathy: ETDRS report number 9. Ophthalmology 1991;98:766-85.
63. Jacobson DR, Murphy RP, Rosenthal AR. The treatment of angle neovascularization with panretinal photocoagulation. Ophthalmology 1979;86:1270-7.
64. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema: Early Treatment Diabetic Retinopathy Study report number 1. Arch Ophthalmol 1985;103:1796-806.
65. Early Treatment Diabetic Retinopathy Study Research Group. Fundus photographic risk factors for progression of diabetic retinopathy: ETDRS report number 12. Ophthalmology 1991;98:823-33.
66. Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus. JAMA 2002;287:2563-9.
67. Elman MJ, Qin H, Aiello LP, et al, Diabetic Retinopathy Clinical Research Network. Intravitreal ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: three-year randomized trial results. Ophthalmology 2012;119:2312-8.
68. Chew EY, Klein ML, Ferris FL III, et al. Association of elevated serum lipid levels with retinal hard exudate in diabetic retinopathy: Early Treatment Diabetic Retinopathy Study (ETDRS) report 22. Arch Ophthalmol 1996;114:1079-84.
69. Brown DM, Nguyen QD, Marcus DM, et al, RIDE and RISE Research Group. Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: RISE and RIDE. Ophthalmology 2013;120:2013-22.
70. Nguyen QD, Shah SM, Khwaja AA, et al, READ-2 Study Group. Two-year outcomes of the ranibizumab for edema of the mAcula in diabetes (READ-2) study. Ophthalmology 2010;117:2146-51.
71. Rajendram R, Fraser-Bell S, Kaines A, et al. A 2-year prospective randomized controlled trial of intravitreal bevacizumab or laser therapy (BOLT) in the management of diabetic macular edema: 24-month data: report 3. Arch Ophthalmol 2012;130:972-9.
72. Do DV, Nguyen QD, Boyer D, et al, DA VINCI Study Group. One-year outcomes of the DA VINCI Study of VEGF Trap-Eye in eyes with diabetic macular edema. Ophthalmology 2012;119:1658-65.
73. Early Treatment Diabetic Retinopathy Study Research Group. Treatment techniques and clinical guidelines for photocoagulation of diabetic macular edema: Early Treatment Diabetic Retinopathy Study report number 2. Ophthalmology 1987;94:761-74.
74. Fong DS, Ferris FL III, Davis MD, Chew EY, Early Treatment Diabetic Retinopathy Study Research Group. Causes of severe visual loss in the early treatment diabetic retinopathy study: ETDRS report no. 24. Am J Ophthalmol 1999;127:137-41.
75. Sivaprasad S, Crosby-Nwaobi R, Heng LZ, et al. Injection frequency and response to bevacizumab monotherapy for diabetic macular oedema (BOLT report 5). Br J Ophthalmol 2013;97:1177-80.
76. Diabetic Retinopathy Study Research Group. Photocoagulation treatment of proliferative diabetic retinopathy: clinical application of Diabetic Retinopathy Study (DRS) findings, DRS report number 8. Ophthalmology 1981;88:583-600.
77. Turner RC. The U.K. Prospective Diabetes Study: a review. Diabetes Care 1998;21 (suppl):C35-8.
78. Nathan DM, Bayless M, Cleary P, et al, DCCT/EDIC Research Group. Diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: advances and contributions. Diabetes 2013;62:3976-86.
79. Ismail-Beigi F, Craven T, Banerji MA, et al, ACCORD Trial Group. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. Lancet 2010;376:419-30. Erratum in: Lancet 2010;376:1466.
80. Bressler SB, Qin H, Melia M, et al, Diabetic Retinopathy Clinical Research Network. Exploratory analysis of the effect of intravitreal ranibizumab or triamcinolone on worsening of diabetic retinopathy in a randomized clinical trial. JAMA Ophthalmol 2013;131:1033-40.
81. Diabetic Retinopathy Clinical Research Network Authors/Writing Committee. Macular edema after cataract surgery in eyes without preoperative central-involved diabetic macular edema. JAMA Ophthalmol 2013;131:870-9.

82. American Academy of Ophthalmology. Clinical Statement. Intravitreal Injections. San Francisco, CA: American Academy of Ophthalmology; 2015. Available at: www.aao.org/guidelines-browse?filter=clinicalstatement. Accessed July 10, 2015.
83. 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.
84. DaCosta J, Hamilton R, Nago J, et al. Implementation of a nurse-delivered intravitreal injection service. Eye (Lond) 2014;28:734-40.
85. 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.
86. American Academy of Ophthalmology. Clinical Statement. Eye MD Examination Report Form. San Francisco, CA: American Academy of Ophthalmology; 2005; Reviewed 2012. Available at: www.aao.org/guidelines-browse?filter=clinicalstatement. Accessed January 14, 2015.
87. American Academy of Ophthalmology Vision Rehabilitation Committee. Preferred Practice Pattern® Guidelines. Vision Rehabilitation. San Francisco, CA: American Academy of Ophthalmology; 2013. Available at: www.aao.org/ppp.
88. 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.
89. Smiddy WE. Economic considerations of macular edema therapies. Ophthalmology 2011;118:1827-33.
90. 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.

AMERICAN ACADEMY® OF OPHTHALMOLOGY
The Eye M.D. Association

P.O. Box 7424
San Francisco,
California 94120-7424
415.561.8500