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# Update on Retinal Vein Occlusion

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**Abstract:** Retinal vein occlusion represents the second leading cause of retinal vascular disorders, with a uniform sex distribution worldwide. A thorough evaluation of cardiovascular risk factors is required to correct possible comorbidities. The diagnosis and management of retinal vein occlusion have changed tremendously in the last 30 years, but the assessment of retinal ischemia at baseline and during follow-up examinations remains crucial. New imaging techniques have shed light on the pathophysiology of the disease and laser treatment, once the only therapeutic option, is now only one of the possible approaches with antivascular endothelial growth factors and steroid injections being preferred in most cases. Nowadays long-term outcomes are better than those achievable 20 years ago and yet, many new therapeutic options are under development, including new intravitreal drugs and gene therapy. Despite this, some cases still develop sight-threatening complications deserving a more aggressive (sometimes surgical) approach. The purpose of this comprehensive review is to reappraise some old but still valid concepts and to integrate them with new research and clinical data. The work will provide an overview of the disease's pathophysiology, natural history, and clinical features along with a detailed discussion on the advantages of multimodal imaging and of the different treatment strategies with the aim of providing retina specialists with the most updated knowledge in the field.

**Key Words:** BRVO, CRVO, review, retinal vein occlusion, update

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## INTRODUCTION

Retinal vein occlusion (RVO) represents the second leading cause of retinal vascular disorders,[1] with a uniform sex distribution worldwide.[2]

Although clinical classification can be challenging, RVO has been traditionally subdivided into 2 main types: (1) central (CRVO) with a prevalence of 0.1% to 0.4% and (2) branch (BRVO) affecting 0.6% to 1.2% of individuals.[2–4]

As several aspects of the pathogenesis remain poorly characterized, the management of RVO and its complications are constantly a matter of debate, including both conservative, medical, and surgical approaches.[5] In addition, new imaging techniques and therapeutic options keep enriching the armamentarium to diagnose and treat these conditions.

In this evolving scenario, the purpose of this review is to reappraise some old but still valid concepts and to integrate them with novelties to provide retina specialists with the most updated knowledge in the field.

## RETINAL VEIN OCCLUSION CLASSIFICATION

Three main subgroups of RVO are frequently recognized based on the location of the specific vein occluded: (1) central, (2) hemicentral, and (3) branch RVO. However, the possible arterial involvement should always be considered (Table 1).[2,6,7]

### Central Retinal Vein Occlusion

CRVO involves the whole retinal venous system as the occlusion is localized at the level of the lamina cribrosa of the optic disc. According to the severity of the occlusion, several clinical findings can develop, including retinal nonperfusion.

Although still debated, a differentiation between ischemic and nonischemic forms was classically made based on the Central Vein Occlusion Study (CVOS) recommendations—the latter being generally exempted from ocular neovascular complications.

Patients with ischemic CRVO typically show[8–11]:

1. Poor visual acuity (VA) (eg, <20/200 Snellen)
2. Relative afferent pupillary defect
3. Several dark, deep intraretinal hemorrhages and cotton-wool spots

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**TABLE 1.** Classification of RVOs

| |
|---|
| (1) CRVO |
| Nonischemic CRVO |
| Ischemic CRVO |
| Juvenile CRVO |
| (2) HRVO |
| (3) BRVO |
| Major BRVO |
| Hemispheric BRVO |
| Macular BRVO |
| (4) RVO + any RAO |

BRVO indicates branch retinal vein occlusion; CRVO, central retinal vein occlusion; HRVO, hemicentral retinal vein occlusion; RAO, retinal arterial occlusion; RVO, retinal vein occlusion.

4. More than 10 disc-areas of retinal capillary nonperfusion on standard ETDRS 7-field fluorescein angiography
5. Electroretinogram alterations (eg, reduced *b*-wave amplitude, reduced *b*/*a* wave ratio, prolonged *b*-wave implicit time)

A crucial point is a potential conversion from nonischemic to ischemic CRVO, which has been reported in 12%–30% of cases over the follow-up.[10–13]

Of notice, information derived from ultra-widefield angiography has revolutionized the assessment of capillary nonperfusion and suggested that posterior pole nonperfusion represents the main risk factor for neovascularization (NV) development.[14] In detail, capillary nonperfusion $>10$ disc-areas at the posterior pole of eyes with CRVO would suggest a high risk of NV.[14]

Moreover, an ischemic index (ratio of capillary nonperfusion/total visible area) $>45\%$ and a total area of nonperfusion $>75$ disc-areas on ultra-widefield angiography have been correlated to ocular NV.[14] Figure 1 shows the multimodal characteristics of CRVO.

Juvenile CRVO occurring in patients younger than 50 years of age is frequently considered a distinct clinical entity due to its more favorable prognosis and sometimes self-resolving course related to inflammatory mechanisms.[15–17] Overall, functional and anatomic results are better, with a significantly lower rate of ocular complications and positive response to periocular and intravitreal therapies.[16,17]

## Hemicentral Retinal Vein Occlusion

When only one fundus hemisphere is involved, the presumed site of occlusion is one of the 2 trunks of an abnormally split intraneural central retinal vein—naturally occurring in about 20% of cases. This entity is defined as hemicentral retinal vein occlusion (HRVO) and is considered a variant of CRVO sharing a similar clinical picture, evolution, and complications.[18–20] RVO needs to be differentiated from hemispheric RVO, which represents a particular form of BRVO.[15–17]

## Branch Retinal Vein Occlusion

BRVO typically occurs in correspondence with an arteriovenous crossing and is classified into 3 main subgroups according to the occlusion site: (1) major, (2) hemispheric, and (3) macular BRVO.[21]

The causative arteriovenous crossing is typically situated along the course of a major venous branch, and the location with respect to the optic disc delineates the extension of the area involved and the clinical severity.

Major BRVO comprises a nonischemic and an ischemic subtype, which can be identified in one-third and two-thirds of cases, respectively.[22] Ocular NV is less frequent than in CRVO and can develop only in ischemic major BRVO.[22]

Hemispheric RVO can be considered a BRVO subtype with an occlusive process involving one hemiretina due to an arteriovenous crossing at or in the proximity of the optic disc.[11] Although discussed separately, it shares the same pathogenesis and clinical features of major BRVO.[18,19] Ischemic and nonischemic subtypes are equally represented and neovascular complication's figures are similar to those found in major BRVO.[18,19]

Macular BRVO is characterized by an occlusion involving a small venous vessel draining a specific sector of the macula.[23,24] Diagnosis requires careful fundus biomicroscopic and angiographic examinations to detect subtle clinical changes.

Multimodal imaging features of BRVO are depicted in Figure 2.

## Retinal Vein Occlusion Associated With Retinal Arterial Occlusion

Occasionally, RVO can be combined with a simultaneous retinal artery occlusion. The severity of the clinical picture is related to the degree of the occlusive process and the extension of the retina involved.

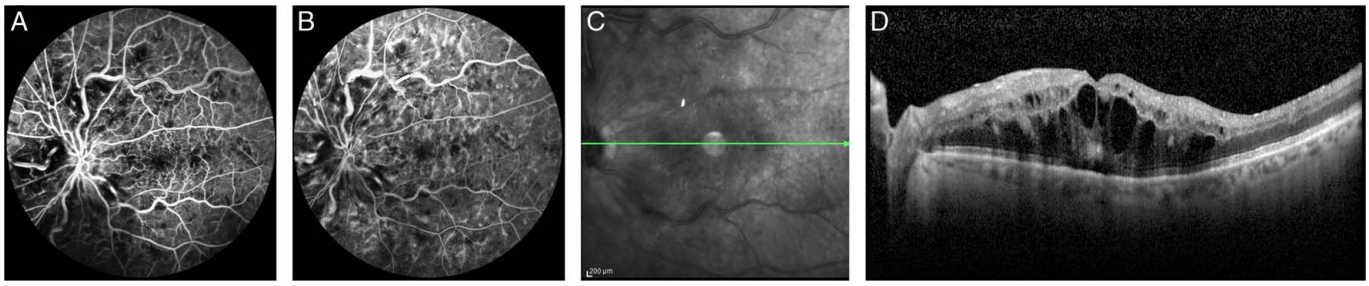


**FIGURE 1.** Multimodal retinal imaging of central retinal vein occlusion. Widefield fluorescein angiography shows delayed venous filling during the early phase (A) with some hypofluorescent areas due to a masking effect caused by retinal hemorrhages and to capillary nonperfusion. Late-phase angiogram (B) instead shows diffuse perivenular leakage. Optical coherence tomography scan passing through the fovea reveals the presence of cystoid macular edema with subtle subfoveal neurosensory detachment (C, D).

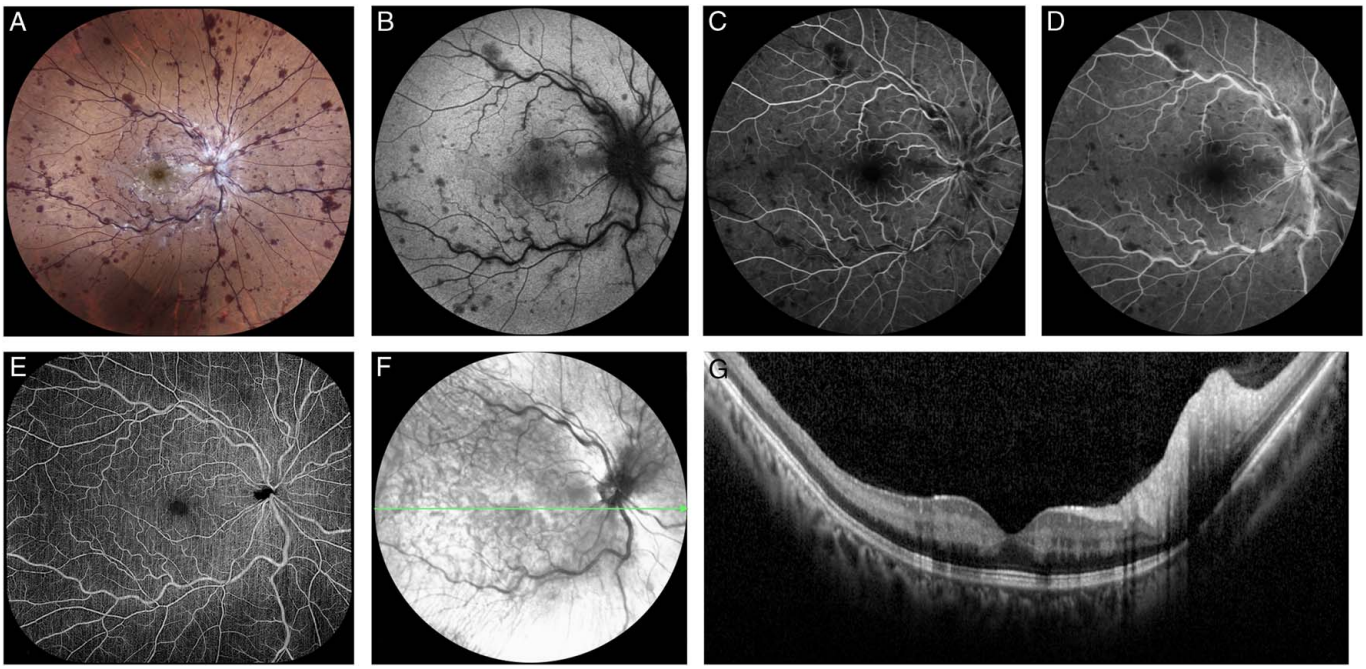


**FIGURE 2.** Multimodal imaging of a patient with juvenile retinal vein occlusion complicated by paracentral acute middle maculopathy. Color fundus photograph (A) shows edema of the optic nerve head, severe tortuosity of the retinal veins and numerous flame-shaped and dot-blot retinal hemorrhages. Some areas of perivenular whitening can be appreciated in the inferior hemimacula corresponding with faintly hypoautofluorescent and hypofluorescent areas on blue autofluorescence (B) and fluorescein angiography (C and D), respectively. These areas seem as hyperreflective lesions at the level of the middle retina on optical coherence tomography (F, G). No further areas of capillary nonperfusion can be identified either on fluorescein and widefield Optical coherence tomography angiography reconstruction (E).

Although all the combinations are possible, most reports focus on CRVO combined with central retinal artery occlusion and commonly associated with systemic comorbidities, hypercoagulability status,[1,25] drug-induced retinal toxicity, and recently coronavirus disease 2019.[26]

CRVO and HRVO may combine also with branch retinal artery occlusion[27] with cilioretinal artery occlusion.[28] However, CRVO associated with cilioretinal artery occlusion constitutes a separate entity, whose pathogenesis is related to transient hemodynamic blockage of the cilioretinal artery secondary to CRVO.[27] In most cases, there is a spontaneous resolution of the retinopathy with a favorable prognosis.[28]

Rarely, BRVO can be associated with branch retinal[29] artery or cilioretinal artery occlusions.[30,31] Figure 3 shows multimodal imaging of a CRVO case complicated by paracentral acute middle maculopathy.

## PATHOPHYSIOLOGY

The pathophysiology of RVO is multifactorial and differs between CRVO and BRVO, the latter being better characterized.

### Central Retinal Vein Occlusion

CRVO is secondary to an obstruction and/or a significant slowing of venous flow in the central retinal vein at the optic nerve head level.[32,33] Several postmortem studies reported the presence of a thrombus in the central retinal vein at the level of or posterior to the lamina cribrosa.[34] However, these studies might be biased since the included subjects had old and atypical forms of CRVO.[34] Thus, whether the described thrombus was the cause or seemed secondarily to the occlusion cannot be determined with certainty. Unfortunately, data from experimental animal models are difficult to apply to humans given the significant variability in the phenotype of RVO lesions among animals.[35]

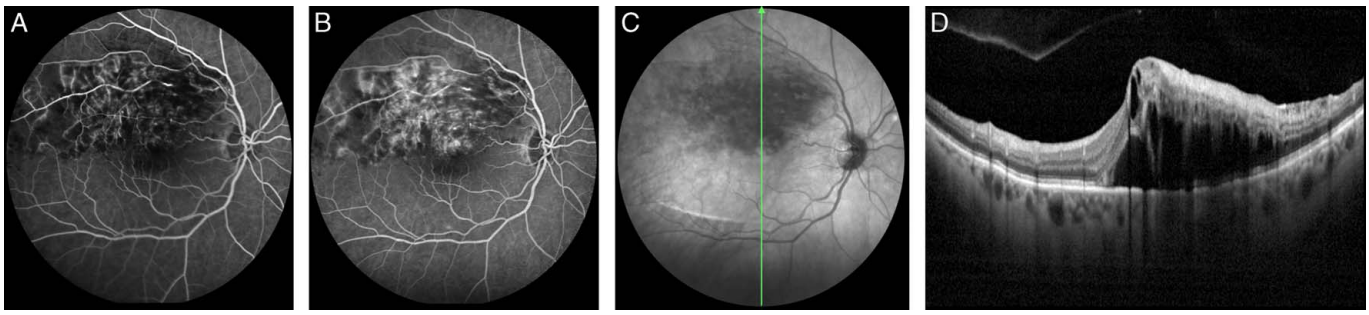


**FIGURE 3.** Multimodal retinal imaging of branch retinal vein occlusion. (A and B) Widefield fluorescein angiography shows compression of a superotemporal retinal vein at an arteriovenous crossing site. Capillary nonperfusion is better visualized in the early phase (A), whereas progressive capillary and perivenular leakage can be appreciated in the late phase (B). The vertical optical coherence tomography scan (C and D) shows intraretinal cystoid edema of the superior hemimacula with significant neurosensory detachment.

Vascular collateralization is the transformation of one or more capillaries into veins, thus affecting the occluded territory and the neighboring areas. The vascular collateral circulation typically persists after the resolution of the vein occlusion, even after a short duration of the venous occlusion, testifying to the precocity of the microvascular remodeling process.[36]

Retinal ischemia can be studied indirectly by measuring the oxygen level in the retina. Retinal hypoxia occurs proximally to the occlusion and the administration of oxygen corrects some consequences of the occlusion, including the vascular endothelial growth factor (VEGF) release.[37] Furthermore, it has been reported that nitric oxide levels—a potent vasodilator—rapidly drop in an experimental pig model, leading to relative arterial vasoconstriction that could further deteriorate the blood flow in the affected territory.[38]

### Branch Retinal Vein Occlusion

To date, histologic and postmortem research on the physiopathology of BRVO is still scarcer than that on CRVO. Still, the mechanisms involved in its pathogenesis seem better characterized and can be summarized by the famous Virchow triad: hemodynamic changes, vascular endothelial damage, and a hypercoagulable state.[39]

The mechanical narrowing of the venous lumen at sites of arteriovenous crossing induces hemodynamic changes. In fact, the retinal artery and vein share a common adventitial sheath and are united at the level of the crossing, where the thin-walled vein crosses and lies posteriorly to the thick and rigid arterial wall providing the best setting for BRVO.[40–42]

Consequently, the increased rigidity of the retinal artery associated with aging may increase the compression and the risk of vein occlusion at these crossing sites.

For these reasons, atherosclerosis and several other cardiovascular risk factors (eg, systemic hypertension, smoking, or diabetes mellitus), which are well-known to exacerbate arteriolar sclerosis, are common in patients with BRVO.[4,43]

The turbulent blood flow generated at the compression site may induce chronic venous endothelial damage leading to endothelial cell proliferation and venous wall remodeling, significantly contributing to occlusion at this site.[40,41,44]

Increased blood viscosity can slow down the blood flow and promote cell aggregation, ultimately favoring thrombus formation.[44]

## RISK FACTORS AND SYSTEMIC WORK-UP

The diagnosis of RVO does not imply a standardized systemic assessment[12] but rather a case-based series of investigations, considering the known association with several cardiovascular risk factors.[45]

In fact, the risk for both BRVO and CRVO increases with age and concurrent cardiovascular conditions such as systemic arterial hypertension, atherosclerosis, and diabetes.[46–48] Dyslipidemia, cigarette smoking, and renal disease have also been associated with RVO.[49] Hypertension with arteriolar narrowing or nicking is an important risk factor for BRVO in the eye but may also increase the risk of CRVO.[50]

Ocular-related risk factors for CRVO include glaucoma or an elevated intraocular pressure, which may compromise venous outflow[49] at the level of the lamina cribrosa.

Although controversial, a hypercoagulable state has also been found to be associated with RVO.[51]

Hyperhomocysteinemia, anticardiolipin antibodies, protein *C* or *S* deficiency, prothrombin gene mutation, and factor V Leiden mutation have all been individually identified to be risk factors for the development of RVO.[52–56] A meta-analysis, however, suggests that only hyperhomocysteinemia and anticardiolipin antibodies are significantly associated with an increased risk.[56]

Some of the most important ophthalmological organizations agree that a multidisciplinary approach should be sought in patients diagnosed with RVO.[57,58] In addition to treating the ocular condition, the ophthalmologist should communicate and collaborate with the patient's primary care provider. A thorough medical history and physical examination focused on the cardiovascular system should be performed to identify possible comorbidities and risk factors and to ensure that these risks can be optimally controlled.[57] Screening for indicators of underlying inherited or acquired hypercoagulable state is highly debated and The Royal College of Ophthalmologists Society suggests leaving this decision to the primary care physician.[57]

As a consequence, laboratory tests should be guided by medical history and by the detection of atypical clinical findings. This is especially true if patients are younger than 50 years of age without significant cardiovascular risk factors or with bilateral disease. In such cases, additional testing for thrombophilia or other conditions associated with a hypercoagulable state might be considered.[59]

Lastly, any sign of intraocular inflammation should lead ophthalmologists to further testing for inflammatory and infectious conditions, including systemic lupus erythematosus, sarcoidosis, tuberculosis, and syphilis. Consider Table 2.

## CLINICAL DIAGNOSIS AND MULTIMODAL IMAGING

### Clinical Diagnosis

On clinical examination, BRVO presents with sectoral hemorrhages (retinal and intraretinal), edema, cotton-wool spots, venous dilations, and tortuosity.[60] In HRVO, these findings are confined to a hemisphere; in CRVO, the findings are in all quadrants. Compared with ischemic CRVO, non-ischemic CRVO is less likely to have disc or macular edema (ME), several hemorrhages, cotton-wool spots, and severe tortuosity.[61]

Late features may also show hard exudates, microaneurysms, sclerosis of veins, vascular shunts at the optic disc, narrowing and sheathing of the artery, vitreous hemorrhage (VH), tractional retinal detachment (TRD), and NV of the retina, optic disc, or iris.[62] Thrombi were detected usually downstream of arteriovenous crossing, although it is unclear if the thrombus is a cause or result of RVO.[63]

### Multimodal Imaging

#### *Optical Coherence Tomography*

In RVO, optical coherence tomography (OCT) has been widely used to assess the presence and the extent of ME, subretinal fluid (SRF), cotton wools, and hard exudates.[64,65]

**TABLE 2.** Laboratory Tests for RVOs

| Routine Investigations | Additional Investigations (Patients Under 50 y/ Bilateral Disease/History of Coagulopathies/Signs of Inflammation) |
|---|---|
| Complete blood count | Homocysteine levels |
| Serum protein electrophoresis | Antiphospholipid antibodies—lupus anticoagulant and anticardiolipin antibodies |
| Renal function tests (serum electrolytes, urea, and creatinine) | Functional protein C and protein S levels |
| Fasting serum levels of glucose and glycated hemoglobin | Antithrombin III levels |
| Fasting levels of lipids | Activated protein C resistance—polymerase-chain-reaction assay for factor V Leiden mutation (R506Q) |
| | Factor XII |
| | Prothrombin gene mutation (G20210A) |
| | Treponemal and nontreponemal tests |
| | Mantoux test, QuantiFERON test |

RVO indicates retinal vein occlusion.

Studies have shown that while SRF is common at presentation, baseline SRF is not a predictor of functional or anatomic results long-term.[66,67]

Assessing the amount and duration of ME is important, as a shorter duration has been associated with better outcomes in BRVO.[68] The junction between the inner and the outer segments of the photoreceptors is particularly important as its integrity is fundamental for the visual prognosis.[69–71]

OCT features associated with refractory ME include thicker central subfield thickness, alteration of the outer plexiform layer, and a larger proportion of external limiting membrane disruption at 3 months.[72] However, macular ischemia, atrophy, and hemorrhages can act as confounders and affect correlation with VA.[73]

OCT allows to carefully evaluate the relationship between the retina and the posterior hyaloid. Eyes with complete posterior vitreous detachments (PVD) have less incidence of ME than cases with incomplete, especially for nonischemic CRVO.[74,75] For ischemic CRVO, there was no relationship between the PVD and development of ME.

### *Optical Coherence Tomography Angiography*

Studies with OCT angiography have been able to allow a clear analysis of superficial (SCP) and deep (DCP) capillary plexus in RVO.[76,77] The foveal avascular zone is increased in both SCP and DCP of RVO eyes.[78,79] Areas of nonperfusion are more frequent in DCP than in SCP, the latter being more connected and proximal to the retinal arterioles.[80] In addition, cystoid pockets, which are black circular areas with no flow signal, have a greater impact on both of the plexuses and are more easily identified than with fundus fluorescein angiography (FFA) or OCT.[81] Treatment with anti-VEGF injections has been associated with the disappearance of the retinal cysts and a decrease in vascular dilation in both plexuses, along with perifoveal capillary arcade recovery.[82]

Recent studies have shown collaterals in both the SCP and the DCP.[83–85] Within 6–24 months, these vessels develop in the optic disc or retina as a consequence of hemodynamic overload and reorganization.[86,87] Optical coherence tomography angiography can identify deep capillaries and intraretinal communications that are not easily identified with FFA and dilated fundoscopy.[88] Although there has been controversy regarding the development and course of these vessels in the context of ME, they are reported to be found more frequently in eyes with major BRVO or the ischemic type than in macular BRVO or the nonischemic type.[83] Collateral vessels, however, have been shown in a recent study to correlate negatively with final VA and positively with central subfield thickness and larger foveal avascular zone.[88] Although in cases of BRVO the collaterals are mostly found in the retina, in HRVO or CRVO collateral vessels are more often seen at the optic disc.[89] The collaterals are protective against anterior segment NV in long-term CRVO.[90]

### *Choroidal Imaging*

Choroidal imaging is not routinely performed in the clinical evaluation of eyes with RVO. Yet, several studies have shown alterations at this level. In a study, the choroidal vascularity index, which evaluates the ratio of the luminal area to the stromal area of the choroid, tended to increase in the nonoccluded hemiretina of BRVO eyes. In addition, in BRVO and CRVO, the presence of ME may correlate with an increased choroidal vascularity index.[91] In the choroid, after BRVO there is decreased choriocapillaris flow density.[91,92]

### *Fundus Fluorescein Angiography*

FFA can be used to analyze the retinal perfusion status and NV following RVO.[60,93] The characteristic findings include delayed filling of the occluded retinal vein and capillary nonperfusion. Intraretinal hemorrhages can result in dye blockage, and late leakage may occur due to ME or retinal NV.

For CRVO, ischemia is described when there are more than 10 disc areas of nonperfusion.[61] Eyes with ischemic CRVO are more likely to have anterior and posterior segment NV.[94] With the diffusion of ultra-widefield angiography, retinal ischemic index (% of the area of capillary nonperfusion in the artero-venous phase/total retinal area) has been progressively used to assess the extent of retinal nonperfusion. Eyes with an ischemic index $>45\%$ were in fact more likely to develop any ocular NV.[95]

Leakage index is another useful parameter that has been recently studied in ultra-widefield fluorescein angiography. It is defined as the ratio of the leakage area to the total area and has been significantly correlated with the severity of cystoid ME.[96]

For BRVO, studies have used modified criteria considering a retinal nonperfusion of ≥5 disc-diameters (DD) as a guide for stratifying NV risk in ischemic BRVO.[97,98] In fact, 36% of eyes with an area of nonperfusion of at least 5 DD had NV. A recent study using ultra-widefield FFA showed a wide variability (5 DD–354 DD) of ischemic retinal territory that led to NV elsewhere development over a period of 2 years.[99] Therefore, periodic FFA may be performed to monitor the track of potential emerging NV elsewhere in patients with ischemic BRVO. Microaneurysms are best detected by means of FFA, although leakage can prevent the detection of some.[100] Microaneurysms are associated with persistent and often refractory ME.[101–103]

## NATURAL HISTORY

To date, most of the data present in the literature derive from collaborative studies carried out in the United States before the introduction of anti-VEGF. Results from these studies may occasionally differ due to different inclusion and classification criteria.

### Visual Acuity

A recent systematic review of the literature reported that VA is generally poor at baseline (< 20/40) in CRVO and tends to slightly decrease over time without treatment.[104]

The CVOS group revealed that baseline VA is a strong predictor of VA for CRVO at 3 years. Eyes with a VA > 20/40 generally maintain a comparable vision, those with poor vision (20/200 or worse) have the worst functional outcomes, whereas patients with an intermediate baseline VA (20/50–20/100) show more variable outcomes.[105]

Moreover, Hayreh et al[106] found that visual outcome is strongly dependent on the extent of retinal capillary nonperfusion.

For what concerns BRVO, a systematic review conducted in 2010[107] found that baseline VA ranged from 20/40 to <20/200. Spontaneous partial recovery has been reported, but an improvement beyond 20/40 Snellen is uncommon.[107] Similar data were reported by the Branch Vein Occlusion Study (BVOS) group at 3 years.[108]

### ME

ME is a major complication of both ischemic and nonischemic CRVO. ME is generally more severe in ischemic CRVO due to retinal pigment epithelium degeneration, serous macular detachments, and irreversible ischemic damage to macular ganglion cells[109]; this explains the lower visual gain in these cases (41%) compared with nonischemic CRVO (59%) after resolution.[106]

Spontaneous resolution of ME is possible. A recent systematic review described its resolution ranging from 0% to 73% over periods of 2–15 months; for nonischemic CRVO, the corresponding proportion was ~30%.[13]

Data on the course of ME in BRVO are largely heterogeneous. In a study on 109 cases, ME was detected in 90% of major BRVO and 97% of macular BRVO at presentation.[110] A systematic review revealed that 5%–15% of BRVO eyes without ME at baseline developed it over a 1-year period, whereas ME resolved in 41% at 7.5 months without treatment in those with ME at baseline.[107]

### Ocular Neovascularization

Ocular NV is one of the most serious complications of CRVO, including both anterior (iris or angle) and posterior segment (retina) NV. In a large prospective series on ischemic CRVO, anterior segment NV was definitely more common than in the posterior segment and the cumulative probability within 6 months from the onset was 49% for the iris, 37% for the angle, 6% for the disc, and 9% for the retinal NV.[111]

The CVOS group reported that the risk of anterior segment NV linearly increased with the extent of capillary nonperfusion. However, caution should be paid as areas of capillary nonperfusion were detected in 34% of initially nonischemic eyes at 36 months.[112]

Neovascular complications are significantly less common in BRVO due to the reduced territory subject to capillary nonperfusion. Of notice, retinal NV is more frequent than anterior segment NV,[113] especially when the filling defect occurs within a major branch artery.[109] Hayreh and Zimmerman[109] found that NV occurs only in major BRVO. The BVOS group assessed ischemic BRVO patients separately and found an incidence of retinal or optic disc NV of ~41%.[108]

The risk of neovascular glaucoma (NVG) closely parallels that of developing anterior segment NV and this risk increases for patients with larger areas of retinal nonperfusion.[105] However, not all the eyes with anterior segment NV will progress to NVG.[5] Hayreh[5] reported that the cumulative probability of developing NVG in ischemic CRVO progressively increased during the first 6–9 months of follow-up, then reached a plateau (Fig. 4). By contrast, NVG seems extremely rare in BRVO eyes.[22] Multimodal imaging of ocular NV is shown in Figure 5.

The incidence of VH in untreated ischemic CRVO was estimated to be 10% at 9 months[114] and 13% at 10 years of follow-up.[115] VH is the second cause of reduced vision after ME in BRVO and was found to occur in 61%–73% of patients with untreated ischemic BRVO and posterior segment NV. Of these, 28% experienced recurrent VH and this was enhanced by PVD exerting traction on neovessels.[116]

Although rare, TRD secondary to retinal NV has been reported to occur in 1.3% of BRVO cases.[117]

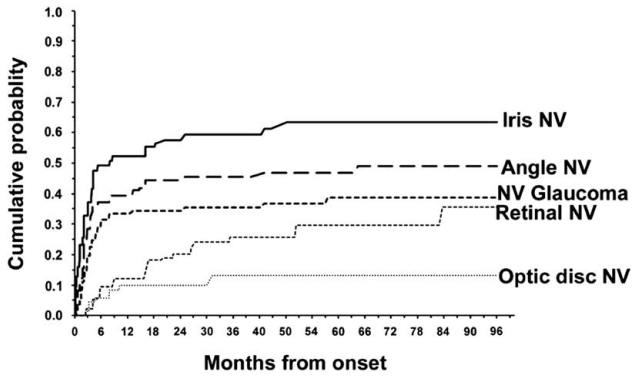


**FIGURE 4.** Cumulative probability of ocular neovascularization development after onset of ischemic central retinal vein occlusion (adapted from Hayreh SS. Progress in Retinal and Eye Research 2021). Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

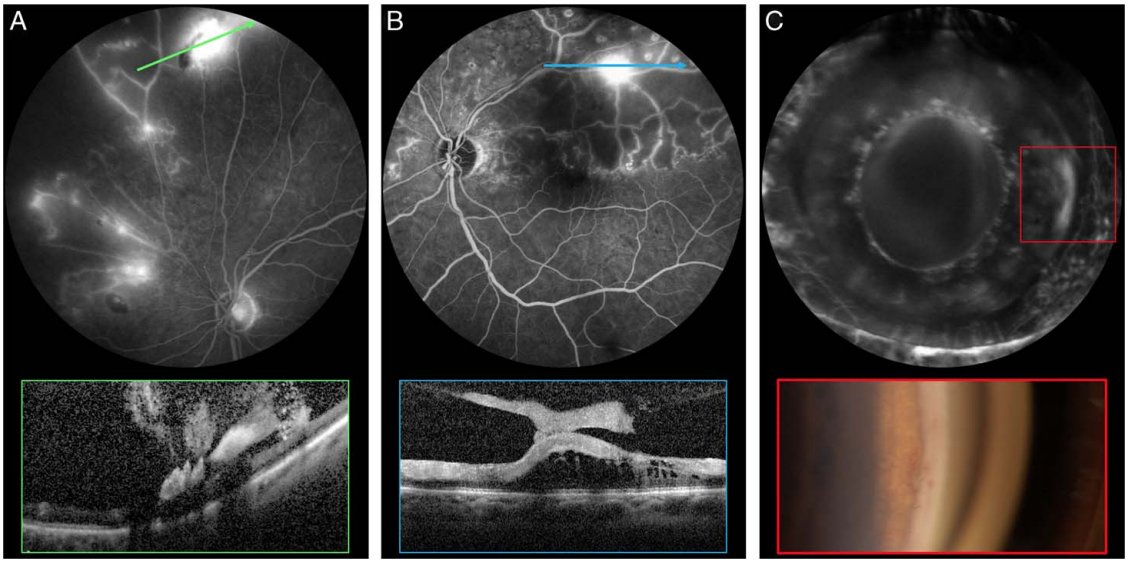


**FIGURE 5.** Ocular neovascular complications in retinal vein occlusions. A, Showing leakage from multiple retinal neovascularizations elsewhere along the borders of capillary nonperfusion on fluorescein angiography in a case of supero-nasal branch retinal vein occlusions. B, Depicting an important leakage on fluorescein angiography in a case of hemicentral retinal vein occlusion complicated by a thick retinal neovascularization along the supero-temporal vascular arcade. C, Showing leakage from iris on fluorescein angiography in a case of ischemic central retinal vein occlusion; gonioscopy reveals angle neovascularization.

### Fellow Eye

The prevalence of bilateral CRVO at presentation is highly variable in the literature, ranging from 0.4% to 43%.[118,119] By contrast, the CVOS group identified a 0.9% increase per year in the risk of developing any vascular occlusion in the fellow eye of patients with unilateral CRVO.[118]

A systematic review revealed that bilateral BRVO is present in 4.5%–6.5% at presentation, whereas the risk of developing BRVO in the fellow eye—if unaffected—increases to 7%–10%.[107]

## MANAGEMENT

### Medical Management of Risk Factors

A systemic work-up in RVO patients is commonly advised at presentation, including detailed medical history, measurement of blood pressure and glucose, and basic laboratory tests.[57,120] This allows to identify systemic conditions facilitating the occurrence of RVO (eg, hypertension, lipid abnormalities, etc) as well as to rule out urgent conditions such as blood dyscrasias or inflammatory causes,[57,120] especially in younger patients.

Management of systemic risk factors should always be coordinated with the general practitioner and other specialists according to the results of the systemic workup. There is currently no supporting evidence for the use of anticoagulation or antiplatelet drugs for the treatment of RVO.[121]

In case of association with the use of contraceptive pills, a decision on the possible discontinuation should be made on a case-by-case basis after having thoroughly informed the patient. Indeed, such therapy should not be commenced in young women with RVO.[57,120]

### Ophthalmological Management

#### *Rationale of Retinal Vein Occlusion Treatment*

To date, there is no treatment that safely and reliably reverses the actual occlusion in RVO.

As such, ocular therapies aim at preventing or treating the previously discussed vision-threatening complications of RVO.

Intravitreal treatments limit the upregulation of VEGF and proinflammatory mediators.

Macular grid laser is hypothesized to increase oxygenation[122] by allowing oxygen to diffuse from the choriocapillaris into the inner retina leading to autoregulatory vasoconstriction and less leakage.[123]

Panretinal laser photocoagulation destroys the ischemic retina, decreasing the production of cytokines (eg, VEGF) and reducing the drive for ocular NV.

#### *Management of Branch Retinal Vein Occlusion*

*Laser Photocoagulation*: Macular grid laser was the gold standard treatment for ME due to BRVO before the advent of intravitreal therapy. Better visual outcomes were reported in BVOS study[108,124] in eyes with VA worse than 20/40, randomized to grid laser compared with sham. Retinal photocoagulation is still considered the gold standard treatment for retinal NV causing VH.

*Intravitreal Steroid*: The SCORE-BRVO study[125] compared the safety and effectiveness of intravitreal triamcinolone to grid laser in eyes with ME due to BRVO. There was no difference in VA gains between the 2 triamcinolone groups (1 mg and 4 mg) and the grid laser group at 12 months, but there was a significant increase in the rate of increased intraocular pressure and cataract with intravitreal triamcinolone. Hence, intravitreal triamcinolone is not advised as a first-line treatment. It continues to serve as a second-line agent in eyes where anti-VEGF is contraindicated or led to a suboptimal response.

An implant containing dexamethasone (Ozurdex) was evaluated in the GENEVA study[124] for ME due to CRVO and BRVO. The study found that the Ozurdex implant group had a higher percentage of patients with CRVO and BRVO gaining $\geq$15 letters at the 90-day period compared with the

sham group and a lower percentage of patients losing ≥15 letters.

*Intravitreal anti-VEGF*: Several anti-VEGF agents given intravitreally are currently available to treat ME due to BRVO including ranibizumab, aflibercept, and bevacizumab.

Intravitreal bevacizumab was found to be superior to macular grid laser in a small study.[126] A real-world study of 135 eyes reported visual improvement of 14 letters at 2 years with a median of 7 injections.[127]

The BRAVO study compared[128] 2 different doses (0.5 mg and 0.3 mg) of ranibizumab injections. At 6 months, ranibizumab-treated eyes gained about 16–18 letters compared with 7.3 letters of the sham group. Moreover, <20% required rescue laser compared with more than 50% of eyes in the sham group. At 12 months, the letter gain in ranibizumab-treated eyes was maintained.

The VIBRANT study compared intravitreal aflibercept to macular grid laser in eyes with ME due to BRVO.[129] At 52 weeks, eyes initially treated with aflibercept improved by 17.1 letters whereas eyes initially treated with laser improved by 12.2 letters. Rescue laser was applied in 80% of the eyes randomized to laser compared with 10% of the aflibercept group.[130]

### *Management of Central Retinal Vein Occlusion/Hemicentral Retinal Vein Occlusion*

*Laser Photocoagulation*: Macular grid laser did not benefit VA compared with observation in eyes with CRVO in the CVOS study,[131] although there was a positive trend in younger patients. Panretinal laser photocoagulation remains the gold standard for eyes with ischemic complications of CRVO.

*Intravitreal Steroid:* The SCORE-CRVO[132] study compared the safety and efficacy of intravitreal triamcinolone (1 mg or 4 mg) for the treatment of ME due to CRVO. At 12 months, eyes randomized to triamcinolone significantly improved vision compared with observation alone. The higher rate of raised intraocular pressure and cataract in eyes receiving 4 mg compared with 1 mg led to the recommendation that 1 mg triamcinolone be used in eyes with ME due to CRVO.

*Anti-VEGF*: Similarly to BRVO, several anti-VEGF agents given intravitreally are available to treat ME due to CRVO including ranibizumab, aflibercept, and bevacizumab.

The CRUISE study[128] compared 2 doses (0.3 mg–0.5 mg) of ranibizumab given monthly for 6 months with sham injections. At 5 months, eyes treated with ranibizumab had better visual outcomes, gaining 12.7 letters and 14.9 letters (0.3 mg and 0.5 mg, respectively) compared with 0.8 letters in the sham group.

The COPERNICUS and GALILEO[133] studies compared 6 monthly intravitreal aflibercept followed by pro-re-nata to sham injections. In these studies, 56%–60% of aflibercept-treated eyes gained at least 15 letters of vision compared with 12%–22% of sham eyes. On average, eyes improved by 18 letters when treated with aflibercept compared with 3.3 letters in the sham group.

The LEAVO study[134] compared the effectiveness of ranibizumab, aflibercept, and bevacizumab for the management of ME due to CRVO. Ranibizumab was not inferior to aflibercept, but fewer injections were required in the aflibercept group. Results were inconclusive whether bevacizumab was inferior to ranibizumab or not.

A real-world study of 221 eyes[135] demonstrated good long-term outcomes of eyes treated with anti-VEGF, with an improvement in vision (14.8 letters in BRVO eyes and 14.4 letters in CRVO eyes) sustained for 8 years.

## Management of Complications

The eyes with untreated ischemia in the setting of CRVO, HRVO, and BRVO can progress to develop several structural complications due to the ongoing effect of VEGF in the intraocular milieu.[136–139] The sections below highlight the management of the 2 most important complications of RVO, NVG, and VH/TRD.

### *Neovascular Glaucoma*

As NVG results from various pathologic effects (direct and indirect) of VEGF such as endothelial cell migration, leukocyte adhesion, fibrovascular proliferation, and mechanical obstruction of the trabecular meshwork, inhibition of VEGF is the most critical step in the management of NVG.[136,137] The steps of managing NVG are provided in the flowchart (Table 3, Fig. 6).[140–143]

*Medical Management:* There are several considerations when treating patients of NVG with anti-VEGF therapy, including maintenance of intraocular pressure, route of injection (intracameral or intravitreal), and the timing of injection [vis-à-vis panretinal photocoagulation (PRP)]. In general, it is important that intraocular pressure is adequately controlled before the injection of anti-VEGF agents to avoid dangerous spikes.[144–146] Ideally, management of intraocular pressure should be promptly instituted with either topical and/or oral

**TABLE 3.** Management Strategies for NVG

| Medical Management | | Surgical Management | |
|---|---|---|---|
| **Retina/Iris** | **Intraocular Pressure** | **Vitreoretina** | **Intraocular Pressure** |
| Intravitreal anti-VEGF injections | Oral carbonic anhydrase therapy | PPV | Trabeculectomy |
| Intracameral anti-VEGF injections | Topical carbonic anhydrase therapy | Endolaser PRP | Trabeculectomy with anti-metabolite injections |
| PRP | Topical beta-blockers | Endocyclophotocoagulation | GDD |
| Anterior retinal cryopexy | Topical alpha agonists | — | — |

GDD indicates glaucoma drainage device; NVG, neovascular glaucoma; PPV, pars plana vitrectomy; PRP, panretinal photocoagulation; VEGF, vascular endothelial growth factor.

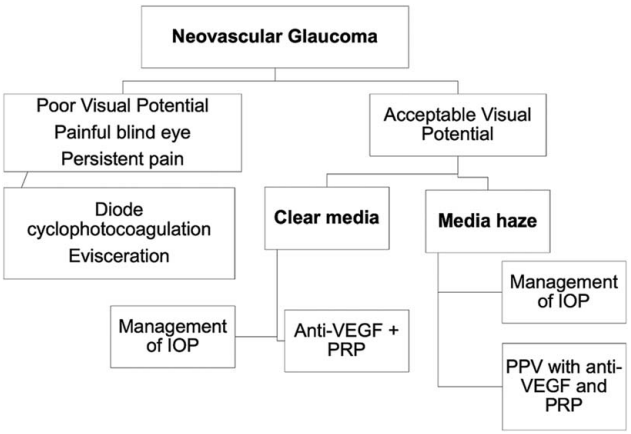


**FIGURE 6.** Flowchart of management of patients with neovascular glaucoma. The management has been classified based on the visual potential and the clarity of the media.

therapies. Generally, pilocarpine and prostaglandins are avoided as they can potentially increase intraocular inflammation. It is possible to inject anti-VEGF agents intracamerally if one is not sure whether there is a concomitant retinal detachment.[144,147]

In general, anti-VEGF action with injections is quick and predictable, and should be used as an emergent treatment strategy for patients with NVG as PRP (though definitive) may take several weeks to act. There have been no comparative studies to identify which anti-VEGF agent is superior in treating NVG, as such the treatment depends on the surgeon's preference and drug availability.[141]

PRP is the recommended treatment strategy for long-term intraocular pressure control of patients with NVG. Studies have recommended about 1200–1600 burns of about 200–400 μm spot size completed in 1–3 sittings. In eyes with NVG but where the media are not clear due to other complications such as VH, it is not possible to complete PRP, but an attempt should be made to do as much laser as possible, before other interventions such as pars plana vitrectomy (PPV).[5,148–150]

*Surgical Management:* PPV is a recommended approach in eyes with NVG and dense, nonresolving, or recurrent VH. Due to VH, red blood cells from the posterior chamber can also block the trabecular meshwork resulting in ghost cell glaucoma, for which PPV becomes an important treatment strategy. Despite adequate PPV and endolaser PRP, these patients may require intravitreal anti-VEGF injections in the future due to nonresolving retinal/iris NV.[151–153]

Management of glaucoma can be performed either with trabeculectomy or glaucoma drainage device (GDD) insertion. In general, trabeculectomy has a high failure rate in eyes with NVG.[154,155] Success can be partially improved by using intraoperative chemotherapeutic agents such as mitomycin *C* or 5-fluorouracil, and even injecting 5-fluorouracil (or anti-VEGF) around the bleb in the postoperative period.[156–158] The success rate of GDD is higher compared with trabeculectomy in eyes with NVG, with no difference in the surgical success at 5 years based on the device used (Ahmed vs Baarveldt study).[159] Several authors have performed simultaneous PPV and pars plana insertion of GDDs to reduce the intraocular pressure.

In eyes with very limited potential and those with failed GDD or multiple glaucoma procedures, diode laser cyclophotocoagulation is an option. Diode laser cyclophotocoagulation can result in permanent hypotony, hyphema, corneal edema, and phthisis bulbi, as such it is reserved for eyes with no other option available. PPV can also be combined with endocyclophotocoagulation to reduce the intraocular pressure.[160–162]

### *Management of Posterior Segment Complications*

*Management of VH*: There are no guidelines or recommendations regarding the timing of intervention in eyes with RVO developing VH.[143] In general, PPV would be recommended in eyes with dense, nonresolving (present for over 4 wk), and recurrent VH. There is no urgency in performing PPV in eyes with VH if there are no other complications such as an underlying TRD or raised intraocular pressure.[163–166] However, in the presence of these complications, prompt surgical intervention should be considered. PPV allows adequate visualization of the blocked vessels in RVO, allowing the surgeon to decide the extent of endolaser photocoagulation. The surgical complications of PPV in eyes with VH remain low. However, there are 5%–10% chances of residual loose blood in the vitreous chamber postoperatively, which may resolve with time or may need reintervention.[167]

*Management of TRD*: Presence of TRD is an indication for a prompt surgical intervention in eyes with RVO. TRD in eyes with RVO develops due to unrelenting fibrovascular proliferation mediated by the effects of VEGF on the posterior segment. PPV can be used to address the structural abnormalities due to this fibrovascular proliferation on the retinal surface.[168,169] During PPV, it is important to remove all the core vitreous and truncate the hyaloid as far peripherally as possible. Usually, eyes with TRD can have a number of posterior hyaloid adhesions to the retinal new vessels, which can bleed if excessive traction is applied with the outcome. Therefore, the surgery consists of a delicate dissection of all the tractional membranes to remove all the adherent hyaloid. The retinal bleeders can be cauterized using an endodiathermy, and the peripheral retina can be subjected to endolaser PRP. In case there is a secondary or iatrogenic retinal break, intraocular tamponade may be necessary.[168]

If performed early, the surgical success in patients operated for TRD with PPV is high. The chances of anatomic and visual success are reduced in patients developing a combined tractional-rhegmatogenous retinal detachment and further reduced if there is significant retinal shortening due to intraretinal or extraretinal proliferative vitreoretinopathy. With modern vitrectomy systems, improved duty cycles, and features such as beveled cutters and close retinal shaving, surgical management has become much safer with improved patient outcomes.[170,171]

## Follow-Up Recommendations

Internationally recognized evidence-based guidelines generally agree that a correct and complete assessment of RVO patients at presentation is crucial to determine the suitable follow-up as this should be tailored according to patients' compliance, disease entity, and risk of complications.[57,58,120,172]

BRVO patients should be followed every 1–2 months after the presentation to rule out the onset of ME and/or NV.[57] In case of ME, follow-up should be adjusted according to the choice of drug and regimen (ie, "pro re nata" or "treat-and-extend").[57,58,120] In case of ischemic BRVO and, specifically, when retinal ischemia involves 1 quadrant or more, follow-up visits should be scheduled every 3–4 months for the first 24 months to exclude ocular NV.[57]

CRVO requires a more careful approach given the higher rate of complications compared with BRVO. However, similarly to BRVO, the presence of ischemia or ME is the main factor that influence the decision process.[57,58,120]

As nonischemic CRVO may resolve spontaneously without complications,[13] patients may be checked up every 3 months in the first 6 months.[57] If no ME, ischemia, or NV occur, follow-up time may be extended with the possibility to discharge the patient from retinal care supervision after 18 months from the first evaluation.

When significant ischemia is present (>10 disc-areas posterior pole nonperfusion) in absence of ME and NV, it is advised to schedule monthly visits for the first 6 months and then follow-up should be every 3 months for 1–3 years.[57]

In case of ischemic CRVO with ME, follow-up should be scheduled according to the choice of drug and regimen.[57,58,120]

After the resolution of the edema and the stabilization of the VA, ischemic CRVO should still be followed for 3 years from the last intervention before discharging the patient.[57]

Although HRVO is a peculiar entity that may have a different prognosis from both CRVO and BRVO, it has been associated with a high rate of complications that is comparable to CRVO (eg, incidence of disc NV in presence of ischemia).[18,22,173,174] Hence, follow-up recommendations are the same as the ones described for CRVO.

## FUTURE THERAPEUTIC OPTIONS

Treatment options for RVO mostly focus on the control of systemic risk factors and the prevention and management of complications. Several new strategies are being investigated with interesting results.

A laser-induced shunt between the retinal and the choroidal circulation has been proposed to bypass the vein occlusion.[175,176] Although this procedure demonstrated a high rate of success and encouraging results in nonischemic CRVO, several complications may occur, and further studies are needed to assess its potential future applications. In 2006, a transvitreal lamina puncture was proposed to create a perivascular opening within the optic nerve head in older CRVO patients with very low vision, but they had no improvements after the procedure.[177]

After a similar rationale, a surgical arteriovenous sheathotomy procedure was proposed to treat BRVO-associated ME.[177] However, a comparison with intravitreal injections of triamcinolone acetonide did not demonstrate the superiority of the experimental treatment.[178]

In the near future, several new drugs are expected to be approved for the treatment of ME, mostly including novel anti-VEGF agents (eg, Faricimab, NCT04740905 and NCT04740931; KSI-301, NCT04592419; and 601, NCT04667897; https://clinicaltrials.gov/) or novel delivery systems for existing drugs (eg, IBE-814 implant for dexamethasone therapy, NCT04576689, https://clinicaltrials.gov/; episcleral dexamethasone, NCT04120311, https://clinicaltrials.gov/; port delivery system for anti-VEGF[179]; and intravitreal hydrogels for anti-VEGF[179]).

New pathways of intervention are also being explored. Minocycline is a broad-spectrum tetracycline antibiotic with immunomodulatory, antiapoptosis, and neuroprotective functions.[180–182] Several studies demonstrated its neuroprotective effects in animal models of retinal diseases, including BRVO.[183] A phase-I/II randomized controlled trial (RCT) is currently ongoing for the evaluation of minocycline for the treatment of ME secondary to retinal diseases, including RVO (NCT05474950, https://clinicaltrials.gov/).

Rho Kinases inhibitors have been recently advised as a novel treatment for ocular diseases given their potential role in the regulation of several functions including apoptosis and angiogenesis.[184] The results of a pilot study on the combined use of intravitreal bevacizumab + Rho Kinase inhibitor (fasudil) on refractory RVO-related ME were recently published with encouraging findings.[185]

Photobiomodulation is a noninvasive treatment consisting of the irradiation of the eye using a near-infrared light (range = 630–900 nm). Although results on center-involving diabetic ME recently failed to demonstrate the efficacy of this treatment, an RCT on RVO-related ME is still ongoing (NCT04847869, https://clinicaltrials.gov/).

Subthreshold laser therapy consists of the application of a laser that does not leave any visible scar on the retina. Several studies reported the efficacy of this treatment in ME, but no RCTs have confirmed them.

Gene therapy targeting VEGF-A production is a technique involving the use of an adenoviral vector[186] to deliver an anti-VEGF gene to retinal pigment epithelium cells. Once transfected, the retinal pigment epithelium cells may express VEGFA antibodies.[187] A phase-1 RCT including patients with RVO-related ME is ongoing (NCT05099094, https://clinicaltrials.gov/).

Finally, intravitreal autologous CD34+ stem cell therapy is attempted in a patient with CRVO-related low vision in a phase-I/II RCT (NCT03981549, https://clinicaltrials.gov/). The rationale is that CD34+ stem cells are usually mobilized into the circulation from the bone marrow in response to tissue ischemia. These cells promote tissue revascularization and repair; hence their intravitreal delivery could benefit vision reducing retinal ischemia in eyes with RVOs.

## CONCLUSIONS

The diagnosis and management of RVOs have changed tremendously in the last 30 years. New imaging techniques have shed light on the pathophysiology of the disease allowing a better understanding of the anatomic relationships between the different vessel plexa and the surrounding structures.

Laser treatment, once the only therapeutic option, is now strategically combined with anti-VEGF and steroid injections allowing to achieve better outcomes and avoiding the most serious complications requiring a surgical approach in the majority of cases.

Many new therapeutic options are in the pipeline and the management of RVO will keep improving in the future further reducing the burden of this condition.

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