Retinal vein occlusion (RVO) is the second leading cause of retinal vascular disease, with reported cumulative annual incidence of 1.8% for branch RVO (BRVO) and 0.5% for central RVO (CRVO),¹² and bilateral or subsequent incidences of 6.4% and 0.9%, respectively.¹³,⁴

The postulated mechanism of action involves impingement of venules at the shared adventitial sheath by crossing arterioles leading to turbulence, stasis, thrombosis, and occlusion.⁵,⁶ Response to anti-VEGF and anti-inflammatory agents has empirically demonstrated that inflammatory factors play a more important role in RVO than previously presumed, beyond the obvious ischemia. These processes, seemingly mediated by released VEGF, induce retinal edema, retinal hemorrhages, and ischemia, thereby compromising visual function (Figure 1).²⁰⁻²⁹

Objective assessing RVO severity and determining prognosis of the condition depend on imaging studies. All clinical trials in RVO have relied heavily on various imaging modalities to standardize eligibility and treatment monitoring. This article reviews the use of some established imaging modalities in these important clinical trials and looks ahead at some promising new imaging technologies.

Established Treatment Options
Management of RVO with laser photoocoagulation, anti-VEGF agents, and corticosteroids has been well established (Tables 1 and 2).¹³⁻²⁹

Laser Photocoagulation
The Branch Vein Occlusion Study (BVOS) recommended focal laser photocoagulation for BRVO causing visual acuity of 20/40 or worse and macular edema.¹³,¹⁴ Evidence of center-involving macular edema on fluorescein angiography (FA) was the critical entry criterion. Separately, scatter photocoagulation to the involved segment was found to prevent occurrence of vitreous hemorrhage if neovascularization developed. The Central Vein Occlusion Study (CVOS) reported that panretinal photocoagulation reduced visual loss when 2 or more clock hours of iris neovascularization or more than 10 disc areas of capillary nonperfusion

### AT A GLANCE

- OCT is the gold standard imaging modality in the management of patients with RVO.
- Fundus photography and fluorescein angiography are acceptable and helpful alternatives.
- Newer imaging methods are promising but should be employed with caution until more data are available.
was present, but macular grid photocoagulation did not reduce visual acuity loss caused by macular edema.\textsuperscript{3,15-18} FA provided the gold standard for eligibility and monitoring of edema and extent of capillary nonperfusion (Figure 2).

Anti-VEGF Therapy

Anti-VEGF agents antagonize the effect of VEGF and generally arrest or even reverse disease progression in a multitude of retinal and choroidal vascular conditions including RVO. The BRAVO,\textsuperscript{19,20} VIBRANT,\textsuperscript{21} and PACORES\textsuperscript{22} trials reported a beneficial role of anti-VEGF therapy for macular edema and retinal neovascularization in BRVO based on visual acuity and features defined by optical coherence tomography (OCT), FA, and fundus photography. The CRUISE,\textsuperscript{23} COPERNICUS,\textsuperscript{24} and GALILEO\textsuperscript{25} clinical trials also used fundus photography and OCT to standardize assessment of macular edema due to CRVO at baseline and during anti-VEGF treatment.

Corticosteroids

Corticosteroids reduce breakdown of the blood-retina barrier and may help in the management of macular edema due

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**TABLE 1. CLINICAL TRIALS AND STUDIES USING LASER PHOTOCOAGULATION, ANTI-VEGF AGENTS, OR STEROIDS IN THE MANAGEMENT OF BRVO**

<table>
<thead>
<tr>
<th>Treatment Arms</th>
<th>Imaging Used</th>
<th>Conclusions of the Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Branch Vein Occlusion Study (BVOS) (1984-1986)</td>
<td>Macular argon laser photocoagulation</td>
<td>Fundus photography, FA</td>
</tr>
<tr>
<td>Bevacizumab for RVO (2009)</td>
<td>- 3 initial IVB (1 mg) at monthly interval &lt;br&gt; - Retreatment based on CRT</td>
<td>OCT, FA</td>
</tr>
<tr>
<td>SCORE-BRVO (2009)</td>
<td>- 1 mg preservative-free IVTA &lt;br&gt; - 4 mg preservative-free IVTA &lt;br&gt; - Standard care (grid photocoagulation)</td>
<td>Stereoscopic fundus photography, OCT</td>
</tr>
<tr>
<td>BRAVO Study (2010)</td>
<td>- IVR 0.3 mg &lt;br&gt; - IVR 0.5 mg &lt;br&gt; - Sham injections</td>
<td>Fundus photography, OCT</td>
</tr>
<tr>
<td>GENEVA (2010)</td>
<td>- DEX 0.7 mg 0.7 mg (n = 427) &lt;br&gt; - DEX 0.35 mg (n = 414) &lt;br&gt; - Sham (n = 426)</td>
<td>OCT</td>
</tr>
<tr>
<td>VIBRANT (2015)</td>
<td>IVA 2 mg every 4 weeks (n = 91) Grid laser (n = 92) at baseline</td>
<td>OCT</td>
</tr>
</tbody>
</table>

**Abbreviations:** BCVA, best corrected visual acuity; BRVO, branch retinal vein occlusion; CRT, central retinal thickness; DEX, dexamethasone; FA, fluorescein angiography; IOP, intraocular pressure; IVA, intravitreal aflibercept; IVB, intravitreal bevacizumab; IVR, intravitreal ranibizumab; IVTA, intravitreal triamcinolone acetonide; OCT, optical coherence tomography
to RVO. The SCORE BRVO,26 SCORE CRVO,27 and GENEVA28 clinical trials established the safety and efficacy of intravitreal triamcinolone acetate injection and the dexamethasone intravitreal implant 0.7 mg (Ozurdex; Allergan) in the management of macular edema associated with RVO. Fundus photography and OCT were the defining imaging modalities for all participating patients.

The SCORE2 trial reported that the effect of intravitreal bevacizumab (Avastin; Genentech) was noninferior to that of aflibercept (Eylea; Regeneron) for visual acuity in patients with CRVO or hemi-RVO.29 OCT-acquired retinal thickness provided the gold standard for eligibility and monitoring of edema in that trial.

### IMAGING MODALITIES

As the information above suggests, imaging technologies have played major roles in pivotal clinical trials in RVO.13-29 Imaging modalities continue to expand in scope and capabilities, and some of these expanded capabilities may prove valuable, but validation, as in the clinical trial setting, is needed before they are fully adopted (Table 3).

### Existing Imaging Options

*Fundus photography* allows documentation and grading of the clinical picture and may be important for correlation with results of other modalities.

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**TABLE 2. CLINICAL TRIALS AND STUDIES USING ANTI-VEGF THERAPY OR STEROIDS IN THE MANAGEMENT OF CRVO**

<table>
<thead>
<tr>
<th>Treatment Arms</th>
<th>Imaging Used</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Central Vein Occlusion Study (CVOS) (1993-1995)</strong></td>
<td>Macular edema • Grid argon laser photocoagulation • No grid laser (control group)</td>
<td>Fundus photography, FA Macular edema • No benefit of grid APC for eyes with macular edema due to CRVO Retinal neovascularization/vitreous hemorrhage • Early PRP • No PRP (control group)</td>
</tr>
<tr>
<td><strong>SCORE-CRVO (2009)</strong></td>
<td>- 1 mg preservative-free IVTA • 4 mg preservative-free IVTA • Observation</td>
<td>Stereoscopic fundus photography, OCT</td>
</tr>
<tr>
<td><strong>GENEVA (2010)</strong></td>
<td>- DEX 0.7 mg (n = 427) • DEX 0.35 mg (n = 414) • Sham (n = 426)</td>
<td>OCT</td>
</tr>
<tr>
<td><strong>CRUISE (2010)</strong></td>
<td>- IVR 0.3 mg • IVR 0.5 mg • Sham injections</td>
<td>Fundus photography, OCT</td>
</tr>
<tr>
<td><strong>COPERNICUS and GALILEO (2012-2013)</strong></td>
<td>- VEGF Trap-Eye (IVA) 2 mg • Sham injection (monthly for 6 months)</td>
<td>OCT</td>
</tr>
<tr>
<td><strong>Bevacizumab for RVO (2009)</strong></td>
<td>- 3 initial IVB (1 mg) at monthly interval • Retreatment based on CRT (OCT)</td>
<td>OCT, FA</td>
</tr>
<tr>
<td><strong>SCORE-2 Study (2017)</strong></td>
<td>- IVB (1.25 mg; n = 182)* • IVA (2.0 mg; n = 182)* *every 4 weeks through month 6</td>
<td>OCT</td>
</tr>
</tbody>
</table>

Abbreviations: AEs, adverse events; APC, argon laser photocoagulation; BCVA, best corrected visual acuity; central retinal thickness (CRT); CRVO, central retinal vein occlusion; DEX, dexamethasone; FA, fluorescein angiography; IOP, intraocular pressure; IVA, intravitreal aflibercept; IVB, intravitreal bevacizumab; IVR, intravitreal ranibizumab; IVA, intravitreal triamcinolone acetonide; OCT, optical coherence tomography; PRP, panretinal photocoagulation; TC-INV/ANV, 2 clock hours of iris neovascularization or any angle neovascularization.
Widefield fundus photography expands the standard 30° to 50° field of view to 200°, which covers approximately 80% of the retina in a single view. It produces a static morphologic rendering, however. 

FA provides functional information—including extent of macular ischemia, vascular leakage, and neovascularization—that was integral to studies delineated above. Other FA features include delayed arm-to-retina time, prolonged arteriovenous transit time, late staining of vessel walls, and distinguishing between collateral vessels and new vessels. Extensive retinal hemorrhages may obscure and limit determination of capillary nonperfusion on FA. Widefield FA, like its fundus photography counterpart, may provide potentially important information on vascular function. An important drawback of FA is the need for intravenous dye instillation, which leads to some morbidity (but minimal risk) and may consume important resources of personnel and clinic time. 

OCT has emerged as the gold standard for qualitative and quantitative assessment of macular thickness and has played an important role in establishing eligibility and response to laser photocoagulation, intravitreal anti-VEGF therapy, and corticosteroid use in clinical trials. Initially OCT depended on a time-domain based methodology; spectral-domain capabilities (aka Fourier domain) have since been applied to produce far superior imaging (approximately threefold better axial resolution and 100-fold faster scan speed). Spectral-domain OCT (SD-OCT) represents the state-of-the-art standard for clinical and research protocols. Another modification, swept-source OCT, uses a short-cavity swept laser instead of the superluminescent diode laser typical of SD-OCT, providing the highest imaging speeds to date, with 100,000 A-scans obtained per second, visualization of deeper tissues, a high axial resolution (5 µm), and an improved signal-to-noise ratio.

OCT angiography (OCTA) allows imaging of the perfused retinal vasculature by acquiring high speed, sequential OCT A-scans at the same retinal locus and then processing complex digital subtraction algorithms to analyze differences created by the moving columns of blood (Figure 3). A limitation of OCTA is that it does not provide imaging of vascular leakage or nonperfused vessels, and its imaging of new vessels might be imprecise. Distortion of the host retina, as with macular edema or atrophy, may also compromise image quality.
Emerging Imaging Modalities

Flow and perfusion data may be vital prognostic and therapeutic monitoring parameters. There are several noninvasive imaging systems that are still unvalidated but that may allow calculation of blood flow, functional assessment such as oximetry, or better vessel resolution.

Blood Flow Assessment

Laser Doppler flowmetry measures capillary blood volumetric flow by using Doppler shifts in laser light scattered from vascularized retinal tissue. Decreased blood volume, flow, and velocity have been reported in BRVO areas compared with age-matched normal areas.

Retinal function imaging is a high-resolution functional imaging technology that, like OCTA, tracks flow elements to yield blood flow velocity (and possibly flow if coupled with vascular volumetrics) and oximetry measurements. It has demonstrated decreased blood flow velocities in both arterioles and venules of the macular region in patients with CRVO and BRVO. As with FA, retinal hemorrhages may limit imaging of retinal vessels.

Laser speckle contrast imaging/flowgraphy visualizes and measures relative blood flow distribution based on speckle pattern measurements in real time (Figure 4). It has shown significant correlation with the flow modalities described above in rabbit and human retinas, and in CRVO treatment response.

Functional Assessment

Two-wavelength oximetry estimates oxygen saturation levels from distinctive spectral signatures of oxyhemoglobin and deoxyhemoglobin in the retinal blood vessels. Studies have shown reduced oxygen saturation values in occluded arteries and veins. Large intravessel variability and the lack of a normative data set limit the diagnostic power of these techniques.

Hyperspectral imaging is an improvement over the existing two-wavelength oximetry technique; it enables complete fundus oximetry by measuring relative changes in oxygen saturation of the retinal macro- and microcirculation.

Better Vessel Resolution

Adaptive optics fundus imaging is based on the same optical principles used in astronomical adaptive optic telescopes to reduce the effect of aberrations. It can yield a transverse resolution of 2.5 µm, allowing visualization of capillaries and the outer segment cones, 3-D cellular imaging, and the detection of fluorescent signals. Various microscopic subclinical vascular changes, such as capillary occlusion, recanalization and reperfusion, have been demonstrated in diabetic retina before they become visible clinically.

Multispectral imaging visualizes the retinal layers at multiple wavelengths ranging from 550 nm to 950 nm. Xu et al reported identifying vascular abnormalities in RVO using this modality.

IMAGE WISELY

OCT is the gold standard imaging modality in the management of RVO. It provides value by supplementing clinical evaluation in the diagnosis and management of RVO. Fundus photography and FA help clinicians to document the disease process, and both have been widely used in clinical trials.
Although the newer diagnostic modalities described above offer non-invasive insights into vascular function, they require extensive validation in larger studies. Thus, management guidelines for RVO should be based upon pivotal clinical trials, but they may need revision in the future. Newer imaging modalities should be used with caution.