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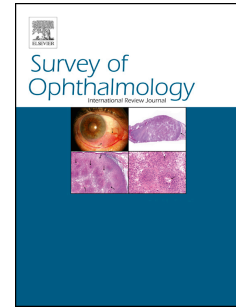
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Ischemic Retinal Vein Occlusion: characterizing the more severe spectrum of retinal vein occlusion

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Outline: Ischemic Retinal Vein Occlusion (iRVO)

Abstract

Retinal vein occlusion (RVO), including central (CRVO), branch (BRVO) and hemicentral and hemispheric RVO, is the second most common vascular cause of visual loss, surpassed only by diabetic retinopathy. The presence and extent of retinal ischemia in RVO is associated with a worse prognosis. On this basis, most previously conducted studies considered iRVO and non-iRVO as separate entities based on set thresholds of existing retinal ischemia, as determined by fundus fluorescein angiography (FFA). Other diagnostic technologies have been used specifically in the differentiation of iCRVO and non-iCRVO. To date there is not a fully accepted definition for iRVO. Some clinicians and researchers may favor establishing a clear differentiation between these forms of RVO; others may prefer not to consider iRVO as a separate entity. Whatever the case, retinal ischemia in RVO confers a higher risk of visual loss and neovascular complications and, thus, should be determined as accurately as possible in patients with this disease and should be considered in clinical and experimental studies. Most recently conducted clinical trials evaluating new treatments for macular edema secondary to RVO, included none or only few patients with iRVO based on previous definitions (i.e. few patients with sizeable areas of retinal ischemia were recruited in these trials) and, thus, it is unclear whether the results observed in recruited patients could be extrapolated to those with retinal ischemia. There has been scarce research aiming at developing and/or testing treatments for retinal ischemia as well as to prevent new vessel formation result of RVO.

This manuscript aims at providing the reader with a detailed review on the knowledge gathered over the years on iRVO, from controversies on its definition and diagnosis to the understanding of its epidemiology, risk factors and pathogenesis, the structural and functional effects of this disease in the eye and its complications, natural history, and outcomes following treatment. In each section, the definition of iRVO used is given so, independently

of whether iRVO is considered a separate clinical entity or a more severe end of the spectrum of RVO, the information contained herein will be useful to clinicians, to determine patient's risk, guide therapeutic decisions and counsel patients and for researchers to design future studies.

Keywords: Retinal vein occlusion (RVO); ischemic retinal vein occlusion (iRVO); ischemic central retinal vein occlusion (iCRVO), ischemic branch retinal vein occlusion (iBRVO); non-perfused retinal vein occlusion; retinal perfusion; retinal ischemia; ischemic retinopathy.

I.   Introduction

Retinal Vein Occlusion (RVO) appears to be the second most common vascular cause of visual loss, surpassed only by diabetic retinopathy [74]. Obstruction of the retinal venous system is a serious condition which may result in devastating complications including irreversible blindness [119,122,196,253]. Classically, RVO has been divided into two main types based on the site at which the occlusion occurs: Central Retinal Vein Occlusion (CRVO) and Branch Retinal Vein Occlusion (BRVO) [2,6].

In CRVO, blockage of the main vein draining the retina, the central retinal vein, occurs [74,114]. In this type, the occlusion usually takes place at or behind the laminal cribrosa. CRVO is the most severe form as it affects the entire retina [74,114]. BRVO is a blockage of one or more retinal vein branches (tributaries) which typically occurs at arteriovenous crossings [74,114]. It can be major, macular or peripheral based on the affected retinal region [74,114]. Two other types of RVO should be considered, hemispheric and hemicentral retinal vein occlusion. In the literature, the terms hemispheric and hemicentral RVO have been used often as synonymous, with no distinction made between these two entities [96,261]. However, hemispheric RVO and hemicentral RVO refer to different entities. Hemispheric RVO affects half of the retina with the site of the occlusion occurring at an arteriovenous crossing, like in BRVO [54-56,109,225]. In contrast, hemicentral RVO occurs in patients with a congenital abnormality involving the presence of a dual trunk central retinal vein; in these cases the occlusion takes place at one of these trunks of the central retinal vein and, on this regard, is closer to CRVO [54-56,109,225]. Herein, we will refer to hemispheric RVO in the BRVO section, although with a clear statement that data presented refers to hemispheric RVO, when data is available. We will refer to hemicentral RVO in the CRVO section and, similarly, we will clearly state that data presented refers to hemicentral retinal vein occlusion. Data from studies where no distinction between the two was made will be presented under the BRVO

section, given the fact that hemispheric RVO appears to be more common than hemicentral RVO, but stating also clearly that distinction between the two was not provided.

Each of these RVO types has been further classified into ischemic or non-ischemic sub-types based on the area of retinal capillary non-perfusion present [2,6,74,109,119,196,253]. This distinction is clinically relevant as the presence and extension of the area of retinal ischemia appears to have important prognostic and management implications [2,6,109,196]. However, as discussed below, there is no consensus on where the threshold of retinal ischemia should be set to define iRVO. Determining the presence and extent of retinal ischemia in RVO is important and agreement exists with regard to the risk it confers to patients with this vascular disorder. Thus, it is essential that retinal ischemia is considered when phenotyping patients with RVO and that patients with retinal ischemia are included in trials testing new therapies for this condition. For example, many of the recently conducted clinical trials on new treatments for macular edema result of RVO did not include or included very scarce numbers of patients with retinal ischemia [29,37,43,99,128,137,153,234,264] (Table-1). As a result, the benefit of these treatments for this group of patients is uncertain (see section VIII. Management, below).

The purpose of the work presented herein is, through a systematic review of published literature, to provide the reader with current knowledge on iRVO, from controversies on its definition and diagnosis to the understanding of its risk factors and pathogenesis, the structural and functional effects of the disease in the eye and its complications, natural history, as well as outcomes following current treatments, their potential side effects and limitations. In each of these sections, the definition of iRVO is given so data can be interpreted appropriately.

II.   Definitions

Many other terms have been used to refer to iRVO including non-perfused, severe, hemorrhagic, or pre-proliferative RVO [39]. The definition of iRVO is controversial. Different authors have adopted different parameters to differentiate iRVO from non-iRVO, making comparison between studies difficult. For example, some have used a single test to define iCRVO namely, fundus fluorescein angiography (FFA) [2,6,18,37,38,45,65,85,128,137,153,177,207,220,226,240,242,248,264,295], electroretinography (ERG) [2,131,155,162,170,190,199,312], or visual acuity of ≤20/200 [22] whereas others have suggested the use of a combination of tests for this purpose [20,123,197,236]. The most commonly used parameter to differentiate ischemic and non-ischemic RVO has been the area of retinal capillary non-perfusion as determined by FFA [6,18,37,38,45,65,95,128,137,153,177,207,220,226,228,240,242,248,264,295]. Most studies using FFA, determined the total area of retinal capillary non-perfusion by measuring it and then dividing it by the optic disc area to calculate the area of retinal capillary non-perfusion in disc areas (DA) [2,6].

A.   Ischemic CRVO

Commonly, ischemic central retinal vein occlusion (iCRVO) is defined by the presence of ≥10 DA of retinal capillary non-perfusion based on FFA [6,38,128,137,226,244]. However, other thresholds to define iCRVO have been used, such as ≥ 5 DA [153] or ≥ 30 DA [240]. As stated above, the risk of neovascular events appears to increase with greater disc areas of non-perfusion. In the Central Vein Occlusion Study (CVOS) the risk of developing iris/ angle neovascularization was found to be 16%, 36% and 52% for eyes with 10-29, 30-74 and ≥75 DA or capillary non-perfusion [6]. For those with ≥10 DA the risk was 28% and for those ≥ 30 DA the risk was 43%, with 96% of neovascularizations occurring during the first year of follow-up [6].

The precision of determining the area of retinal capillary non-perfusion may be enhanced by the use of newer and improved technologies, such as wide angle-FFA (WA-FFA) which allows a larger area of the retina (>200°) to be imaged; this corresponds to ~ 82% of the entire fundus area in comparison to standard FFA which is restricted to 30-55° [274,290,300]. Even when each quadrant of the retina is imaged by standard FFA, the area of retina visualized is not as extensive as that observed by WA-FFA.

An earlier study by Magargal and colleagues used the ischemic index to define the ischemic status of the retina in CRVO [183]. The ischemic index (ISI) was defined as follows:

$$\text{Ischemic index (ISI)} = \frac{Area\ of\ non-perfused\ retina}{Total\ area\ of\ visible\ retina} \times 100$$

As with the DAs, different ISIs have been used to differentiate between iCRVO and non-iCRVO. Magargal and colleagues defined non-iCRVO by an ISI of ≤10%, intermediate when ischemic index was 11-50%, and iCRVO when the ISI was >50% [183]. Giuffre et al. used an ischemic index of ≥30% to define iCRVO [90]. It would be expected that the more the retina visualized the more accurate the estimate of the area of retinal ischemia and, thus, wide angle technologies would be preferred when evaluating patients with RVO.

The relationship between the ISI and the presence of ocular neovascularization of any type [anterior segment (iris or angle) and/or posterior segment (retinal) neovascularization] was investigated using WA-FFA and it was found that an ISI of ≥45% was associated with the presence of concurrent new vessels [300] (see section VI. Clinical Findings and Ancillary Studies). The relationship between ISI and macular edema was also investigated using WA-FFA and it was found that an ISI of >10% was associated with the presence of this complication [274] (see section VI. Clinical Findings and Ancillary Studies). It is possible to have a relatively low ISI but significant ischemia involving the macula [274].

None of the definitions discussed above take into consideration the location of the area of retinal ischemia (i.e. macula, midperipheral or peripheral retina). The center of the macula (fovea) is the area responsible for the central vision. Thus, it seems essential when evaluating CRVO that the perfusion status of the macula as well as whether or not there is preservation or destruction of the perifoveal capillaries is determined and considered, in addition to the evaluation of the presence/absence and extension of ischemia in the midperipheral and peripheral retina. Recently introduced technologies, such as optical coherence tomography angiography (OCT-A) may facilitate, the gathering of this information (see section VI. Clinical Findings and Ancillary Studies, below).

Some studies have utilized ERG as a single tool to diagnose iCRVO and determine risk of neovascularization instead of FFA. It was observed that prolonged implicit times in the 30 Hz flicker ERG (33.8-42 ms) appeared to be more accurate than FFA in defining iCRVO and predicting risk of neovascular complications [169] (See section VI. Clinical Findings and Ancillary Studies, below). It was suggested that iCRVO should be defined by an implicit time of ≥37 ms in the 30 Hz flicker ERG in one study [129,170]; a very similar threshold (>35ms) was proposed in another study [155] (see section VI. Clinical Findings and Ancillary Studies, below). It was also reported that interocular amplitude difference of 23 µV and interocular amplitude ratio of 60% on 30 Hz flicker ERG could be also used as cut-off points to differentiate between iCRVO and non-iCRVO [161] (see section VI. Clinical Findings and Ancillary Studies, below). Other authors have suggested that a reduction of the b/a ratio on the scotopic ERG (mean ± standard deviation of 14.8±13 in uncomplicated CRVO compared to 3.5 ±2 in CRVO which developed iris neovascularization) and/ or photopic ERG (mean ± standard deviation of 3±2 in uncomplicated CRVO compared to 1.5±0.5 in those who developed iris neovascularization) is also appropriate to define iCRVO [312] (see section VI. Clinical Findings and Ancillary Studies, below).

10

Hayreh and associates found no single test to have 100% sensitivity and specificity for the distinction between iCRVO and non-iCRVO [123]. Standard FFA was informative in two thirds of patients in the acute phase of the disease [123]. A combination of the following six anatomical and functional tests was proposed by Hayreh and colleagues to establish the diagnosis of iCRVO [123]:

1. Visual acuity (VA) of ≤ 6/60 (20/200).

2. Peripheral visual fields (VF) defects using the I-2e, I-4e, and V-4e in the Goldmann perimeter.

3. Relative afferent pupillary defect (RAPD) of ≥ 0.9 log units using neutral density filters (see section VI. Clinical Findings and Ancillary Studies, below).

4. ERG parameters: b-wave amplitude reduction by ≥60% of normal mean value (normal fellow eye) in photopic and scotopic ERG, as well as b/a ratio reduction by ≥60% for photopic and scotopic ERG in the CRVO eye when compared with values of the fellow normal eye.

5. Retinal capillary non-perfusion on FFA classified into mild, when the area of retinal capillary non-perfusion is ≤ 30 DA, which carries a low risk of developing neovascularization; and severe, defined by the presence of retinal capillary non-perfusion of > 75 DA and which poses a high risk of developing neovascularization.

6. Extensive retinal hemorrhage and cotton wool spots in the acute stage, and disc/retinal neovascularization in a later stage of the disease on ophthalmoscopy.

It was observed that the presence of a RAPD has the highest sensitivity and specificity for the diagnosis of iCRVO [123,267]. Combining the RAPD with ERG findings it is possible to diagnose up to 97% of cases of iCRVO in the acute phase of the disease [119,123].

11

Other studies have used different combinations of the above tests to establish the diagnosis of iCRVO, for example visual acuity, visual fields, RAPD, and ERG [36]; visual acuity, RAPD and area of capillary non-perfusion on FFA [255]; visual acuity, findings on ophthalmoscopy and FFA [236] and visual acuity, visual field and RAPD [197].

Clearly, there is variability on how the diagnosis of iCRVO is determined; this should be taken into consideration when appraising current literature on this disease. It may not be possible to find an agreement among clinicians and researchers with regard to how to define iCRVO. However, if a consistent evaluation of patients with iCRVO were to be agreed and used, including determining the minimum core outcome measures required for RVO studies, this would allow for a homogeneous patient assessment. The latter would facilitate future comparisons among studies and meta-analysis, it would enhance the understanding of the disease and provide a more accurate identification of phenotypes and estimation of their prognosis as well as their response to treatment. Suggestions on this regard are proposed in section IX, below.

Similar suggestions as those given to differentiate iCRVO from non-iCRVO were proposed by Hayreh & Zimmerman [115] to discriminate ischemic from non-ischemic hemicentral RVO. These included inability to see I-2e, and defective or absent I-4 isopter in Goldmann perimeter, extensive retinal hemorrhage and a large number of cotton wool spots, and > 10 disc areas of retinal capillary non-perfusion, in the affected half of the retina [115].

B. Ischemic BRVO

Ischemic BRVO was defined by the Branch Vein Occlusion Study (BVOS) group by the presence of ≥5 DA of retinal capillary non-perfusion on standard FFA [2]. This definition has been widely used since by many investigators [45,210,226,228,264,295]. In the BVOS, 41% of eyes with ≥5 DA of capillary non-perfusion developed neovascularization during a mean follow-

up of 3 years.   Some studies used the presence of ≥10 DA of retinal capillary non-perfusion to define iBRVO [43,45,257]. The risk conferred to patients with BRVO by having a determined extension of retinal capillary non-perfusion (≥5 DA, ≥10 DA or other) has not been investigated as widely in BRVO as in CRVO.

There is no accepted definition and classification of iBRVO or of ischemic macular RVO. Like in CRVO, the area of retinal capillary non-perfusion seems to contribute to the risk of neovascular complications in patients with BRVO[49]; other factors contributing to this risk remain to be elucidated. As for iCRVO, finding consensus among clinicians and researchers on a definition of iBRVO may be challenging. An agreed standard evaluation and characterization of these patients, however, should be the starting point and suggestions on this regard are provided on this manuscript (see section IX, below).

III.   Epidemiology

RVO is a common disease with an estimated 16.4 million adults affected worldwide (2.5 million with CRVO and 13.9 million with BRVO), based on a pooled analysis of population-based studies from the United States, Europe, Asia, and Australia [252]. Many population-based studies have looked at the epidemiology of RVO, such as the Gutenberg Health Study of RVO [237], Beijing Eye study [323], the Central India Eye and Medical Study [142], Hisayama Study [15], Beaver Dam Eye Study [157], and Blue Mountains Eye Study [61], among others; none of these, however, differentiated between iRVO and non-iRVO. In general, these studies showed that the prevalence of RVO varies between 0.40 - 2.2% [15,61,142,157,237,323], with BRVO being apparently more common than CRVO. The incidence also varied between 0.2 – 2.3%, with BRVO having a higher incidence than CRVO [15,61,142,157,237,323].

A. Ischemic CRVO

In a hospital-based study by Hayreh, 1,108 RVO patients (1,229 eyes) were studied and classified into ischemic (22%) and non-ischemic (78%) (as defined by Hayreh's criteria described above, section II: Definitions) [112]. It was found that 13.2% and 18.6% of eyes with non-iCRVO at baseline convert to iCRVO at six and 18 months, respectively [112]. During the follow-up period of three years in CVOS, 34% of non-iCRVO converted to iCRVO (defined as an area of retinal ischemia of >10 DA)[6]. It was reported that 67% of patients with iCRVO have their first onset of the disease at ≥ 65 years compared to 44% of those with non-iCRVO with statistical significant difference between the two groups [112]. Moreover, development of the same type of RVO in the fellow eye was reported in 3.8% of patients with iCRVO in comparison to 8.8% of those with non-iCRVO [112]. In a study which included all consecutive new incident cases of RVO (557 RVO in total; 203 with CRVO and 354 with BRVO) identified between May and November 2010, which excluded RVO secondary to diabetic retinopathy or other ocular disorders, it was found that 100% of CRVO eyes presented with ≥5 DA of retinal capillary non-perfusion on FFA [173].

Ischemic hemicentral RVO was reported in 31 out of 130 eyes (23.8%) in comparison to 99 out of 130 eyes (76.2%) for non-ischemic hemicentral RVO in a study by Hayreh et al. which looked at the systemic diseases associated with the various types of RVO [120].

B. Ischemic BRVO

A population-based study in Korea found a very high rate of iBRVO (96%) using a ≥5 DA of non-perfusion as definition for this disease [173]. In other epidemiological studies, data on iBRVO form, in particular, was lacking.

IV.   Risk Factors

It is believed that RVO is a multifactorial disease, since more than one risk factor may contribute to its pathogenesis [74]. Most studies investigating the epidemiology and risk factors of CRVO and BRVO did not differentiate between ischemic and non-ischemic forms [3,61,77,142,156,157,185,198,237,271,280,281,284,292,293,323]. In general, risk factors for both CRVO and BRVO include increased age, hypertension, cardiovascular disease, dyslipidemia, diabetes mellitus and smoking [5,61,84,142,157,198,237,247,323]. Local ocular conditions, such as increased intraocular pressure and glaucoma, have been found to be risk factors for CRVO [5,61,84,142,157,237,247,323].

A.   Ischemic CRVO

The Eye Disease Case-Control Study evaluated risk factors for CRVO in 258 patients with CRVO and 1142 controls, and differentiated between the risk factors for iCRVO (iCRVO=84) and for non-iCRVO (non-iCRVO= 148) [5], with iCRVO defined by the presence of ≥10 DA of capillary non-perfusion on FFA. The ischemic status could not be determined in 26 patients. This study found increased systolic blood pressure, increased diastolic blood pressure, and hypertension associated with both iCRVO and non-iCRVO, but with greater odds ratios for iCRVO [5]. Cardiovascular disease, electrocardiographic abnormalities (unspecified), increased albumin-globulin ratio, increased serum α1-globulin level, history of treatment of diabetes mellitus and high blood glucose levels were found to be associated only with iCRVO [5]. In another large study by Hayreh et al.[120], which included 143 patients with iCRVO (as defined by Hayreh's criteria described above, section II: Definitions) and 469 patients with non-iCRVO, arterial hypertension and diabetes mellitus were significantly more prevalent in patients with iCRVO than those with non-iCRVO [120].

In a small study including young individuals aged < 40 years with iCRVO (n=8) (defined by either the presence of RAPD, visual acuity ≤3/60, severe retinal capillary non-

15

perfusion on FFA (no definition of "severe" capillary non-perfusion given), or iris/retinal neovascularization) and non-iCRVO (n=17), end stage renal disease was found in three patients with iCRVO and hypercholesterolemia, β-thalassemia, and hypertension were found, each, in one patient with iCRVO[98]. Due to the very small number of patients included, the role of these systemic conditions in young patients with iCRVO remains uncertain.

Only one study, conducted by Hayreh et al, evaluated risk factors for hemicentral RVO and differentiated between ischemic and non-ischemic forms [120]. This study did not find a statistical significant difference between ischemic and non-ischemic hemi-central RVO in the prevalence rate of various systemic diseases such as arterial hypertension, ischemic heart diseases, and diabetes mellitus among others [120].

B. Ischemic BRVO

No studies were found providing information on risk factors for iBRVO and non-iBRVO separately.

V. Etiology and Pathogenesis

A. Etiology

The etiology of iRVO has not been fully elucidated. A retinal vein can be occluded by thrombosis or, less commonly, by inflammation (vasculitis) [74]. According to Virchow's triad, venous thrombosis in general can develop by one or more of three mechanisms: 1) abnormal blood flow; 2) abnormal blood vessel and 3) abnormal blood components [305]. Retinal vein thrombosis is thought to develop by one of these mechanisms, namely, abnormal blood flow due to compression from an abnormal adjacent structure: the lamina cribrosa or an adjacent retinal artery [74,138]. In CRVO, abnormal blood flow is commonly due to age-related sclerosis of the lamina cribrosa, through which the central retinal vein passes, and/or a hardened retinal artery result of cardiovascular diseases [74,138]. In BRVO, abnormal blood

16

flow usually occurs at an arteriovenous crossing, where the artery and vein share a common adventitial sheath, due to the degree of arteriovenous nipping caused by the arteriosclerotic artery [74,138]. A much less common cause of retinal vein thrombosis is thought to be increased blood viscosity and hyper-homocysteinemia [57,71,241,304,311]. A study by Lahiri et al. compared the levels of plasma homocysteine in adult age ≥ 50 years old affected with iCRVO (n=108) (defined by Hayreh's morphological criteria described in section II. Definitions, above), with non-iCRVO (n=144) and age and sex matched healthy controls [166]. Homocysteine level was significantly increased in patients with iCRVO when compared with that in non-iCRVO patients and control subjects [166]. Other reported potential associations include deficiencies of the coagulation inhibitor proteins C and S and antithrombin III, whereas the role of reduced levels of Factor XII remains controversial with some studies suggesting an association while others do not [8,23,160,278].

It is unclear why some patients with RVO develop retinal ischemia whereas others do not. Similarly, the factors determining the extension and location of the area of retinal ischemia, if present, are not fully determined. Much research is needed to better understand the pathogenesis of retinal ischemia in RVO.

B.   Pathologic Mechanisms following Retinal Venous Thrombosis and its Clinical Consequences.

The severity of the RVO depends mainly on site of the thrombosis [74]. Once the thrombosis has formed, the retinal blood flow decreases. As a result, the intravenous hydrostatic pressure increases leading to a series of events that will damage vascular endothelial cells, disrupt the inner blood retinal barrier (BRB) and increase blood vessel permeability which, in turn, will result in retinal hemorrhages and edema throughout the extension of the retina drained by the occluded vein [74,273,303].

1. *Macular edema*

Macular edema is the most common cause of visual impairment in RVO and is a complication of both ischemic and non-ischemic forms of RVO [1,4,38,45,243]. Increased levels of serum albumin in the aqueous humor have been detected in iCRVO, reflecting the breakdown of the BRB [32]. Fluid accumulates in the extracellular spaces within the retina disrupting its normal anatomy and possibly leading to retinal neural degeneration by mechanical compression [62,148,250,306]. Chronic macular edema may damage glial (Muller cells) and retinal pigment epithelial (RPE) cells, further reducing retinal fluid clearance [34,35,250]. Fluid usually accumulates within the macula in a characteristic cystic pattern, known as cystoid macular edema. In severe retinal edema, neurosensory retinal detachment may also occur which may indicate the additional breakdown in the outer retinal barrier [301].

It has been suggested that intracellular retinal edema plays a role in the pathogenesis of ischemic retinopathies [34], but this has not been extensively studied for iRVO and remains less well understood. In this regard, it is likely that Muller cells are implicated in the pathogenesis of iRVO [34]. Muller cells normally transport water and salt from extracellular spaces into the retinal capillaries of the inner retina. In an experimental study in which BRVO was induced in rats, a decrease in potassium currents and an altered distribution of water channels, namely the Kir4.1 protein, were observed in Muller cells resulting in an increased size of their soma and cellular swelling under hypo-osmotic stress, altering their function [249].

Macular edema in RVO often shows a diurnal variation, with edema being worse in the morning and improving late in the day; this relates to the fact that, during sleep, nocturnal hypotension occurs resulting in a decrease in blood flow and an increase in intravenous pressure and, as a result, an increase in edema [Reviewed by Hayreh] [108,110].

18

2. *Retinal capillary non-perfusion*

The increased intravenous hydrostatic pressure occurring following an RVO leads to a decrease in the retinal capillary perfusion or, when severe, to capillary non-perfusion [158]. The capillary perfusion depends on the pressure difference between the artery/arteriole and the vein/venule proximal and distal to the capillary network respectively; when the pressure difference decreases, the capillary perfusion also decreases [158]. As a result, insufficient oxygen reaches the retina leading to retinal ischemia and hypoxia; carbon dioxide and other metabolites cannot be adequately washed out and accumulate in the affected part of the retina causing cell damage. Ischemia in CRVO is often more severe than in BRVO, as the area of the retina affected is more extensive in the former when compared with the latter. Not all patients with RVO, however, develop retinal ischemia and in those that do, the extension of the area of ischemia can vary considerably; the reasons for this remain poorly understood [2,6,181]. In humans, it has been postulated that blood is normally shunted between the collaterals of arterioles and venules in the far peripheral arcades. It is believed that these peripheral arcades are poorly perfused, as they require high perfusion pressure to push blood through them, making the peripheral retina more sensitive to changes in blood flow [19].

3. *Retinal and vascular cell damage*

Retinal hypoxia secondary to RVO causes loss of retinal capillary pericytes and damage to mural endothelial cells which leads to their apoptosis and capillary degeneration, as reported in experimental studies on BRVO [63,69,126,127,321]. Ischemia damages the different layers of the neurosensory retina causing them to lose their transparency and leading to visual loss. Ischemia results in cell death, by necrosis and/or apoptosis, of ganglion, amacrine, bipolar, and Muller cells and loss of their function as shown in animal studies [64,100,101,126,159,238]. Although photoreceptors receive their blood supply chiefly from the choroid, photoreceptor cell loss/damage may occur in patients with macular edema secondary to RVO; the damage

may persist even after resolution of the edema. This has been documented using OCT in eyes with BRVO in which the perfusion status was not determined [217,219,268] and in eyes with ischemic and non-ischemic CRVO [218,268]. Similar findings were observed in an experimental study on monkeys in which RVO was induced by laser photocoagulation; loss of photoreceptors was detected distal to the site of the occlusion in histopathological studies of eyes enucleated 48 months after RVO induction [306]. An association between the integrity of foveal photoreceptors and the final visual acuity, after resolution of the macular edema, has been reported [217-219,268]. The mechanism of photoreceptor cell loss in iRVO is still unclear.

The ganglion cell layer (GCL) and nerve fiber layer (NFL) of the retina, sensitive to acute and mild hypoxic distress, are believed to be the first layers affected in iRVO, which are lost in severely ischemic cases [175,176,322]. Experimental studies showed that damage to the inner retinal layers may occur within one to three weeks following occlusion [70,322]. Both apoptotic and necrotic changes have been reported in ganglion cells in experimental models of iCRVO and iBRVO [70,322]. In CRVO, GCL loss is significant in both central and peripheral retina, whilst in BRVO GCL loss is significant only in the peripheral retina [322]. The reason behind this characteristic pattern is not clear [322]. Clinical studies suggest that, regardless of the duration of iBRVO, RGL and NFL display significant thinning when the disease is present [12,175]. Lu and Zang [179] studied the effects of retinal ischemia on retinal NFL in 53 patients with RVO [CRVO=20; hemicentral RVO (no definition given) =4; BRVO=29). The definition used for ischemic CRVO was that proposed by Hayreh et al. [123] NFL defects were found in 75.5% of patients; they were significantly more in eyes with cotton wool spots and capillary non-perfusion and significantly more severe in ischemic eyes than in non-ischemic eyes [179].

4. *Collateral vessels and neovascularization*

Excessive amounts of Vascular Endothelial Growth Factor (VEGF) (see below) secondary to iRVO appear to play a major role in vascular remodeling and development of collateral vessels and neovascularization [9,32,231,232]. Collateral vessels develop in eyes with RVO as a compensatory response to venous occlusion [60,158,191,235,256,275,289,308]. Neovascularization is a characteristic feature of iRVO, often leading to visual threatening complications including neovascular glaucoma, vitreous hemorrhage and tractional retinal detachment (See section VI. Clinical Findings and Ancillary Studies) [14,117,119,122,134,196]. It has been reported that aqueous and vitreous VEGF concentration is significantly higher in iRVO than that in non-iRVO [143,211-213]. VEGF levels of 849-1569 pg/ml have been associated with the presence of neovascularization in iCRVO (normal values estimated ~550 pg/ml) [32].

5. *Inflammatory, angiogenic and hypoxia induced factors*

Many inflammatory, angiogenic and hypoxia-induced factors are produced and released in response to retinal ischemia, leading to further retinal damage. These factors have been detected in vitreous, aqueous and/or serum and believed to play a major role in the complications related to RVO (summarized below).

a. Vascular endothelial growth factor (VEGF)

VEGF is the most studied cytokine in the pathogenesis of iRVO [9,32,231,232] and is currently a therapeutic target of RVO treatments [37,38,43,45,46,58,79,128,167,215,243,244,288]. VEGF is an inflammatory, angiogenic and permeability factor produced by many cells, including vascular endothelial cells, pericytes, retinal pigment epithelium (RPE), Muller cells, astrocytes, and retinal ganglion cells [184]. Excessive production of VEGF secondary to iRVO further increases vascular permeability and worsens retinal and macular edema. VEGF along with other cytokines leads to increased adhesion of leukocytes to the vascular walls worsening

21

blood flow and retinal ischemia [75,147]. High levels of VEGF and IL-6 correlated with both the severity of macular edema and the extent of retinal ischemia in patients with CRVO and BRVO [Reviewed by Karia, 2010] [147].

b. Other factors

Other factors including Intercellular Adhesion Molecule-1 (ICAM-1), Monocyte Chemotactic Protien-1 (MCP-1), basic Fibroblast Growth Factor (bFGF), Interleukin 6 , 8 & 1β (IL-6, IL-8 & IL-1β), Erythropoietin (EPO), Tumor Necrosis Factor-α (TNF-α), Placental Growth Factor (PGF), transforming growth factor (TGF)-beta1, matrix metalloproteinases (MMP)-2 and -9 and serum amyloid A (SAA), Nitric Oxide (NO) among others, have been reported also to play a role in the pathogenesis of the ischemic form of RVO and the associated neuronal cell death occurring within the retina [75,80,83,133,143,144,172,205,224,269,302].

As outlined above, the pathogenesis of iRVO is complex. Although insight has been gained over the years, further research is still needed to help us to understand why dropout of retinal capillaries occurs in some but not all eyes affected with RVO as well as which factors determine the extension of this capillary loss. Deepening our understanding on how different types of neuronal and non-neuronal cells in the retina, including RPE, react to ischemia secondary to RVO and, crucially, how long it takes for the ischemic insult to cause permanent and irreversible damage beyond which therapeutic intervention may not be beneficial should be sought. Animal models of RVO are available to study its pathogenesis; these models have been used to improve the understanding of this condition and have shown their value on this regard [149].

VI.   Clinical Findings and Ancillary Studies

A patient with iRVO typically presents as an elderly individual with unilateral sudden blurred or deteriorated vision, and may seek care anywhere from a few days to several months after the onset of symptoms [74]. The affected individual is usually known to have one or more risk factors for RVO most commonly arterial hypertension followed by dyslipidemia, glaucoma and/or diabetes mellitus [5] (see section IV. Risk Factors, above). The condition is usually painless unless it is complicated with neovascular glaucoma in which case the increased intraocular pressure is often accompanied of severe pain [6,182]. Visual symptoms of iRVO are usually more prominent in the morning as the patient wakes up [110] (see V. Etiology and Pathogenesis section).

A.   Visual Acuity

In general, visual impairment is more severe in iRVO than in non-iRVO and more severe in iCRVO than in iBRVO [107,119,196,253]. Best-corrected visual acuity varies widely in both CRVO and BRVO depending on the presence/absence and extension of central macular involvement, including non-perfusion, edema and retinal hemorrhage as well as whether vitreous hemorrhage or retinal detachment are present. The visual acuity is usually ≤20/200 (6/60) in iCRVO [107,119,196] [85% of patients with iCRVO have vision of ≤ 20/200 at presentation [119]]. A study by Hayreh *et al* showed that a visual acuity of ≤6/120 at presentation has the highest sensitivity (91-100%) and specificity (78-88%) as a cut-off point of visual acuity for the differentiation between iCRVO and non-iCRVO [123]. The Central Vein Occlusion study group (CVOS) reported that the median visual acuity in patients with iCRVO at baseline was 20/400 with 79% of iCRVO having visual acuity of ≤20/125 [6]. In hemicentral RVO, visual acuity at presentation was ≤20/40 in all eyes (10/10) with ischemic hemicentral RVO when compared with 47% (27/57) of eyes with non-ischemic cases [115]. In iBRVO, visual acuity is ≤20/70 in ~35% of cases [2] and ≤20/60 in ~82-89% of cases of

ischemic macular BRVO [85,228] (see VII. Natural History section, below). Visual acuity at baseline is believed to be one of the most important prognostic factors in patients with RVO, with better final visual acuity in patients with better visual acuity at presentation[92].

B. Clinical Findings

The diagnosis of iRVO is usually established by fundus examination. In general, findings on fundus examination are similar in iRVO and non-iRVO, but often more prominent in iRVO. The affected retina typically looks edematous with dilated, engorged, tortuous retinal veins and flame-shaped and dot-blot retinal hemorrhages [74,116]. Specifically, the ischemic form of RVO can demonstrate cotton wool spots, which reflect focal infarcts within the nerve fiber layer and anterior or posterior segment neovascularization in more advanced stages [74,179,196,253]. Marked and extensive intraretinal hemorrhages are very suggestive of the presence of iRVO.

In iCRVO retinal hemorrhage and other fundus findings involve the entire retina. It has been reported that the presence of hemorrhages in more than one-fourth of the posterior retina has 81-84% sensitivity and 72-74% specificity for detecting iCRVO [123]. Neovascularization secondary to iCRVO can develop in the iris, angle, optic nerve head or retina [122]. In iCRVO the neovascularization is more common in the anterior segment, which can be observed using slit lamp and gonioscopic examination [122] than in the posterior segment (see section VII. Natural History, below). Vitreous hemorrhage and neovascular glaucoma can develop. The incidence of neovascular glaucoma in eyes with pre-existing glaucoma was found to be significantly higher in CRVO patients with intraocular pressure greater than 20 mmHg at presentation as well as in patients with iCRVO compared to those with non-iCRVO [50]. Optic disc edema in iCRVO is more marked and takes longer to resolve than in non-iCRVO [116]. Moreover, macular edema is often more severe in iCRVO than in non-iCRVO [116] and macular RPE degeneration, serous macular detachment and retinal

24

perivenous sheathing develop also more commonly in iCRVO [116]. Optociliary vessels have been reported in about 30% of patients with CRVO without a statistically significant difference between ischemic and non-ischemic forms [90].

In iBRVO, the retinal hemorrhage and other fundus findings are confined to the affected retinal quadrant or macula [118,253]. Unlike iCRVO, neovascularization in iBRVO involves the posterior segment, retina and optic nerve head, more commonly than the anterior segment, iris and anterior chamber angle [122] (see section VII. Natural History, below). Neovascular complications can be detected by clinical examination and with the help of ancillary studies in patients with iBRVO (see sections VII. Natural History, and C Findings on Ancillary studies, below)

C.   Findings on Ancillary Studies

Ancillary studies, including functional, structural examinations and patient reported outcomes (PROs) can be undertaken for the investigation of patients with iRVO. Some of these studies are routinely used in clinical practice, such as FFA and spectral domain – optical coherence tomography (SD-OCT), whereas others, although widely used for the purpose of research, such as visual fields, microperimetry, electroretinography, oximetry, flowmetry, ocular surface temperature, ophthalmodynamometry, and PROs, not commonly performed in the clinical setting to assess patients with RVO. This may be due to their impracticality, being time consuming, needing more patient cooperation and fixation, requiring specifically trained technical staff to obtain them or due to their unavailability, high cost, insufficient value to guide patient's care, and/or underestimation of their usefulness. It may be attributed also to the lack of evidence through robust diagnostic accuracy studies evaluating and comparing these different technologies and providing information on cost-effectiveness and patient acceptability and preference, which, if available, would guide clinical practice. This level of evidence is indeed not available for any of the diagnostic technologies used. Values obtained

using some of these diagnostic tests that have been suggested to aid in the differentiation

between ischemic and non-ischemic RVO have been summarized in Tables 2 and 3.

1. Functional tests

a. <u>Pupillary Examination</u>

Pupillary examination, specifically the presence of a RAPD appears to be extremely helpful

in differentiating between iCRVO and non-iCRVO; the presence of a RAPD points to the

diagnosis of iCRVO [31,123,197,245,267]. To undertake this test, filters with different densities

measured in log units and ranging from 0 to 3.0 log units can be used to grade the severity of

the RAPD [294]. The swinging flashlight test is performed with increasing density of the filter

in front of the healthy eye until RAPD disappears [294]. The eye with the RAPD is first

identified. Then, filters of known densities are placed over the not affected eyes until the two

eyes are equal (until there is no asymmetry of the pupillary reactivity to light) [267].

It was found that the mean RAPD value in non-iCRVO was $0.24 \pm$ SD 0.36 log units

of neutral density filters, whilst that in iCRVO was 1.44 ± 0.64 log units [123]. The comparison

between iCRVO and non-iCRVO showed a statistically significant difference [123]. A study

by Servais *et al*. showed that all eyes with ocular neovascularization and/or extensive

capillary non-perfusion had RAPD of ≥ 1.2 log units using neutral density filter, while none

had a RAPD <0.6 log units [267]. A RAPD of ≥ 0.70 log units when using a neutral density

filter as a cut-off provided a sensitivity of 88% and specificity of 90% to diagnose iCRVO

and a RAPD ≥ 0.9 log units provided a sensitivity and specificity of 80% and 97%,

respectively [123]. A different study reported that RAPD ≥ 0.6 log units had a sensitivity of

83% and specificity of 70% for identifying patients with iris neovascularization [31].

Pupillary examination is non-invasive and, as summarized above, appears to be a very useful test to differentiate between iCRVO and non-iCRVO. This test is non-invasive, cheap (the neutral density filters can be purchased for ~$60), easy to undertake, gives reliable information even in the presence of hazy media, may recognize the disease (iCRVO) at an early stage (within days of onset) and is positive throughout the course of the disease [123,197]. However, the test requires a normal optic nerve and pupil in the fellow eye and, in the presence of a large central scotoma, a RAPD may be present even in the absence of iCRVO [123]. Despite the advantages mentioned above, testing for RAPD does not seem to be a routinely used test in the evaluation of patients with CRVO. It would seem important to introduce this test to clinical practice as it would contribute towards the identification of patients with the ischemic form of the disease who are clearly at higher risk of visual loss as well as development of severe complications.

b. Visual fields (VF)

Assessment of visual fields for peripheral retinal function using perimetry has been suggested to be a helpful tool in differentiating between iCRVO and non-iCRVO [123]. With the Goldmann perimeter and I-2e, I-4e, and V-4e stimuli, visual field defects were described in the majority of iCRVO patients [123]. Visual field defects were detected with the I-2e stimulus in 100% of patients with iCRVO, with the I-4-e in 96-100% and with the V-4e in 71-82% during the first year of the disease. In contrast, using I-2e, I-4e and V-4e stimulus visual field defects were present in 54-78%, 38-48% and 12-17% of eyes with non-iCRVO [123]. The sensitivity and specificity of identifying iCRVO with the I-2e stimulus was 92% and 72%, respectively. The sensitivity and specificity of detecting iCRVO with the I-4e stimulus was 95% and 84%, respectively, and 81% and 79%, respectively, for the V-4e [123]. Significant differences between iCRVO and non-iCRVO were observed throughout the whole first year following diagnosis [123]. Automated perimetry, which is the standard test used currently in

clinical practice (the use of Goldman perimetry has been abandoned in most eye clinics) has not been used for differentiating between iCRVO and non-iCRVO.

In eyes with macular BRVO central visual field defects are often detected; major BRVO presents with a peripheral field defect corresponding to the affected retinal quadrant [135]. The visual field defects on central 10-2 Humphrey perimetry are more prominent in cases of iBRVO than in non-iBRVO and can become absolute scotomas in long-standing iBRVO [135].

Visual field testing is time consuming and requires patient's cooperation and adequate fixation, which may be difficult for individuals with poor vision making it unpractical for the testing of all patients with RVO. Indeed, visual field testing is not commonly used for the evaluation of patients with RVO in the clinical setting and it would not be probably recommended with the goal of differentiating between ischemic and non-ischemic forms.

c. Microperimetry

Unlike visual acuity, which only assesses the function of the fovea, microperimetry evaluates the function of the entire macular region and, on this basis it could potentially provide important information on the evaluation of patients with iRVO.

Noma *et al* compared macular sensitivity in patients with iCRVO (n=6) and non-iCRVO (n=4) and found that mean macular sensitivity was lower in iCRVO when compared with non-iCRVO, with mean sensitivity values of 0 dB at 4°, 1 dB at 10° and 2 dB at 20° in iCRVO when compared with 8.25 dB at 4°, 12 dB at 10° and 13 dB at 20° in non-iCRVO [207]. In a study including 41 consecutive patients with unilateral BRVO, it was found that the mean macular sensitivity within the 10° and 20° fields was significantly correlated with the area of non-perfusion as observed on FFA, with higher macular sensitivity in eyes with smaller areas of non-perfusion [204]. Similarly, in another study by Rodolfo *et al*. which

28

included 20 patients with CRVO and 40 with BRVO, macular sensitivity at 8° was significantly influenced by the presence of macular ischemia, with lower sensitivity in patients with macular ischemia when compared to those with no macular ischemia on FFA [251].

Microperimetry may be a useful tool to assess macular sensitivity following treatments of macular edema secondary to RVO [208,209]. In a study including 23 patients with macular edema secondary to RVO, Noma and colleagues found that although at baseline there was a statistically significant lower macular sensitivity within the central 4°, 10° and 20° fields in eyes with iRVO compared with those with non-iRVO, higher recovery was observed in iRVO eyes following treatment with pars plana vitrectomy [208].

At present, there is scarce data in the literature demonstrating the value of microperimetry as diagnostic or prognostic test for the evaluation of patients with iCRVO and iBRVO and, thus, it would not be required routinely for the clinical evaluation of patients with RVO.

d. Electroretinography (ERG)

Findings on full-field ERG have been used to define iCRVO in many studies and have been shown to be a good tool to differentiate between iCRVO and non-iCRVO, as well as to predict the risk of iris neovascularization and neovascular glaucoma (see section II. Definitions, above) [113,123,130,132,139,154,155,161,169,170,190,199,312,315].

It has been reported that the implicit times of the 30 Hz-flicker electroretinograms (ERGs) are significantly correlated with the degree of retinal capillary non-perfusion in eyes with CRVO [139,154,155,169,170]. Hvarfner and associates, in a study including 74 patients with CRVO, reported that 75% of those with an implicit time of >37 ms of the 30Hz flicker ERG developed neovascular complications during a follow-up period of one year when compared

to 7% of CRVO patients with an implicit time of ≤37 ms [129]. Kjeka and colleagues [155] found the mean implicit time of the 30 Hz flicker ERG in patients with iCRVO at baseline to be 39.8 ms (range 35.0-43.9) and suggested a cut-off point of ≥35 to define iCRVO [155]. Kuo *et al.* [162] retrospectively studied 30 Hz flicker ERG in iCRVO (n=11) and non-iCRVO (n=11) and reported that in iCRVO, the mean amplitude was 24μV (± 15μV SD) in affected eyes and 94 μV (± 38 μV SD) in fellow eyes, while in non-iCRVO, the mean amplitude was 79 μV (± 25 μV SD) in affected eyes and 81 μV (± 18 μV SD) in fellow eyes [162]. This study showed that an interocular amplitude difference of 23 μV and an interocular amplitude ratio of 60% were very good cut-off points to differentiate ischemic from non-ischemic CRVO with a sensitivity and specificity of 100% for each of these measures [162] (Table 2).

It was found that in iCRVO, the b-wave amplitude and the b:a ratio are reduced by >60%, when compared to unaffected fellow eye [123]. Hayreh *et al.* found that, for both, photopic and scotopic ERG, the b-wave amplitude had a sensitivity of 80-90% and a specificity of 70-80%, and the b:a amplitude ratio a sensitivity of 60-70% and a specificity of 70% during the early acute phase (59% of cases evaluated within the first 3 months from onset) for the diagnosis of iCRVO [123]. Williamson *et al.* [312] found that the b:a ratio of the photopic ERG appeared to be the best predictor of iris neovascularization in patients with CRVO with a sensitivity of 87.5% and specificity of 78% (Table 2). It was reported also that a photopic b-wave amplitude of 56 μV gives a sensitivity of 87.5% and specificity of 86% to discriminate patients at risk of iris neovascularization, while 76 μV gives a sensitivity of 100% and specificity of 66% [312].

Serial full-field ERG testing, obtained within less than 24 hours after the onset of symptoms and every second to third day during the first three weeks of follow-up and during a period of six months, showed that the ERG in people with CRVO changes over time and is unstable during the first three weeks. As a result, it was recommended that the optimal time

30

to perform ERG to predict development of iris neovascularization in patients with CRVO is after three weeks from the onset of symptoms [171].

Comparison between FFA (≥10 DA of capillary non-perfusion) and full field ERG (b-wave implicit time in the 30 Hz-flicker ERG >37 ms) in 32 patients with CRVO who were followed for at least one year showed that iris neovascularization could be predicted in 82% of patients using FFA, but in as high as 94% using full field ERG [168].

In a prospective cohort study including 25 consecutive patients with hemicentral RVO six (24%) developed retinal/disc neovascularization 3-12 months following RVO onset [130]. The mean photopic b-wave implicit time (±SD) was 37.7±1.3 ms (range: 36.4-39ms) in people that develop neovascularization when compared with 34.0±4.6 ms (range 31.8-36.2) in those that did not [130]. This study did not classify patients into ischemic and non-ischemic forms [130].

A study conducted in 62 patients with cystoid macular edema secondary to BRVO found that the implicit time of the photopic negative response of the photopic ERG was significantly correlated with the area of non-perfused retina (mean 44.3±SD 3.2 ms in BRVO vs mean 41.9± SD 2.2 ms in unaffected fellow eye) [206]. However, there was no significant correlation between other photopic full field ERG parameters and the area of non-perfusion [206].

Multifocal ERG has been used also in the evaluation of patients with RVO demonstrating local macular retinal dysfunction [7,132]. The implicit times of the multifocal ERG are prolonged in ischemic macular BRVO (defined by a break of ≥50% of perifoveal capillaries) (n=13) (31 ± SD 2 ms) compared with the non-ischemic form (n=12) (29 ± SD 2 ms) [132] and the amplitudes are reduced (ischemic macular BRVO 10 ± SD 6 nv compared with non-ischemic cases 19 ± 13 nv) [132]. Similar findings was observed by Abdel-Kader et

31

al.[7], in which macular ischemia was defined broken perifoveal ring. Clear cut off values in any of the parameters of the multifocal ERG that could be used clinically to differentiate between iBRVO and non-iBRVO are not available.

Full field ERG is a non-invasive diagnostic technology that, as summarized above, appears to be very informative in the evaluation of patients with RVO specially to distinguish those with iCRVO at higher risk of developing neovascular complications. However, full field ERG is time consuming and requires equipment and trained staff able to undertake and interpret its results. Likely, for these reason, full field ERG is not obtained routinely in clinical practice for the evaluation of patients with RVO. New handheld ERG devices, which are easy to use and interpret and which have allowed reduced testing time, should facilitate the introduction of the use of ERG more routinely in clinical practice [318].

e. Oximetry

Few studies have been conducted evaluating the oxygen saturation in retinal vessels using oximetry; this test has been suggested to be of value in the assessment of patients with RVO.

It has been shown that in eyes with CRVO the oxygen saturation in the retinal venules is lower than that in fellow unaffected eyes [76,103], whereas in retinal arterioles, it is similar to or even higher [103]. Specifically, in iCRVO the oxygen saturation within the central retinal vein appears to be significantly lower (<40%) than that in healthy eyes (60-70%) [320].

In a prospective controlled interventional study, oxygen partial pressure (PO2) was measured in patients with iCRVO (n=6) and in those with macular hole or epiretinal membrane (n=6), which were used as controls [314]. It was found that in iCRVO the mean pre-retinal and mid vitreous cavity PO2 was lower (8.1 ± SD 3.5 mmHg and 19.8 ± SD7.3 mmHg, respectively) than that in controls (15.0 ± SD 5.7 mmHg and 33.7 ± 12.8 mmHg, respectively) [314].

32

Oximetry has been used to evaluate the response to therapy in RVO (e.g. following anti-VEGF treatment and vitrectomy) [283,298,314]. Oxygen saturation in retinal veins of non-iCRVO eyes was found to be improved to levels closer to normal values after anti VEGF treatment and this increase was associated with improved visual acuity and reduction in macular edema [298]. No studies were identified evaluating oxygen saturation in retinal arteries and veins in eyes with iCRVO following treatment.

Oxygen saturation in BRVO appears to be highly variable in both iBRVO and non-iBRVO, which may reflect severity of disease, degree of venous occlusion, recanalization, collateral vessels, tissue atrophy, arteriovenous diffusion or vitreal transport of oxygen [104,178].

Further studies, specifically longitudinal cohort studies, are required to better understand the correlation between changes in oxygen saturation in retinal blood vessels and disease severity and prognosis. Prospective longitudinal studies evaluating the ability of oximetry to identify patients with iRVO at risk of developing neovascular complications, as well as changes in oxygen saturation occurring following treatment that may predict a long-term treatment response and improved outcomes would be beneficial. The use of oximetry in clinical practice is not yet widespread; however, as oximetry is a simple, fast and non-invasive test requiring only imaging of the fundus, it could be easily introduced to clinical practice once its clinical applicability in the evaluation of patients with RVO is demonstrated.

f. Retinal blood flow

Retinal blood flow can be estimated using various technologies including color Doppler imaging (CDI), laser doppler flowmetry and doppler fourier-domain optical coherence tomography (OCT) [17,18,20,26,282,296,307,310]. It has been suggested that measures of blood flow are helpful in evaluating the severity of RVO and differentiating between iCRVO and non-

iCRVO [17,18], although at present time the usefulness of this technology to establish this differentiation remains controversial [20,26,296,310].

Venous flow velocities were found to be significantly lower in iCRVO than in non-iCRVO [17,26,296]. Tranquart *et al.* reported that means of minimum and maximum venous flow velocities using CDI were statistically significantly lower in iCRVO (n=18) (1.83 ± SD 0.94 and 2.94 ± SD 1.34 cm/s, respectively), than in non-iCRVO (n=50) (2.28 ± SD 0.73 and 3.66 ± SD 1.19 cm/s, respectively) [296]. Using CDI, a brief decrease in arterial diastolic velocity was measured in patients presenting with iCRVO, which correlated with arteriovenous passage time on FFA [17]. The impairment in venous blood flow velocity in CRVO was found to be persistent whereas the changes in the arterial velocity recovered rapidly [17]. Using a confocal scanning laser doppler flowmeter, Arvas *et al.* [18] found that the blood flow of the supero-temporal retina (one of the areas selected for the measures of blood flow) was statistically significantly lower in patients with iCRVO (n=12) than in fellow eyes or eyes of healthy volunteers, whereas it was not significantly different at the macula [18].

A study which included 10 patients with ischemic macular BRVO found a statistically significant reduction in the overall retinal blood flow when compared with healthy controls, as measured using the Heidelberg retinal flowmeter (HRF), in most patients tested (n=7) [282]. Other studies including patients with iBRVO and non-iBRVO failed to identify differences in blood flow between RVO and fellow unaffected eyes; these studies did not provide separate data, however, for iBRVO and non-iBRVO [17,296].

At the present time, literature is still scarce on the potential benefits of using measures of retinal blood flow in the evaluation of patients with iRVO. As its value is yet to be demonstrated and due to lack of availability of the instrumentation required in most eye

34

clinics, measures of retinal blood flow would not be recommended currently for the clinical evaluation of patients with RVO.

g. Ocular surface temperature

Although ocular surface temperature (OST) is affected by many factors such as body and environmental temperature, it has been suggested that it could be a useful tool to assess the severity of CRVO, being potentially a good indicator of the blood flow in the posterior segment [277]. OST is an easy and non-invasive test that is undertaken using infrared thermography. OST is measured at five anatomical points: 1) the medial canthus, 2) half-way from the medial canthus and nasal limbus, 3) the center of the cornea, 4) half-way from the temporal limbus and lateral canthus and 5) at the lateral canthus. The center of the cornea was found to be the best indicator of the blood flow of the posterior segment and the most reliable measure in CRVO, since it is avascular and the point influenced least by the conjunctival blood vessels [277]. In a study including 36 patients with CRVO it was found that the mean OST at the center of cornea in iCRVO (n=9) was statistically significantly lower (mean 34.7± SD 0.66) than in non-iCRVO (n=27) (mean 35.3± SD 0.50) [277]. OST has not been used to evaluate BRVO. Given that this study included only a small number of patients and that results have not been confirmed by other studies the value of SOT in the evaluation of patients with RVO remains to be elucidated.

h. Ophthalmodynamometry

Ophthalmodynamometry is an easy and non-invasive test that allows measuring the pressure in the central retinal artery and central retinal vein. It has been suggested that ophthalmodynamometry can be used to differentiate iCRVO from non-iCRVO [140,141,194]. McAllister et al. [194] studied 88 patients with iCRVO and found an association between elevated central venous pressure and low visual acuity, reduced retinal blood flow, larger area

35

of capillary non-perfusion and incidence of rubeosis iridis [194]. In a study by Jonas [140] which included 15 patients with CRVO and 4 patients with BRVO, the central retinal vein collapse pressure was, on average, 1.8 times greater in iCRVO (n=8) than in non-iCRVO (n=7). Central venous pressure was significantly higher in iCRVO (103± SD 25.4 AU) (AU=arbitrary units) than in non-iCRVO (mean 58.1± SD 37.5 AU) and BRVO (mean 43.8±SD 25.5 AU) [140], whereas the pressure in the central retinal artery was significantly lower in iCRVO than in non-iCRVO [140]. These results were replicated in another study which included 28 patients with CRVO (7 with iCRVO and 21 with non-iCRVO) and demonstrated that central retinal venous pressure was statistically significantly higher in iCRVO than in non-iCRVO (mean 91.5 ± SD 30.1 AU vs 52.4 ± SD 32.5 AU) [141]. Central retinal venous pressure was higher than the diastolic central retinal arterial pressure more frequently in the iCRVO (7/7 or 100%) than in the non-iCRVO (8/21 or 38%) [141]. Central retinal arterial pressure was significantly lower in iCRVO (46.0 ± 10.6 AU) than in non-iCRVO (64.5 ± 22.8 AU) [141]. The finding of higher pressure in the central retinal vein when compared with the diastolic pressure of the central retinal artery appears to be characteristic of the ischemic form of CRVO and could potentially be used to establish this diagnosis [141,194]. Furthermore, ophthalmodynamometry appears to be helpful to predict visual outcomes in patients with CRVO [68]. Thus, in a study including 73 patients with CRVO a high venous collapse pressure (VCP) in the central retinal vein of 100 gm or greater and a VCP greater than the arterial collapse pressure (ACP) appeared to be predictive of a worse visual outcome [68].

The above studies suggest that ophthalmodynamometry aids in the differentiation between iCRVO and non-iCRVO and provides prognostic information. This test is not part, though, of the routine clinical evaluation of patients with RVO. However, a simplification of this test is commonly used by clinicians to elucidate whether or not the venous pressure is

increased in patients with CRVO. It relays on the clinical maneuver of exerting pressure on the eye at the same time that the blood vessels are visualized by slit-lamp biomicroscopy. As the pressure in the eye is increased (by pressing on the eye) the central retinal artery may collapse at the same time or even before the central retinal vein does, indicating very high venous pressure (venous pressure in normal circumstances is much lower than that in arteries and, thus, veins should collapse earlier than arteries when pressure is exerted on the eye).

2.   *Structural tests*

a.   Fluorescein angiography

As discussed in section II. Definitions (above), fundus fluorescein angiography (FFA) is the most widely used test to establish the diagnosis of iRVO. Indeed, FFA allows the direct visualization of blood vessels and blood flow in the retina. FFA provides very useful information on the vascular status of the retina, presence of neovascularization, presence/ absence of delayed venous filling, presence/absence of retinal leakage (from breakdown of the inner or outer retinal barriers) and retinal edema and presence/absence of areas of retinal capillary non-perfusion (Figures 1 & 2).

On FFA more prominent leakage and retinal capillary dilatation are often observed in iCRVO and iBRVO than in the non-ischemic forms [85,181].   In RVO, diffuse hyperfluorescence is detected in the area affected by retinal edema in the late phase of the FFA [265]. If there is no marked intra-retinal hemorrhaging, FFA will demonstrate capillary telangiectasis, dilated collateral vessels and a petaloid pattern of hyperfluorescence from cystoid macular edema, if these features are present [265]. Marked hyperfluorescence will be seen at the site of new vessels in the retina and optic nerve head, with blurring of their margins in late phases of the FFA [265]. Hypofluorescence is present in areas of capillary non-perfusion [265].

Most clinicians and researchers use the extent of the area of retinal capillary non-perfusion as the main determinant of the differentiation between ischemic and non-ischemic RVO; most, following the criteria provided by the CVOS and BVOS (i.e. > 10 DA of capillary non-perfusion = iCRVO; > 5DA of capillary non-perfusion = iBRVO) [2,6]. It appears that the risk of developing neovascular complications, and thus, of having a more guarded prognosis, relates chiefly to the presence/extension of the area of retinal ischemia. It was reported that 16% of eyes with CRVO and area of retinal capillary non-perfusion on FFA of 10-29 DA developed anterior segment neovascularization; this risk increased to 43% and 52% in eyes with ≥30DA and ≥75 DA of capillary non-perfusion, respectively [6]. A study by Margargal and colleagues found that 33% and 45% of eyes with CRVO with an ischemic index ≥50% (which in their study corresponded to ≥10 DA) developed retina/disc or neovascular glaucoma, respectively [181]. 93% of eyes with neovascular glaucoma and 91% of eyes with retina/disc neovascularization secondary to iCRVO had ischemic indices of ≥50% [181].

Wide angle FFA (WA-FFA) appears to be particularly helpful in the evaluation of patients with RVO as this imaging technology allows for the visualization of the peripheral retina, in addition to the macula and midperipheral retina, which is believed to be the first area affected by ischemia in RVO [11,239,290,322]. Using WA-FFA, Tsui, et al. [300] studied 69 eyes with CRVO and correlated the ischemic index (see section II. Definitions, above) with the presence of neovascularization. The mean (±SD) ischemic index was 25 (± 26%); eyes with neovascularization had a mean ischemic index of 75% (range, 47-100%) compared with eyes without neovascularization that had an ischemic index of 6% (range, 0-43%) [300]. The average ischemic index of eyes with anterior segment neovascularization was 78% and the average ischemic index of eyes with retinal neovascularization was 72% (SD, 20%; range, 47–99%). It was found that the ischemic index significantly correlated to the presence of

38

neovascularization, and eyes that had evidence of neovascularization had an ischemic index >45% [300].

WA-FFA was used to evaluate the extent of retinal ischemia in 12 out of 20 patients with iCRVO included in RAVE (for further details on this trial, see section IX. Management and outcomes, below). In this study, iCRVO was defined by the presence of three out of four criteria: BCVA ≤20/200, loss of I-2e isopter on Goldman visual field, RAPD ≥0.9 log units and b-wave reduction to ≤60% of the corresponding a-wave. The mean total field of gradable retina was 290 DA (range, 178–452 DA) with a mean area of retinal non-perfusion of 184 DA (range 141-323 DA) which is approximately 63.4% of the total area of the retina [317].

Recently, a stereographic projection software was introduced by Tan et al. to calculate "anatomically correct" area of retinal non-perfusion and total area of visible retina on WA-FFA in mm^2 [290]. WA-FA images cannot be mapped onto a flat surface without a resultant warp of the image; this is due to the projection from three-dimensional (retina) to two-dimensional (retinal image) by preserving directionality from a central point. This method presents vascular landmarks accurately, but at the cost of increasing distortion of size and shape at the periphery. Tan et al. used the stereographic projection software to determine the anatomically correct area of retinal non-perfusion and total area of visible retina in mm^2 in 32 patients with RVO; the authors also determined how the former compared with the "uncorrected" ISI, previously used in other studies [290]. The ISI was determined by using the central FFA image (image centered in the macula) obtained with the Optos 200Tx (Optos, Dumfermline, UK) and by manually outlining areas of capillary non-perfusion and total area of visible retina using the GRADOR software, which automatically provides the number of pixels within these established regions. Using the stereographic projection software the regions determined by the above method were then evaluated and "corrected" to determine the "anatomically correct" area of retina on these. No statistically significant differences

were found between the "uncorrected" ISI (% of non-perfused retina from total area of retina measured) and the "corrected" non-perfusion %. The "corrected" area of non-perfusion measured in mm^2 also correlated well with the "uncorrected" ISI. The median total area of visible retina was 690.6 mm^2 and ranged from 559.4-797.7 mm^2.

WA-FFA was used in a study including 32 patients with RVO, 13 with CRVO and 19 with BRVO [274] and demonstrated that peripheral non-perfusion at baseline correlated with both baseline retinal thickness and the magnitude of reduction of edema, on SD-OCT, following ranibizumab or dexamethasone treatment [274]. An area of non-perfusion of >10% of the total retina on WA-FFA in both CRVO and BRVO patients was statistically significantly associated with worse macular edema and worse visual acuity [274].

WA-FFA appears to be an even more valuable tool than standard FFA to image retinal ischemia in RVO, likely to detect it at earlier stages, and to predict the likelihood of development of complications [274,300]. It should be noted, however, that properly conducted diagnostic studies comparing these two diagnostic technologies (standard FFA and WA-FFA) for the evaluation of retinal ischemia in RVO are not available. However, given that the availability of WA-FFA in clinics is increasing and that a larger extension of retina is imaged with this technology when compared with standard FFA, it would seem appropriate to incorporate its use for the evaluation of patients with RVO. Using standard fundus cameras, it was reported that the detection of areas of capillary non-perfusion could be compromised by the presence of marked and extensive intra-retinal hemorrhages. This is likely to be less of a problem now when using wide-angle scanning laser ophthalmic systems. If WA-FFA is obtained using scanning laser, the amount of fluorescein required to undertake this test is also reduced (good quality angiograms can be obtained with 2ml of fluorescein, from 1g in 5 ml vial), which would be expected to reduce the potential rare side effects of this test. WA-FFA appears to be widely accepted for this purpose [274,290,299,317].

Iris fluorescein angiography has been used also for the evaluation of patients with RVO and for the differentiation between ischemic and non-ischemic forms. In a study comparing patients with iCRVO (n=24) and non-iCRVO (n=24) it was found that all patients with iCRVO have dilation of the iris vessels and leakage independently of the presence or absence of iris neovascularization, while in non-iCRVO, no or minimal changes in the iris vasculature were observed [164].

b. Spectral domain optical coherence tomography (SD-OCT)

SD-OCT is widely used in the evaluation of patients with RVO [36-38,43,45,137,215,264]. SD-OCT allows to examine the integrity of the different retinal layers and to determine overall thickness of the central retina, individual thickness of the retinal layers and the presence of cystic intraretinal edema and subretinal fluid secondary to RVO [36-38,43,45,137,215,230,264]. SD-OCT is routinely used in clinical practice and has been used to evaluate changes in central retinal thickness in patients included in RVO trials (RAVE, COPERNICUS, GALILEO, VIBRANT, BRAVO, CRUISE, SCORE; details on these studies can be found in section VIII. Management of iRVO and outcomes following treatment, below). Central subfield thickness (CST) on SD-OCT is commonly used to determine the response to current therapies for macular edema secondary to RVO [36-38,43,45,137,215,230,264].

The mean CST on SD-OCT at baseline was reported to be statistically significant greater in patients with iCRVO (n=203) (499.65 µm) when compared with those with iBRVO (n=354) (444.38 µm) in one study; both iCRVO and iBRVO were defined by the presence of ≥ 5 DA of capillary non-perfusion [173]. In a retrospective study by Martinet *et al* [188], which included 53 consecutive patients with CRVO and in which macular ischemia was defined as an enlarged foveal avascular zone (larger than 1000µm) or a broken perifoveal capillary ring,

41

CST was greater in ischemic macular RVO (mean 754µm; SD not provided) when compared with non-ischemic macular RVO (mean 520µm; SD not provided). Macular ischemia was also associated with absent/incomplete IS/OS line on SD-OCT in 73% of eyes during the follow-up (mean follow-up 13 months; range 1-66 months) as well as with RPE atrophy or RPE fibrosis at last follow up [188]. Furthermore, a CST of 700 µm or greater appeared to be associated with peripheral ischemia, poor visual prognosis and irreversible damage to photoreceptors cells [188]. Some of the patients included in this study (n=11) received panretinal or grid laser photocoagulation therapy; none received intravitreal therapy [188].

In a study on patients with BRVO, a non-ischemic maculae (n=13) (defined as absence of any distinct area of capillary non-perfusion within one disc diameter of the center of the fovea) had an early and more rapid drop in CST during a follow-up of six months (and without intervention) when compared with an ischemic maculae (n=7) (defined as presence of any distinct area of capillary non-perfusion within one disc diameter of the center of the fovea)[272]. The presence of a visible IS/OS and external limiting membrane on SD-OCT, which indicates the integrity of the photoreceptor cell layer, was correlated with a more favorable visual prognosis in patients with BRVO [221].

SD-OCT provides an indication of damage/atrophy of photoreceptors as well as NFL, GCL, inner plexiform layer (IPL) and inner nuclear layer (INL) in the advanced stages of iCRVO and iBRVO, all of which have been associated with poor prognosis [175,176]. A loss of foveal IS/OS and a larger defect in the external limiting membrane at presentation, and a loss of inner retinal layers at six months' follow-up in patients with iCRVO correlated with poorer final visual outcomes [176,221]. In CRVO, macular ischemia, as detected by FFA, correlated with reduced CST when macular edema is absent, and loss of *inner* retinal layers in early stage (three months) and with presence of intraretinal fluid and loss of inner retinal layers in late stage (six months) on SD-OCT images [176]. In iBRVO, the thickness of the GCL and

NFL (mean 86.26 ± SD 5.95 and 95.53 ± SD 8.87 µm, respectively) appeared to be significantly reduced when compared with non-iBRVO (mean 79.03 ± SD 7.84 µm and 88.83 ± 8.96 µm, respectively) [175].

c. <u>Optical coherence tomography angiography (OCT-A)</u>

Unlike FFA, OCT-A is a non-invasive (i.e. does not require the injection of a dye) imaging modality that allows the visualization of retinal blood vessels [53,151,263]. Using the split-spectrum amplitude decorrelation algorithm (SSADA), detection of blood motion within the vascular lumen can be achieved by measuring the variation in reflected OCT signal amplitude between consecutive cross-sectional B-scans; high quality angiograms of the retina and choroid can be, in this manner, generated [53,151,263]. Superficial and deep retinal capillary networks can be separately visualized using OCT-A. This technology, however, has a smaller field of view than conventional FFA or WA-FFA [53,151,263,279].

It has been suggested that OCT-A may be useful for the evaluation of areas of capillary non-perfusion, non-perfused vessels, vascular density and FAZ morphology in patients with RVO [59,203,214,251,259,260,287]. OCT-A is the first imaging technology that enables a selective evaluation of the deep retinal capillary network, which, for unexplained reasons, seems to be more severely affected than the superficial capillary network in CRVO and BRVO [59].

A retrospective study by Coscas and colleagues including 54 RVO patients (29 with CRVO and 25 with BRVO) and comparing OCT-A with FFA and SD-OCT suggested that OCT-A may provide a better rate of detection of cystoid spaces, macular edema and disruption of perifoveal capillaries than FFA and SD-OCT [59]. Cardoso et al. [203], in a retrospective study including 76 patients (81 eyes) with RVO [CRVO (n=40 eyes), HRVO (n=7 eyes) and BRVO (n=34 eyes)], 36 (44%) of which were of the ischemic type (no

43

definition of iRVO given) and in which images were adequately assessed in an independent manner by a masked grader (i.e. the results observed in an imaging modality would not be affecting the reading of a subsequent imaging modality) found good agreement between FFA and OCT-A for determining the area of ischemia and for grading of the foveal avascular zone when using 3x3 mm OCT-A scans but poor when using 8x8 mm OCTA scans. Artifacts appeared to be a major limitation of OCT-A with non-gradable images in 28% and 15% of cases for 3x3 mm and 8x8 mm scans, respectively [203] when compared with 3% for FFA. Motion artifacts and media opacity appeared to be a major contributing factors to obtaining good quality images on OCT-A [203]. Restrictions of OCT-A in identifying features of ischemia and retinal new vessels when present outside the 8 mm scan where noted [203].

Using OCTA it was found, in a retrospective study including 12 patients with RVO (eight with BRVO, six of these ischemic; and four with CRVO, one of these ischemic), that the FAZ in the deep retinal capillary network was enlarged in eyes with RVO when compared with fellow unaffected eyes [287]. The vascular density in the macular region as detected with OCT-A was found to be significantly lower in eyes with CRVO and BRVO, affecting both superficial and deep capillary networks, than in fellow eyes; differences between ischemic and non-ischemic forms were, however, not sought [91,260]. In a prospective study including 21 eyes of 21 patients with CRVO, disruption of the ellipsoid zone was significantly correlated to a larger FAZ area in the superficial retinal capillary plexus and poorer visual acuity [259].

To date, studies using OCT-A for the evaluation of patients with RVO are scarce, the majority retrospective and including small number of patients. The technique, however, appears to be promising to determine the area involved by edema as well as areas of non-perfusion. OCT-A has some limitations currently including the small field of view and the fact that images are prone to artefacts; these drawbacks will likely be overcome in the future

44

by further development of the technology. In this regard, a recently develop technique refer to as "extended field imaging technique" (EFI) using trial frames fitted with a +20 diopter lens, seems to provide adequate OCT-A images of a larger area of the fundus, on average 188.5% more than those without EFI [152].

Prospective, adequately powered diagnostic studies are required to determine the value of OCT-A and OCT-A EFI for the diagnosis and evaluation of patients with iCRVO and iBRVO as well as to determine how this technology compares with other imaging modalities available such as FFA and wide-angle FFA. The major restriction of OCT-A for its use in RVO, at present, is the small field of view; however, it would seem very useful for the evaluation of the perifoveal capillary network.

d. Fundus autofluorescence (AF)

Fundus autofluorescence (AF) is a non-invasive imaging modality that provides information on the status of the RPE and, indirectly, of the photoreceptors [89]. Given that the outer retinal barrier can be affected by iRVO (see section V. Etiology and Pathogenesis, above) it could be envisaged that AF could be useful in the evaluation of patients with this disorder. Indeed, foveal AF has been found to serve as a prognostic indicator in patients with RVO [28,221,265,266]. There have been, however, no studies evaluating fundus AF specifically in iRVO.

3. *Patients reported outcomes (PRO)*

Studies have shown that both CRVO and BRVO are associated with a significant decrease in vision related quality of life using the 25 item National Eye Institute Visual Function Questionnaire (NEI VFQ-25) [21,67]. The NEI VFQ-25 provides scores for 12 subscales: general health, general vision, near vision, distance vision, driving, peripheral vision, color

vision, ocular pain, role limitations, dependency, social functioning and mental health, in addition to an overall composite score [187].

NEI VFQ-25 scores are significantly lower in patients with CRVO and BRVO than in people with no ocular disease [21,67]. Scores were significantly lower in people with bilateral CRVO than in those with unilateral disease [67]. NEI-VFQ-25 scores in patients with BRVO were significantly higher in all subscales when compared with those in patients with CRVO [21]. NEI VFQ25 scores appear to be driven, predominantly, by the visual acuity in the better-seeing eye [67]. However, a decrease in NEI VFQ-25 score in BRVO correlated with visual acuity in the affected eye, even when there was good visual acuity in the non-affected fellow eye [21].

There have been no studies evaluating visual-related quality of life, using the NEI-VFQ25, or health-related quality of life, using the EQ-5D (a health-related quality of life questionnaire consisting of five domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression) specifically in patients with iRVO and how these compare with non-iRVO.

VII.   Natural History

A.   Ischemic CRVO

The CVOS reported that untreated patients who had poor visual acuity at presentation (≤20/200) had an 80% chance of having final visual acuity of ≤20/200, whether perfused or non-perfused initially [6]. In an large observational natural history study (iCRVO=109; non-iCRVO= 588 eyes) by Hayreh and colleagues, final visual acuity, on resolution of macular edema, was reported to be 20/100 or better in 83% in non-iCRVO when compared to 12% in iCRVO. Thus, in over 80% of patients with iCRVO visual acuity remained poor even after

resolution of macular edema [119]. Thus, the iCRVO phenotype appears to confer a more guarded prognosis. In eyes with initial visual acuity of 20/70 or worse, visual acuity improved, on resolution of the macular edema, in 59% of the non-iCRVO eyes, with no significant improvement in eyes with iCRVO [119]. This study showed that 90/146 (60%) of patients with non-iCRVO had a visual acuity >20/40 after resolution of macular edema in comparison to 0/13 (0%) of those with iCRVO during a follow-up of 2-5 years [119]. The median time to resolution of macular edema was found to be 29 months for patients with iCRVO and 23 months for those with non-iCRVO [119].

COPERNICUS reported improvement of ≥15 ETDRS letters in only 4.3% of untreated patients with iCRVO at six months follow up [38] (See section VIII. Management and outcomes following treatments, below, for more details on this study). Another study by Laatikinen *et al.* [165] showed improvement of ≥2 Snellen lines in the same proportion, 4.3% of untreated patients with iCRVO at 12 months follow-up [165]. Kjeka *et al.* [155] reported change of mean visual acuity from 1.95 to 2.74 LogMAR during a mean period of 41 months of follow-up in patients with untreated iCRVO (range 26-63 months) [155].

A large prospective cohort study by Hayreh and Zimmermann, which involved 239 eyes with iCRVO [117], reported that the cumulative probability, within 6 months of onset, of development of neovascularization was 49% in the iris, 37% in the anterior chamber angle, 6% in the disc and 9% in the retina. At 12 months, the corresponding rates were 10% for neovascularization in disc and 12% in retina [117]. CVOS reported that 35% of untreated eyes with iCRVO developed anterior segment neovascularisation during the first 12 months [6]. The overall incidence of posterior segment neovascularization at 3 years was 33% in a cohort study reported by Magargal et al, which included 86 eyes with iCRVO, 85 eyes with non-iCRVO and 29 eyes with indeterminate RVO [181].

In the CVOS, untreated iCRVO showed an increase in the area of retinal capillary non-perfusion, from a median of 50 DA at baseline to 111 DA at the visit at which anterior segment neovascularization developed, in comparison to a median increase in non-perfusion of only four DAs in those who did not develop anterior segment neovascularization at the first annual visit [6]. The greatest risk of developing anterior segment neovascularization in eyes with iCRVO appears to be during the first year of follow up (usually within the first three months) in untreated iCRVO patients [6]. Hayreh et al. reported that anterior segment neovascularization commonly develops during the first 6-7 months following diagnosis of iCRVO [117,122].

The cumulative probability of development of neovascular glaucoma in eyes with iCRVO was reported by Hayreh and Zimmerman to be 29% within 6 months of onset [117] and by Magargal et al to be 60% within 24 months of onset [182]. Vitreous hemorrhage was reported in 10% of iCRVO by nine months after onset of the occlusion [196]. Hayreh et al reported that 9/67 (~13%) of untreated patients with iCRVO developed vitreous hemorrhage during a follow-up of 10 years [121]. Vitreous detachment was identified in 38 out of 52 (73%) iCRVO eyes; patients with complete vitreous detachment did not develop vitreous hemorrhage in comparison with 57% in whom absent or incomplete vitreous detachment was detected [125]. Retinociliary collaterals developed in 41% of patients with iCRVO in a median period of 13 months [119].

In an observational natural history study including 67 patients with hemicentral RVO classified into ischemic and non-ischemic [115] (for definition, see II. Definitions), Hayreh and Zimmerman found that when the presenting vision was $\geq$ 20/60, 75% of patients maintained or experienced improvement in vision; if the presenting vision was $\leq$ 20/70, visual acuity improved in 60% [115].

48

The incidence of neovascularization in patients with hemicentral RVO at 12 months follow up was reported to be 12%, 10%, 12% and 29% in iris, anterior chamber angle, disc and retina, respectively [117]. Neovascular glaucoma was reported to occurred in 5% of eyes within 6 months of onset [117].

B.   Ischemic BRVO

Although information on the natural history of BRVO is available [118,253], there is very scarce data specifically on iBRVO; this applies to most aspects of this type of RVO.

A study by Parodi et al. [228] showed that none of the untreated patients with exudative retinal detachment secondary to iBRVO (defined by presence of ≥5 DA of retinal capillary non-perfusion on FFA) gained ≥3 Snellen lines of visual acuity whereas 93% lost ≥3 Snellen lines during a follow-up of 24 months [228] (Parodi et al. 2008). However, reabsorption of exudative retinal detachment was observed in all patients after a mean of 15.8±3.4 months follow-up [228].

Finkelstein followed a group of 30 patients (30 eyes) with macular edema secondary to BRVO; 23 patients with macular capillary non-perfusion (20 of which had a broken perifoveal capillary ring) and seven with good macular perfusion (one of the latter had a broken perifoveal capillary ring). Finkelstein found that a greater improvement in visual acuity occurred in eyes with macular ischemia, which achieved a median final visual acuity of 20/30, when compared with eyes with a perfused macula (29%), which achieved a median final visual acuity of 20/80, after a mean follow up of 39 months [85].

According to BVOS study, 41 % of untreated patients with at least 5 DA of retinal capillary non-perfusion (group X) developed neovascularization (unspecified) during the follow-up [2]. A cohort study by Hayreh et al. [122] reported the incidence of neovascularization in eyes with major BRVO to be 1.6%, 0.5%, 11.5% and 24.1% in the iris,

49

anterior chamber angle, disc and retina, respectively (range 3 months-20 years)".

Approximate incidence of retinal and disc neovascularization, extracted from Kaplan-Meier

survival curves presented in this study, were 10% at ~2 years and 20% at ~4 years,

respectively[122].   Vitreous hemorrhage developed in 61-73% of patients with iBRVO and

neovascularization during follow-up periods between 2-4 years, [2,111] with 28% of patients

with untreated retinal or disc neovascularization experiencing recurrent vitreous hemorrhage

[111].

VIII.   Management and outcomes following treatments

A.   Current treatments of ischemic RVO

Currently, there is no effective treatment for patients with iRVO. The present

therapeutic options are aimed at treating the complications of iRVO, namely macular edema

and neovascularization and its results, rather than at re-vascularizing the ischemic retina

[33,86,87]. Local treatments include laser photocoagulation, intravitreal anti-VEGF,

corticosteroids and vitrectomy, or combination of these therapies. Each of these treatments

has advantages and inconveniences as well as potential complications; these are reviewed

below.

Management of underlying medical conditions is important [150]. Therefore, it is

recommended to evaluate patient's medical history, blood pressure, serum glucose, lipid

profile, full blood cell count (FBC) and erythrocyte sedimentation rate (ESR) "A,H".

Patients with iRVO will require follow-up at different intervals depending on the type

of occlusion (CRVO or BRVO), presence/absence and severity of retinal non-perfusion,

presence/absence of complications or high risk of developing them, and the requirement and

type of treatment selected.

Monthly follow up during the first six months was recommended for patients with iCRVO, with slit lamp examination and gonioscopy, to detect signs of anterior segment neovascularization [6]. Follow-up would be guided by whether or not complications develop and by the need for treatments and type of therapy chosen (see below) [H]. Similarly, the follow-up in patients with BRVO would be determined by clinical findings, such as the presence or absence of macular edema or neovascularization and the need and type of treatment selected (see below) [40].

1. *Treatment for macular edema secondary to iRVO*

Treatment for macular edema secondary to iRVO includes macular laser photocoagulation, intravitreal injections of anti-VEGF, local corticosteroid therapies and vitrectomy. Ten studies on CRVO (2 RCTs and 8 prospective interventional studies) and nine studies on BRVO (5 RCTs and 4 prospective interventional studies) which addressed outcomes of these therapies on the ischemic form of RVO were identified and included in this review and are summarized below.

a. Macular laser photocoagulation

The CVOS and BVOS were the first large, randomized clinical trials (RCTs) evaluating the effect of laser treatment in patients with CRVO and BRVO [1,4]. The CVOS did not find macular laser photocoagulation of value for the treatment of macular edema secondary to CRVO [4]. The CVOS (group M) [4] excluded patients with macular non-perfusion (no definition of macular non-perfusion was given), retinal new vessels and vitreous hemorrhage; among the included eyes only 21/155 (14%) had ≥10 DA of retinal capillary non-perfusion on FFA (13 treated and 8 untreated) and the outcomes of macular laser were not addressed separately for ischemic and non-ischemic cases. In contrast, for patients with macular edema secondary to BRVO, laser photocoagulation was proved to be beneficial [1]. The BVOS

recommended macular laser after three months of the onset of symptoms, given the possibility of spontaneous resolution of the macular edema during this period of time, in patients with visual acuity of 20/40 or worse with absence of foveal capillary non-perfusion on FFA and absence of blood involving the fovea [1]. Retreatment was required in some patients (range, 1-5 treatments given) when macular edema persisted [1]. The BVOS showed a mean 3-year improvement of 1.33 Snellen lines of vision following macular laser in comparison to 0.23 lines of vision in untreated patients; visual acuity improved > 2 Snellen lines in 65% of patients and 60% attained visual acuity of > 20/40 or better, in comparison to 37% and 34% of untreated patients, respectively [1]. The BVOS [1] excluded patients with foveal non-perfusion and outcomes of macular laser were not given specifically for the group with iBRVO [1].

Macular laser photocoagulation has been proposed as a potential treatment for patients with iBRVO, defined by the presence of ≥ 5 DA of retinal capillary non-perfusion on FFA, and exudative retinal detachment based on the results of a small (n=31) prospective RCT [228]. In this study, 16 patients were assigned to grid laser photocoagulation and 15 to observation. A visual acuity improvement of > 3 lines on ETDRS charts was observed in 37% of patients in the laser treated group when compared to no patients in the untreated group, while visual acuity deterioration of ≥ 3 ETDRS lines occurred in 93% of untreated eyes when compared with none in laser treated eyes [228]. Mean final visual acuity was 20/125 Snellen equivalent in the treated group and 20/400 in the untreated group at 24-months follow-up from a mean baseline of 20/160 in both groups [228]. Resolution of subretinal fluid occurred in all patients, both treated and untreated, with an earlier resolution observed in the treated group (9.1±1.7 months; range 6-12 months) when compared with the untreated group (15.8±3.4 months; range 12-24 months).

In another prospective RCT, Tomomatsu et al. [295] compared combined targeted laser photocoagulation and intravitreal bevacizumab (1.25 mg) (n=19) with bevacizumab (1.25 mg) alone (n=19) in patients with macular edema secondary to iBRVO, defined by the presence of ≥ 5 DA of retinal capillary non-perfusion. Significant reduction of CST was observed 2 and 3 months following combined therapy in comparison to intravitreal bevacizumab monotherapy, which showed increase in CST three months following treatment [295]. The number of injections in the bevacizumab monotherapy group was statistically significantly greater (mean $1.57 \pm$ SD 0.69) than that in the combined laser + bevacizumab group (mean $0.83 \pm$ SD 0.62) [295]. Moreover, the visual acuity improved significantly with combination therapy at six months (0.6 Log MAR at baseline to 0.3 LogMAR), but not with bevacizumab monotherapy (0.65 LogMAR at baseline to 0.5 LogMAR) [295].

b. Anti-VEGF

Intravitreal anti-VEGF has become the first line therapy for patients with macular edema secondary to both CRVO and BRVO. Intravitreal anti-VEGF therapies routinely used in clinical practice include ranibizumab, aflibercept and bevacizumab. Intravitreal ranibizumab and aflibercept are licensed for the treatment of macular edema secondary to RVO; in the United Kingdom these treatments have been appraised and are recommended by the National Institute for Health and Care Excellence (NICE) for people with visual impairment caused by macular edema following CRVO or BRVO [B-E]. Aflibercept is recommended by NICE as an option for the treatment of visual impairment in adults caused by macular edema after BRVO [D] or CRVO [E]. Ranibizumab is recommended as an option for treating visual impairment caused by macular edema following CRVO or following BRVO, the latter only if treatment with laser photocoagulation has not been beneficial, or when laser photocoagulation is not suitable because of the extent of macular hemorrhage [B, C]. Intravitreal bevacizumab is used

also as an off-label alternative. Anti-VEGF drugs, by inhibiting the effects of VEGF; decrease blood vessel and possibly RPE permeability leading to reduction in macular edema.

Several studies, including RCTs have been conducted to investigate the efficacy and safety of anti-VEGF therapies in patients with CRVO and BRVO. Most of these, however, excluded or included only a very scarce number of patients with the ischemic forms of RVO (Table-1). For example, the CRUISE (Central Retinal Vein OcclUsIon: Evaluation of Efficacy and Safety study), which evaluated the effect of ranibizumab on CRVO, excluded patients with brisk RAPD [37] and, thus, would have excluded patients with severe retinal ischemia [123] (See section VI. Clinical Findings and Ancillary Studies, above). Furthermore, of the 392 patients included in CRUISE only two had ≥10 DA of capillary non-perfusion on FFA (0.5%) [37]. Similarly, ROCC, an RCT comparing ranibizumab to sham in patients with macular edema secondary to CRVO, included only five out of 29 patients (17%) with ≥ 5 DA of capillary non-perfusion on FFA [153]. Moreover, none of the BRVO patients in BRAVO (RanibizumaB for the treatment of macular edema following BRAnch retinal Vein Occlusion) had ≥10 DA of retinal capillary non-perfusion [43]. The branch Retinal vein occlusion Associated Macular Edema Study (RABAMES), which also evaluated ranibizumab for the treatment of macular edema secondary to BRVO, excluded patients with macular ischemia and did not classify or give separate data for iBRVO and non-iBRVO [234]. Other studies that may have included patients with iRVO did not provide data separately for ischemic and non-ischemic forms [46,79]. Studies providing information, specifically, in iRVO are summarized below.

RAVE (the Rubeosis Anti-VEGF) was an open-label clinical trial in which treatment with intravitreal ranibizumab was investigated in 20 patients with iCRVO. iCRVO was defined by the presence of three out of four criteria: visual acuity ≤20/200, loss of I-2e isopter on Goldman visual field, RAPD ≥0.9 log units and reduction of b:a ratio by≥60% of the

corresponding a-wave [36]. All patients received monthly intravitreal ranibizumab (0.3 mg in 5 patients; 0.5 mg in 10 patients; 1 mg in 5 patients; no separate outcomes were given for these three groups) during the first nine months and as needed during the remaining study period of 36 months. Eighteen patients (90%) were followed for 9 months; 17 (85%), 15 (75%) and 13 (65%) were followed for 12, 24 and 36 months, respectively. The mean visual acuity at baseline was 15 ETDRS letters (range 0-37 ETDRS letters). At 36 months, the mean visual acuity gain was + 21.4 (range -23 to +40) ETDRS letters with five out of 13 patients (38%) who completed the 36 months follow-up gaining ≥ 15 ETDRS letters. The high loss of follow-up at 36 months should be taken into consideration when interpreting this data. Seven eyes (39%) had a final visual acuity worse than 20/400 [36]. Mean reduction of CST was -294 µm (range, -47 to -652 µm) at nine months of follow-up from baseline. However, subsequently, after a three months-period of observation (12 months- follow-up) recurrence of macular edema was observed in 44% of patients and retreatment required. After retreatment (as needed), the CST improved by -163 µm (range, -636 to -602 µm) at 24 months and -191 µm (range, -623 to -58 µm) at 36 months-follow-up compared to values at 12 months [36].

CRYSTAL was an open-label, single arm, multicenter prospective study which included 357 patients with CRVO.[167] Patients were treated with monthly 0.5 mg ranibizumab for a minimum of three injections and until stable visual acuity was maintained for three consecutive months. Macular ischemia, defined by presence of any capillary non-perfusion on FFA (mild, moderate, severe or completely destroyed) in at least one of the three subfields using ETDRS grid (central, inner ring subfield or outer ring subfield) on the macular region at baseline in 107 patients (30%) [167]. Of the eyes included, 54 eyes had iCRVO (definition was not given); data was not provided separately for iCRVO and non-iCRVO. Intravitreal ranibizumab resulted in a significant improvement of visual acuity, with

63.8% of patients gaining ≥ 10 letters, 49.2% gaining ≥15 letters and 9% gaining ≥ 30 letters at 12 months- follow-up [167]. In this study, an exploratory analysis showed that the mean gain in visual acuity was not statistically significantly different between CRVO patients with macular ischemia (11.6±14.92 ETDRS letters) and those without macular ischemia (12.1± 18.10 ETDRS letters) [167]. The number of intravitreal ranibizumab injections from baseline to 12 months was also not statistically significant different between patients with macular ischemia (7.5±2.9) and those without macular ischemia (8±2.9) [167].

BRIGHTER [288] was an RCT that evaluated the effect of monthly 0.5 mg ranibizumab until stable visual acuity was maintained for three consecutive months (n=183), ranibizumab (0.5 mg) combined with macular laser (n=180) and macular laser monotherapy (n=92) in patients with macular edema secondary to BRVO [288]. BRIGHTER included patients with macular ischemia, defined as the in CRYSTAL study (see above); macular ischemia was present in 113 out of 455 patients (24.8%) (ranibizumab, n=47; ranibizumab combined with macular laser, n=42; and macular laser monotherapy, n=24) [288]. Of the eyes included 47 eyes had iBRVO (definition was not given), but data was not provided separately for iBRVO and non-iBRVO. The mean visual acuity at baseline was 57.7 ± 12.88 ETDRS letters. Improvement in visual acuity was greater following six months ranibizumab therapy with or without laser therapy (14.8 ±10.7 and 14.8 ±11.13 ETDRS letters, respectively) when compared to macular laser monotherapy (6.0 ± 14.7 ETDRS letters) [288]. At six months, 65% and 54.5% of patients attained a visual acuity of ≥ 73 letters in the ranibizumab and ranibizumab plus laser treatment groups, respectively, in comparison to 31% of patients receiving laser monotherapy [288]. An exploratory analysis found no statistically significant difference in outcomes between patients with and without macular ischemia [288].

COPERNICUS [38], GALILEO [128,215] and VIBRANT [45,58] evaluated the effect of intravitreal aflibercept on macular edema secondary to CRVO and BRVO. A statistically

56

significant reduction of macular edema as well as improvement in visual acuity and vision-related quality of life was demonstrated following intravitreal aflibercept therapy [38,45,58,128,215]. COPERNICUS and VIBRANT provided data on visual outcomes for patients with iRVO and non-iRVO separately, but not for macular edema or vision related quality of life [38,45,58], while GALILEO did not provide separate data on any of these outcomes for iRVO and non-iRVO cases [128,215].

COPERNICUS included 187 patients with CRVO; only 29 (15%) of these had retinal ischemia, defined by the presence of ≥10 DA of capillary non-perfusion (127 patients had perfused retina and 31 had an indeterminate perfusion status) [38]. Patients were randomized to monthly injections of 2 mg aflibercept for six months followed by PRN (*pro re nata*) for the remaining period of the study of 12 months (n=115, with 17 non-perfused CRVO) or to monthly sham for six months and PRN aflibercept thereafter (n=73, with 12 non-perfused CRVO). In this study the mean visual acuity at baseline was 50.0 ±14.09 ETDRS letters. At six months-follow-up, a gain of ≥ 15 ETDRS letters was observed in a statistically significantly higher number of patients (56.1%) in the aflibercept arm when compared with the sham-treated group (12.3%) [38]. A secondary analysis showed that in patients with iCRVO, the proportion of eyes that gained ≥15 letters at six months was 51.4% in the aflibercept group and 4.3% in the sham group; in non-iCRVO, these proportions were 58.4% and 16% in aflibercept and sham groups, respectively [38].

GALILEO also studied the effect of aflibercept on macular edema secondary to CRVO and included a total of 177 patients; 14 (8%) had non-perfused retina, defined by the presence of ≥10 DA of capillary non-perfusion, 143 patients had good retinal perfusion and in 14 retinal perfusion was indeterminate [128,215]. Patients were randomized to monthly 2 mg aflibercept for six months (n=103, with 7 non-perfused CRVO) or monthly sham for six months (n=68, with 7 non-perfused CRVO) [128]. Due to the small number of patients

57

included with iCRVO outcomes were not evaluated separately for iCRVO and non-iCRVO [128,215].

VIBRANT evaluated the effect of aflibercept (2 mg) versus macular laser photocoagulation for the treatment of patients with macular edema secondary to BRVO [45,58]. Of the 181 patients included in this study, iBRVO, defined as ≥10 DA of capillary non-perfusion on FFA, was present in 36 patients (20%). Patients were randomized to receive monthly aflibercept (2 mg) for six months (n=91, with 16 iBRVO) or macular laser (n=90, with 20 iBRVO). At six months a gain of ≥ 15 ETDRS letters occurred in a statistically significant higher number of patients treated with aflibercept (52.7%) than laser (26.7%) [45]. A secondary analysis showed that eyes with iBRVO experienced a mean change in visual acuity of 19.1 EDTRS letters at six months-follow-up following aflibercept and of 11.3 ETDRS letters following laser, with no statistically significant differences between these two treatment groups [45]. In contrast, the mean change in visual acuity in non-iBRVO was significantly higher in the aflibercept group (14.3 EDTRS letters) when compared with the laser-treated group (5.7 ETDRS letters) [45].

Two RCTs compared the effects of intravitreal bevacizumab and intravitreal triamcinolone acetonide (IVTA) in patients with macular edema secondary to CRVO (n=86) [244] and BRVO (n=86) [243]. Patients were randomized to receive intravitreal bevacizumab (three monthly injections of 1.25 mg) or intravitreal triamcinolone acetonide (IVTA) (two injections of 2 mg IVTA 2 months apart). Ischemic CRVO was defined by the presence of ≥10 DA of capillary non-perfusion on FFA and was identified in 40 patients (46%) [244]. In iCRVO, visual acuity significantly improved in both intravitreal bevacizumab (1.09 ± 0.62 logMAR at baseline to 0.57 ± 0.44 log MAR at six months) and IVTA groups (0.95 ± 0.35 log MAR at baseline to 0.79 ± 0.31 log MAR at six months) with the improvement being significantly greater following intravitreal bevacizumab [244]. Similarly, significant reduction

58

in CST was observed in both intravitreal bevacizumab (200 ± 126 µm) and IVTA (77 ± 104 µm) groups at six months, with greater CST reduction following intravitreal bevacizumab [244]. No statistically significant differences in visual acuity or CST were observed between iCRVO and non-iCRVO [244]. In patients with BRVO, iBRVO was present in 52 patients (60%), as defined by the presence of ≥ 5 DA of capillary non-perfusion on FFA [243]. In iBRVO, visual acuity significantly improved in both the intravitreal bevacizumab group (0.77 ± 0.24 logMAR at baseline to 0.37 ± 0.19 log MAR at six months) and the IVTA group (0.75 ± 0.31 log MAR at baseline to 0.58 ± 0.29 log MAR at six months) with improvement in visual acuity being significantly greater following intravitreal bevacizumab [243]. Similarly, significant reduction in CST was observed in both intravitreal bevacizumab (125 ± 101 µm) and IVTA (68 ± 175 µm) groups at six months, with CST reduction being significantly greater following intravitreal bevacizumab [243]. A statistically significant difference in CST between iBRVO and non-iBRVO was detected, but no statistically significant difference in visual acuity was observed between iBRVO and non-iBRVO [243].

A prospective interventional study evaluated the effect of intravitreal bevacizumab (1.25 mg) in 16 patients with iCRVO defined by the presence of >30 DA of retinal capillary non-perfusion and 30 patients with non-iCRVO (≤30 DA of retinal capillary non-perfusion) [240]. In both, iCRVO and non-iCRVO, mean visual acuity and CST improved from baseline to six months with no statistically significant difference between these groups in both outcomes [240].

Anti-VEGFs improve visual acuity and reduce macular edema in patients with CRVO and BRVO. Intravitreal injections of anti-VEGF, however, are unpleasant for patients, carry a small risk of complications such as endophthalmitis, and require repeated treatments and close and long-term follow-up over many years to preserve vision [44,124]. At present time,

there is insufficient data available on the efficacy and cost –effectiveness of anti-VEGFs for the treatment of iCRVO and iBRVO.

c. Steroids

Corticosteroids reduce retinal capillary permeability and leakage as well as inflammation and, hence, could provide benefit in reducing macular edema in patients with RVO [30,47,48,99,136,137,220,257,264]. Intravitreal corticosteroids used for the treatment of patients with macular edema secondary to RVO include triamcinolone acetonide (TA) and dexamethasone (DEX). TA is not licensed for intraocular use in these patients. In the United Kingdom DEX implants were appraised by NICE who recommends this therapeutic option for patients with macular edema secondary to CRVO and for patients with BRVO unsuitable or unresponsive to laser treatment [F,G]. Corticosteroids are associated with potential adverse effects including elevated intraocular pressure and cataract [30,47,48,99,136,137,220,257,264].

SCORE (Standard Care vs COrticosteroid for REtinal vein occlusion) [137,264] compared IVTA with standard care (observation in CRVO [137] and macular laser in BRVO [264]) for the treatment of patients with macular edema secondary to CRVO (n=271) [137] and BRVO (n=411) [264]. SCORE included only three patients with iCRVO, defined by the presence of ≥10 DA of capillary non-perfusion on FFA, and 41 patients with iBRVO, defined by the presence of ≥5 DA of capillary non-perfusion. No separate data was given for iRVO and non-iRVO with regards to clearance of macular edema or visual acuity improvement [137,264].

The use of IVTA (4 mg) was evaluated in patients with iCRVO (n=11) (defined by the presence of ≥10 DA of retinal capillary non-perfusion) and was compared to non-iCRVO (n=11) in a prospective interventional study by Ozdek et al. [220]. The study showed a significant reduction of CST in both iCRVO (from 766 ± 320 µm at baseline to 441.7 ± 166.9

μm, at nine months) and non-iCRVO (from 667 ± 223 μm at presentation to 320 ± 175.5 μm, at nine months) following treatment, with no statistically significant difference between these groups [220]. Complete resolution of macular edema was reported in seven patients with non-iCRVO and four patients with iCRVO [220]. Improvement in visual acuity was also observed in both iCRVO and non-iCRVO, but was significant in non-iCRVO only [220]. An improvement of ≥ 3 Snellen lines of visual acuity was observed in 81.8% of the eyes with non-iCRVO but in only 18.2% of those with iCRVO at nine months-follow-up [220]. Moreover, the mean final visual acuity among patients with iCRVO was very poor (20/800 Snellen/ 1.61 LogMAR) [220].

In a prospective interventional study including 18 patients with BRVO and macular ischemia (defined by a broken perifoveal capillary ring at the border of the FAZ associated with a distinct area of capillary non-perfusion within one disk diameter of the foveal center) a single injection of IVTA (4 mg) led to a significant reduction in macular edema (CST on SD-OCT) at one month (n=17, 94%) and three months (n=13, 72%) follow-up[51]. There was, however, no significant improvement observed at six, nine or 12 months follow-up [51]. Improvement of visual acuity was significant at one month follow-up only, but not at the other time points [51]. Only six out of the 12 patients that completed the 12-months follow-up (50%) showed improvement in visual acuity, ranging from one to six lines, and five out of these 12 had a final visual acuity of ≤ 20/200 [51].

In another prospective study of 17 patients with macular edema secondary to BRVO, iBRVO, defined as the presence of ≥ 5DA of capillary non-perfusion on FFA, was present in 10 patients [209]. In this small study there were no statistically significant differences found in changes from baseline to six months follow-up in macular thickness, macular volume, macular sensitivity within the central 4°, 10°, and 20° fields or visual acuity when comparing cases with iBRVO and non-iBRVO [209].

Treatment of macular edema with DEX implant in patients with CRVO and BRVO was evaluated in the GENEVA RCT (Global Evaluation of implaNtable dExamethasone in retinal Vein occlusion with macular edemA) [99]. This study, however, did not provide data separately for perfused and non-perfused cases [99]. In a prospective interventional study which included 29 patients with iCRVO, defined by the presence of ≥10 DA of capillary non-perfusion (n=15) and iBRVO, defined by the presence of ≥5 DA of capillary non-perfusion (n=14), DEX implant showed a statistically significant reduction in macular edema and an improvement in visual acuity at 12 months following treatment [25]. In this study, 87% of iCRVO and 92% of iBRVO patients showed stabilization or improvement in vision at 12 months, with 80% of eyes affected by iCRVO gaining more than one ETDRS line and 46% improving by over three lines, while 85% of eyes with iBRVO improved by one line and 35% by three lines [25]. Despite this improvement, the mean final visual acuity was ≤ 20/200 in iCRVO and ≤20/63 in iBRVO [25]. In iCRVO, the median CST was reduced from 749 µm at baseline to 363 µm at 12 months. Similarly, the median CST in those with iBRVO improved from 459 µm at baseline to 323 µm at 12 months [25].

d. Pars plana vitrectomy

Pars plana vitrectomy with or without adjuvant procedures such as internal limiting membrane peeling was found to be effective in treating macular edema secondary to iCRVO and iBRVO in several prospective interventional studies and retrospective case series [27,66,146,174,186,210,246,270]. However, none of these studies were RCTs and all had a small number of patients.

Vitrectomy with posterior hyaloid removal appeared to confer benefit improving macular edema and reducing CST (from $976 \pm$ SD 196 µm at baseline to $640 \pm$ SD 191 µm at six months) in a prospective interventional study that included 10 eyes with iCRVO [174].

Visual acuity improved in six patients from a median of 20/600 to 20/300, while did not change in the remaining four (20/1600) [174].

A small study evaluated outcomes of pars plana vitrectomy in patients with macular edema secondary to iBRVO (n=13) and non-iBRVO (n=10) and showed statistically significant improvement in visual acuity (from 0.85 to 0.5 logMAR), macular thickness and macular volume on SD-OCT, and mean macular sensitivity on microperimetry within the central 4° (from 3 to 8 dB), 10° (from 4.5 to 10.5 dB) and 20° fields (from 5.5 to 10 dB) at six months following treatment [210]. There were no significant differences between iBRVO and non-iBRVO regarding macular thickness, macular volume, and visual acuity. However, there was a significant difference in the macular sensitivity within the central 4°, 10°, and 20° fields between iBRVO and non-iBRVO, with better sensitivity in non-iBRVO [210].

2. Therapies to treat or prevent proliferative retinopathy secondary to iRVO

Studies have been conducted to test the effect of panretinal photocoagulation to prevent or treat neovascularization and its consequences in patients with iRVO. Anti-VEGFs and steroids have not been adequately tested in powered RCTs for this purpose. However, several studies that aimed at determining the effect of these treatments on macular edema in patients with RVO evaluated the occurrence of new vessels and complications related to these and, thus, provided information on this regard. The studies identified have been summarized below.

a. Pan-retinal photocoagulation (PRP)

Panretinal photocoagulation (PRP) leads to regression of neovascularization in iCRVO [6,97,121,155,165,183,201,248]. PRP was associated with regression of angle and iris neovascularization in patients with iCRVO in which this complication was present [6].

Prophylactic PRP (i.e. prior to the development of anterior segment neovascularization), however, did not prevent the neovascular complications in patients with iCRVO in the CVOS [6]. Although PRP lowered the incidence of neovascular complications, the difference between treated and observed groups was not statistically significant and, thus, it was recommended that PRP should be undertaken only as soon as neovascularization develops [6,121,155,165,183]. A study by Hayreh et al. [121] comparing PRP-laser treated and observed untreated eyes of patients with iCRVO (n=123) over a period of ten years found no statistical significant differences in visual acuity or incidence of neovascular complications including angle neovascularization, neovascular glaucoma, posterior segment neovascularization and vitreous hemorrhage between the two groups [121]. The incidence of iris neovascularization in PRP-treated patients, however, was reduced if PRP was performed within the first 90 days of iCRVO onset [121]. Using Goldmann perimetry, the peripheral visual fields showed a statistically significant worsening in the laser-treated eyes in comparison with the untreated eyes [121].

Retinal arterial blood flow was evaluated using color Doppler flowmetry one month following PRP in patients with iCRVO (n=13) (defined by the presence of ≥10 cotton wool spots in a 45° fundus photography, ≥10 DA of capillary non-perfusion on FFA, and/or presence of neovascularization of the iris) and compared to that in patients with non-iCRVO (n=20) and healthy controls (n=22) [20]. Patients with iCRVO had statistically significantly lower blood flow within the ophthalmic and central retinal artery than those with non-iCRVO and healthy controls; PRP in iCRVO group was found to further reduce the arterial blood flow [20]. In contrast, it was observed in another study which involved 12 patients with iCRVO, defined by the presence of ≥ 10 DA of capillary non-perfusion on FFA, that there was a significant increase in the retinal blood flow, using Heidelberg retinal flowmetry, one month following laser photocoagulation, but the blood flow was still lower than in control

64

subjects [18]. Hence, it is not clear how PRP affects the retinal blood flow in patients with iCRVO as different technologies used have shown different results.

The BVOS showed that prophylactic sector laser photocoagulation prior to development of neovascularization and vitreous hemorrhage in patients with iBRVO lowered the risk but did not completely prevent the development of new vessel formation and its complications. Thus, like in the case of iCRVO, laser photocoagulation is recommended only when neovascularization is established in iBRVO [2]. Hayreh et al. [111] reported that untreated BRVO patients have 3.5 times higher risk in developing retinal neovascularization than laser-treated patients [111], but noted that treatment with laser did not have a beneficial effect in the visual acuity and resulted in worsening of the visual field defects in comparison to no treatment [111].

a. Anti-VEGF

Treatment with intravitreal ranibizumab did not eliminate the risk of developing ocular neovascularization in patients with CRVO [36,37]. However, CRUISE reported lower incidence of iris neovascularization and neovascular glaucoma in CRVO patients in ranibizumab-treated eyes when compared with sham-treated eyes [37]. In the RAVE, neovascular complication still occurred in 50% of patients with iCRVO following intravitreal ranibizumab during a follow-up period of 36 months [36]. Of these, 33% developed posterior segment neovascularization, 28% anterior segment neovascularization and 11% both [36]. In this study, 12 patients with iCRVO were assessed with WA-FFA and the extension of the area of non-perfusion continued to progress over time even with ranibizumab therapy [317]. In contrast, a retrospective post hoc analysis of CRUISE and BRAVO [42] evaluating the effect of ranibizumab therapy on the area of retinal capillary non-perfusion on standard FFA found that in CRVO the percentage of patients with no capillary non-perfusion increased in

ranibizumab-treated groups at six months (from 77.1% at baseline to 84% with 0.3 mg ranibizumab and from 78.8 at baseline to 82% with 0.5 mg ranibizumab) and was significantly greater than that of the sham group, which showed a decrease in the percentage of patients with no capillary non-perfusion from 83.0% at baseline to 67.0% at six months [42]. Reperfusion of non-perfused retina was rare (1%) in sham-treated patients with CRVO, but occurred in 6% to 8% of patients treated with ranibizumab [42].

In BRVO, the percentage of patients with no capillary non-perfusion decreased in both ranibizumab-treated and sham treated groups over time but was significantly greater in the ranibizumab-treated group when compared to the sham-treated group [42]. Thus, 67% of sham-treated eyes had retinal capillary non-perfusion compared with approximately 50% of ranibizumab-treated eyes [42]. In BRIGHTER, none of the patients with BRVO developed iris or retinal neovascularization or neovascular glaucoma during the six-months follow-up period of the study; vitreous hemorrhage occurred in 0.06 % of patients treated with ranibizumab, 1.1% of those receiving combined ranibizumab and laser photocoagulation and in none of those receiving laser monotherapy [288].

A RCT by Epstein et al. [79] that included a total of 60 patients with CRVO reported development of iris neovascularization in 16.7% of patients with CRVO at six months in the sham-treated group in comparison to none in the bevacizumab-treated group [79].

Similar to the effects observed following intravitreal ranibizumab and bevacizumab, intravitreal aflibercept does not eliminate the risk of neovascularization in patients with iRVO but may reduce the risk of its development. Thus, GALILEO reported occurrence of anterior as well as posterior segment neovascularization secondary to CRVO in 2.9% of aflibercept-treated eyes in comparison to 4.4% of eyes in the sham-treated group at 24-weeks; four-weekly aflibercept injections were given for the first 20 weeks in aflibercept treated eyes [128].

This difference was no longer observed at 76-weeks but aflibercept was administered as needed after 24 weeks in both groups. At 76-weeks, a higher incidence of anterior and posterior segment neovascularization than at 24 weeks follow-up was detected in both aflibercept-treated (7.8%) and sham-treated eyes (8.8%) [215]. COPERNICUS, which also administered four-weekly aflibercept for the first 20 weeks in the aflibercept treated group and as needed afterward in both groups, reported development of anterior segment neovascularization in none of the aflibercept-treated group, in comparison to 6.8% of patients with CRVO in the sham-treated group, at 12 months-follow-up, who then received PRP to treat the neovascularization [38].

VIBRANT also administered aflibercept four-weekly for the first 20 weeks in the aflibercept group and as needed afterwards in both aflibercept and macular laser groups (see above), and reported retinal neovascularization secondary to BRVO in 3% of patients in the laser-treated group at six months but in none in the aflibercept-treated group [45]. The proportion of patients with a perfused retina (defined by the presence of <10 DA of capillary non-perfusion on FFA) at baseline was 60% in the aflibercept group and 69% in the laser group whereas at six months it increased to 80% in the aflibercept group but decreased to 67.1% in the laser treated group [45].

A small RCT including 19 patients with iCRVO evaluated the effect on neovascular glaucoma, defined by the presence of iris or anterior chamber angle neovascularization and IOP greater than 22 mmHg, of a single intravitreal bevacizumab injection (1.25 mg) followed by PRP one week after injection (n=10) and compared it to that of PRP alone (n=9) [315]. This study reported faster regression of iris/ angle neovascularization with the bevacizumab/PRP group than in the PRP group suggesting that intravitreal bevacizumab in combination with PRP is useful in the treatment of neovascular glaucoma by speeding up the resolution of iris/ angle neovascularization [315].

b. Steroids

In SCORE, intravitreal triamcinolone acetonide did not appear to modify the risk of development of ocular neovascularization, including iris neovascularization, neovascular glaucoma, posterior segment neovascularization and vitreous hemorrhage/pre-retinal hemorrhage, when compared with laser [49]. A multivariable analysis in SCORE-BRVO estimated a 9% increased risk of a neovascular event for each disc area of increase in retinal capillary non-perfusion at baseline [49]. Further analysis was undertaken in which disc areas of retinal capillary non-perfusion were considered a time-varying covariate from baseline and throughout the course of the follow-up using a multivariate Cox regression model. In this analysis for the SCORE-BRVO, there was a 5% increase in hazard of a neovascular event for each disc area of increased retinal capillary non-perfusion, and 3.8 times increase in hazard for a neovascular event when comparing eyes with ≥ 5.5 disc areas versus < 5.5 disc areas of retinal capillary non-perfusion [49]. In contrast, in SCORE-CRVO multivariable analysis did not show significant associations of any baseline factors with neovascular events [49].

In GENEVA, the incidence of retinal neovascularization was statistically significantly lower in the 0.7 mg and 0.35 mg DEX-treated groups (0.7% and 1%, respectively) than in the sham group (2.6%) at six months for CRVO and BRVO [99]. However, a post-hoc analysis showed an increase in the mean area of overall non-perfusion and in the mean area of macular capillary non-perfusion from baseline to six months in both DEX and sham groups with no statistically significant differences between the two [257]. In a small prospective interventional study by Parodi *et al.* [25] none of the 29 eyes with iCRVO (n=15) or iBRVO (n=14) treated with DEX implant developed ocular neovascularization at 12 months following treatment [25].

c. Pars plana vitrectomy

Vitrectomy could be expected to reduce, at least temporarily, the concentrations of intraocular angiogenic and inflammatory cytokines, such as VEGF and, subsequently may lower the risk of development of ocular neovascularization secondary to iRVO. Data, however, on the potential benefit of pars plana vitrectomy in patients with iCRVO is very scarce.

A prospective interventional study of 10 patients with iCRVO demonstrated that none of the patients treated with pars plana vitrectomy developed new vessels in the retina or disc, but iris neovascularization was still observed in 30% of patients at six months following surgery [174]. Neovascular glaucoma was reported in a prospective interventional study in five of 31 patients with CRVO (iCRVO=15; non-iCRVO=16) but in none of 19 patients with BRVO (iBRVO=6; non-iBRVO=13) following vitrectomy and internal limiting membrane peeling [186]. The very scarce data available, thus, suggests that pars plana vitrectomy does not prevent the occurrence of neovascularization.

Vitrectomy is, however, very useful to manage complications associated with RVO such as tractional retinal detachment, vitreous hemorrhage and epiretinal membrane and can result in improvement of the visual acuity in patients with BRVO with these complications [13,258,291,319]. It was also suggested that early vitrectomy before development of vitreoretinal proliferation and retinal detachment maybe beneficial for management of BRVO in patients with high risk of developing complications [291]. However, further studies are needed to confirm the benefit of early vitrectomy in these cases.

B.   Other therapies for ischemic RVO

Several studies have been conducted to evaluate the role of other therapies, besides those mentioned above, for the treatment of iBRVO and iCRVO, but have not been approved either

because they are still under investigation, they are impractical, have adverse effects or have no or limited benefit. Examples of these therapies are summarized below.

1. *Photodynamic therapy*

Photodynamic therapy (PDT) with verteporfin as a photosensitizer was evaluated for the treatment of anterior segment neovascularization secondary to iCRVO in an RCT and in a prospective interventional study [227,229]. The laser energy in PDT was directed to the anterior chamber angle and the iris using a Goldmann three-mirror contact lens [227,229]. In the RCT, patients with iCRVO, defined by the presence of $\geq$ 10 DA of capillary non-perfusion on FFA and reduced b-wave amplitude on ERG, were randomized to PDT (n=17), standard PRP (n=19) and selective PRP (n=20), the latter being performed only if iris/angle neovascularization showed progression on weekly follow-up [229]. At 12-months follow-up, the extension of iris neovascularization expressed in clock hours was 2.27, 0.52 and 2.55 in PDT, standard PRP and selective PRP groups, respectively, while the extension of anterior chamber angle neovascularization was 1.27, 0.57 and 1.50 clock hours, respectively. Regression of iris/ angle neovascularization was statistically significant only in the PRP group; the incidence of neovascular glaucoma did not differ between treatment groups [229]. A prospective interventional study including ten patients with iCRVO and iris/angle neovascularization suggested that PDT can partially obliterate anterior segment neovascularization [227].

2. *Radial optic neurotomy (RON)*

Radial optic neurotomy (RON) was designed to release the pressure from the occluded central retinal vein. In RON, vitrectomy is performed and then an incision is made in the lamina cribrosa [216]. Several studies evaluated the efficacy and safety of RON [10,16,24,41,88,186,189,216,262,313]. ROVO (Radial Optic neurotomy for central Vein Occlusion study) randomized 83 patients with CRVO (both iCRVO, defined by the presence of $\geq$ 10 DA of

capillary non-perfusion on FFA and non-iCRVO) to three treatment groups, RON (n=38), IVTA (n=25) and sham (n=20) [10]. At 12-months, a statistically significant increase in visual acuity was detected in 47% of patients following RON when compared to 10% of sham and 20% of triamcinolone treated patients [10]. A statistically significantly higher number of patients in the sham group experienced visual acuity deterioration (35%) (>3 logMAR lines of visual acuity loss) compared with those treated with RON (8 %) [10]. In non-iCRVO, the median vision increased from 1 logMAR (range, 0.72–1.35) to 0.75 logMAR (range, 0.45–1.55) after 12 months; in iCRVO, the median visual acuity also increased from 1.09 logMAR (range, 0.97–2) to 0.9 logMAR (range, 0.71–2) after 12 months, with no statistically significant differences between iCRVO and non-iCRVO [10]. Smaller studies have provided mixed results with regard to benefits of RON, and high rates of complications have been noted [16,189,313]. In a prospective interventional study which included 13 patients with iCRVO, defined by the presence of ≥10 DA of capillary non-perfusion, a significant improvement in visual acuity and retinal perfusion on FFA from baseline to one year were observed in 10 patients; chorioretinal anastomosis at the surgical site was also observed in ten patients following RON [88]. A prospective interventional study including 13 patients with CRVO (iCRVO=10, indeterminate=2, perfused=1) showed an improvement of ≥2 Snellen lines in six patients; in two of these the final visual acuity was ≤ 20/200 [262]. Two patients developed neovascularization and underwent PRP, six showed visual field loss using Goldmann perimetry and three of those showed an absolute nerve fiber bundle defect at the surgical site [262]. Hence, beneficial effects of RON on vision have not been clearly demonstrated and RON is associated with its own potential complications and costs and has not been shown to prevent complications resulting from CRVO. Thus, RON is not a standard treatment for patients with iCRVO.

3. Chorioretinal Anastomosis

Chorioretinal anastomosis was developed to allow blood to bypass the occluded vein into the choroidal blood vessels [52,73,163,192,193,195,233]. This procedure has been used to treat both CRVO and BRVO and can be undertaking by means of laser or surgery [52,73,163,192,193,195,233]. In non-iCRVO, a functionally effective chorioretinal anastomosis can be achieved in around one third to a half of patients; this however, is considerably more challenging and difficult to achieve in iCRVO [163]. Although a successful anastomosis may prevent ischemia from getting worse [193], the visual results of chorioretinal anastomosis are poor [81,192,193]. Chorioretinal anastomosis is associated with many complications including vitreous hemorrhage, choroidal neovascularization, and pre-retinal fibrosis which were more pronounced in the ischemic form of CRVO [81,193].

4. *Thrombolysis*

Thrombolysis using intravitreal or endovascular recombinant tissue plasminogen activator (rt-PA) has also been evaluated in small studies including patients with iCRVO [78,82,105,106,254]. These studies showed significant improvement of visual acuity in 36-71% of patients with iCRVO [78,82,93,105,106] and a reduction in the area of retinal capillary non-perfusion if thrombolysis is initiated in the acute phase of iRVO [78,105,106]. However sufficient evidence is lacking to justify thrombolysis for RVO in clinical practice.

5. *Isovolemic hemodilution*

Isovolemic hemodilution has been investigated for the treatment of iRVO in several RCTs and prospective interventional studies [94,102,297,309,316]. This treatment aims at reducing the viscosity of the blood and increasing its fluidity [94,102,297,309,316]. Although many of these studies suggested an improvement in visual acuity following isovolumetric hemodilution [94,102,297,309,316] due to the impracticality and complexity of this procedure, this treatment has not been adopted in clinical practice [40].

6.   *Neuroprotective* agents

The efficacy of neuroprotective agents such as, minocycline, activated protein-C, glutamate antagonists and free radical scavengers (Edaravone MCI-186) has been evaluated in patients with iRVO [72,145,180,200,286].

Minocycline is a broad-spectrum tetracycline antibiotic which was found to have neuroprotective effects and is currently under investigation in patients with BRVO. Preliminary results on experimental studies suggest that minocycline can inhibit apoptosis of retinal ganglion cells and it has been suggested that using minocyclin in the acute stage of the disease could preserve retinal function [286]. A RCT on the effect of minocycline on RVO patients is currently under way (ClinicalTrials.gov Identifier: NCT01468844 and NCT01468831).

Experimental and clinical studies using intravitreal activated protein-C have shown reduction in retinal cell apoptosis secondary to iCRVO by blocking the activation of caspase-3, -8 and -9 [72,145]. In a prospective interventional study of ten patients with macular edema secondary to iCRVO, significant reduction in central foveal thickness was reported in all patients following administration of intravitreal activated protein-C [145]. Moreover, visual acuity significantly improved in 60% of patients and complete reperfusion of non-perfused retina was observed in 30% one year following treatment [145]. Thus, intravitreal protein-C appears to be a promising new therapy but requires further investigation.

7.   *Cell therapy*

Cell therapy using bone marrow-derived stem cells or endothelial progenitor cells has also been suggested for the treatment of ischemic retinopathies [222,223,276,285]. These cells are believed to play an important role in tissue regeneration by promoting the repair of damaged retinal blood vessels to re-perfuse the ischemic areas of the retina. To date, there are only two

case reports with only one patient with iCRVO in each, both suggest benefit of bone-marrow stem cells for the treatment of patients with iCRVO [222,276]. Further research into this area is warranted.

IX.   Summary – Proposed characterization of the disease and practical points for the clinician.

Ischemic retinal vein occlusion (iRVO) [including central (iCRVO), branch (iBRVO), hemicentral RVO and hemispheric RVO] poses significant risk of visual loss to those suffering from this vascular retinal disorder. Data available, contained in this review, suggests a more guarded prognosis for the natural history of patients with iRVO when compared with those with non-iRVO, independently of the definition of iRVO used. This appears also to be true for outcomes following treatment, although scarce data are available.

There is no widely accepted definition for iCRVO and iBRVO; the lack of agreement in diagnostic criteria used may explain reported differences in functional and anatomical outcomes observed as a result of the natural history of the disease or that modified by treatment. The CVOS and BVOS defined iCRVO and iBRVO by the presence of >10 DA and >5 DA of retinal capillary non-perfusion respectively. These definitions, which have been the ones most widely used in published studies, were based on risk of development of neovascularization.

Data available strongly suggest that the larger the area of retinal ischemia the higher the risk of visual loss and development of neovascular complications; it is unclear whether this risk depends not only on the extent but also on the location of the ischemia (i.e. peripheral, midperipheral, macular, perifoveal) and further information on this is needed. An agreement as to whether iRVO (iCRVO, iBRVO and ischemic hemi-central and hemispheric

RVO) could be considered as a separate entity from non-iRVO and, if so, whether iRVO could be defined by a particular threshold of area of retinal ischemia would require an international consensus. In any case, the authors of the current review strongly encourage clinicians and researchers to determine the presence/absence, extent and location of areas of retinal ischemia in patients with any RVO. This information should be provided consistently in RVO studies and should be considered when evaluating outcomes of therapies. A proposed characterization of patients with RVO is provided in Figure 3.

Currently and until other imaging modalities (e.g. OCT-A) allow visualization of the entire retinal vascular tree, identification of areas of retinal ischemia by WA-FFA is the preferred method to be used. Determining the extent of the area of retinal ischemia in mm^2 would be advisable; appropriate software that allows this measure to be obtained would be of great help. This and aiming to image as much of the retina as possible, even when using WA-FFA, is essential for adequate interpretation of the data and comparison between studies to be made. Ideally a WA-FFA should be obtained at presentation in patients with RVO, unless very marked and extensive retinal hemorrhages which could prevent adequate visualization of the retinal capillaries were present. Hemorrhages may be less of a problem when using scanning laser WA-FFA systems. Automated detection of areas of retinal ischemia would be ideal but, at present, this remains challenging. Determining the integrity of the perifoveal capillaries may be done now more accurately with the use of OCT-A than with WA-FFA (Figure 3).

With the evidence available and considering the time and staff limitations often encountered in clinical practice, the authors of this review recommend patients with CRVO at presentation to undergo visual acuity testing, testing of the pupillary reflex, preferably using neutral density filters (see section VI. Clinical Findings and Ancillary Studies above), WA-FFA and SD-OCT. Presence/absence and degree of RAPD has been shown to strongly

predict risk and, thus, should be included in clinical studies on CRVO. From the clinical perspective, current knowledge suggests that patients with CRVO and visual acuity of <6/60, an RAPD (of ≥ 0.9 log units using neutral density filters) and extensive retinal capillary non-perfusion (ISI $\geq 45\%$ on WA-FFA or ≥ 30 DA if using standard FFA) are at high risk of developing neovascular complications (if not already present) and should be followed closely so timely treatment can be initiated. Patients should be also considered at high risk if marked and extensive retinal hemorrhages in four quadrants are present as these are likely to be associated with extensive retinal ischemia. Electrophysiology testing and visual fields have been shown to be also of prognostic value in CRVO but they are less accessible to clinicians and more difficult to obtain in busy retinal clinics. If obtained, several electrophysiology parameters are highly suggestive of patients with iCRVO having a higher risk of neovascular complications: prolonged implicit times in the 30 Hz flicker (>37 ms), reduction of > 60% of values obtained in the fellow healthy eye in the b-wave amplitude or b/a ratio of scotopic and/or photopic ERG, or photopic b-wave amplitude values of $< 56 \mu V$. Hand-held portable electrophysiology devices recently developed (RETeval®) may facilitate electroretinography in clinical practice. As the risk of anterior segment neovascularization in iCRVO is highest in the first year following onset, especially during the first three months, monthly follow-up during this period has been recommended. Besides controlling underlying risk factors (hypertension, intraocular pressure), laser panretinal photocoagulation should be applied immediately if new vessels in the iris or anterior chamber angle, or posterior segment are detected. Data on the effect of therapeutic strategies for macular edema in patients with CRVO and retinal capillary non-perfusion is very scarce; most randomized clinical trials (RCTs) on CRVO did not include or included very few of these patients. Anti-VEGFs are advised to treat macular edema secondary to CRVO; their efficacy and cost-effectiveness in patients with retinal ischemia, however, remains to be elucidated.

For patients presenting with BRVO, visual acuity, WA-FFA and OCT are advisable. Prognostic indicators for retinal ischemia and its complications have been less extensively studied in BRVO when compared with CRVO. Lower levels of vision at presentation (<20/60) are most commonly observed in patients with retinal ischemia; the lower the presenting vision the more guarded the visual prognosis for the patient. Sector panretinal photocoagulation should be applied if new vessels develop but not prophylactically, just like for CRVO. In the presence of macular edema patients with BRVO should be treated with anti-VEGF therapy; the efficacy and cost-effectiveness of this treatment, in patients with retinal ischemia, however, remains to be elucidated.

X.   Conclusion

Finding consensus on a definition of iRVO may be challenging. A separation between iRVO and non-iRVO may not be required, provided there is homogeneity on the phenotyping of patients with this disease and that important features determining risk are measured and are considered when managing patients with RVO and undertaking studies on this condition. Many studies have shown that retinal ischemia confers increased risk of sight loss and neovascular complications in patients with RVO. Information on the presence, extent and location of areas of retinal ischemia should be provided in studies evaluating RVO. To date, no treatments are available to prevent or treat retinal ischemia; research on this area is urgently needed.

XI.   Method of Literature Search

Five databases were searched including Medline, EMBASE, SCOPUS, Web of Science and Cochrane library with no years' limitations. Keywords included retinal vein occlusion, retinal venous thrombosis, retinal venous obstruction, central retinal vein occlusion, and branch retinal vein occlusion which were combined with ischemic, non-perfused or proliferative terms. Further search was conducted combining the stated keywords with epidemiology, prevalence, incidence, risk factors for the epidemiology and risk factors sections; mechanisms, pathogenesis, macular edema, neovascularization, the different retinal cells, and experimental models for the etiology and pathogenesis section; the different ancillary technologies for the ancillary studies section; natural history for the natural history section; and the different therapies for the management section. From the literature retrieved, only articles that provided data on the ischemic form of RVO, specifically, or differentiated between iRVO and non-iRVO were included. For the current treatments section, priority was given to RCTs while prospective interventional studies were included only if ≥ 10 patients with iRVO were studied. Retrospective studies that reviewed ≥ 100 patients' records were planned to be included but none of the retrieved articles met this criterion. All articles included were limited to the English language.

Figure-1: Fluorescein angiogram (left) obtained from the right eye of a patient with ischemic central retinal vein occlusion. Marked retinal capillary drop out is observed. A relative preservation of the capillaries around the foveal avascular zone is, however, observed. Marked intraretinal edema was evident on spectral domain optical coherence tomography (right). Visual acuity was 9 ETDRS letters.

Figure-2: Fluorescein angiogram of a patient with ischemic branch retinal vein occlusion. Note marked macular and midperipheral retinal non-perfusion. Breakdown of the perifoveal capillary network was noted (inset).

Figure-3: (A) Diagram depicting the proposed strategy to identify and classify retinal ischaemia in retinal vein occlusion (RVO). Wide angle fundus fluorescein angiography (FFA) would allow visualisation of a large proportion of retina. Then, areas of retinal ischaemia within the midperipheral / peripheral retina (all areas outside the central red circle) could be marked and measured in mm^2 using appropriate software. In order to determine the area of macular ischemia, a central area with a diameter of 5.5 mm centered at the fovea could be drawn (red circle) and retinal capillary drop-out within this region measured in mm^2. Magnification of the centre of the macula showing the perifoveal capillary network (top, right). Drop-out of perifoveal capillaries could be then specified in clock hours (yellow circle). For this purpose, optical coherence tomography angiography (OCT-A) could be also used **(B).** For all patients with RVO, total area of visible retina, total area of capillary drop-out in the midperipheral/peripheral retina and macula and extent of drop-out of perifoveal capillaries in clock hours, should be provided.

Table-1: Randomized clinical trials in which small number of patients with ischemic retinal vein occlusion were included and/ or in which specific data from ischemic and non-ischemic cases was not provided.

Author	Year	Information provided on the ischemic status of patients included
BVOS [1] group III	1984	Excluded patients with foveal capillary non-perfusion No data available separately iBRVO and non-iBRVO
CVOS [4] group M	1995	Excluded patients with macular non-perfusion, retinal neovascularization and vitreous hemorrhage Only 21/ 155 (14%) eyes had ≥10 DA of retinal capillary non-perfusion No data available separately for iCRVO and non-iCRVO
SCORE-CRVO Ip et al.[137]	2009	Only 3/271 (1%) patients had ≥10 DA of retinal capillary non-perfusion No data available separately for iCRVO and non-iCRVO
SCORE-BRVO Scott et al.[264]	2009	Only 41/411 (10%) patients with ≥5 DA of retinal capillary non-perfusion No data available separately for iBRVO and non-iBRVO
CRUISE Brown et al.[37]	2010	Excluded patients with RAPD Only 2/392 (0.5%) patients had ≥10 DA of retinal capillary non-perfusion
BRAVO Campochiaro et al.[37]	2010	0/397 (0%) patients had ≥10 DA of retinal capillary nonperfusion
GENEVA Haller et al.[99]	2010	Excluded patients with ocular neovascularization No data available separately for iRVO and non-iRVO
ROCC Kinge et al.[153]	2010	Only 5/ 24 (21%) patients with ≥10 DA of retinal capillary non-perfusion No data available separately for iCRVO and non-iCRVO
Epstein et al. [79]	2012	No data available separately for iCRVO and non-iCRVO
HORIZON Heier et al.[124]	2012	No data available separately for iRVO and non-iRVO
GALILEO Holz et al.[128]	2013	Only 14/177 (8%) patients with ≥10 DA of retinal capillary non-perfusion No data available separately for iCRVO and non-iCRVO
RETAIN Campochiaro et al.[44]	2014	No data available separately for iRVO and non-iRVO
RELATE Campochiaro et al.[46]	2015	No data available separately for iRVO and non-iRVO
MARVEL Narayanan et al.[202]	2015	No data available separately for iBRVO and non-iBRVO
RABAMES Pielen et al.[234]	2015	Excluded patients with macular ischemia and neovascular complications 0/30 patients (0%) had ≥10 DA of retinal capillary non-perfusion

iBRVO = ischemic branch retinal vein occlusion; iCRVO = ischemic central retinal vein occlusion; DA= disc areas; RAPD = relative afferent pupillary defect

Table-2: Suggested parameters on functional diagnostic modalities to differentiate between iCRVO and non-iCRVO			
Diagnostic modality	**Parameter**	**Findings**	**Study**
Visual acuity	≤6/120	Sensitivity 91-100% Specificity 78-88%	Hayreh et al., 1990 [123]
	≤6/60	85% of patients with iCRVO have visual acuity ≤6/60	Hayreh et al., 2011 [119]
Pupillary examination	RAPD≥0.6 Log unit	Sensitivity 83% Specificity 70%	Bloom et al., 1993 [31]
	RAPD ≥0.7 Log unit	Sensitivity 88% Specificity 90%	Hayreh et al., 1990 [123]
	PAPD ≥0.9 Log unit	Sensitivity 80% Specificity 97%	Hayreh et al 1990 [123]
	RAPD ≥1.2 Log Unit	All eyes with ocular NV and/or extensive retinal CNP had RAPD of ≥ 1.2 log units ND	Servias et al., 1986 [267]
Visual field Goldmann perimetry	I2e defect	Sensitivity 94-100% Specificity 67-78%	Hayreh et al., 1990 [123]
	I4e defect	Sensitivity 92% Specificity 87%	
	V4e defect	Sensitivity 71-82% Specificity 83-88%	
ERG	Reduction of b-wave amplitude by > 60% of normal fellow eye (in photopic and scotopic ERG)	Sensitivity 80-90% Specificity 71-80%	Hayreh et al., 1990 [123]
	Reduction of b/a ratio by > 60% of normal fellow eye (in photopic and scotopic ERG)	Sensitivity 60-70% Specificity 70%	
	b/a ratio=0.88 in photopic ERG	Sensitivity 87.5% Specificity 78%	Williamson et al., 1997 [312]
	b-wave amplitude=56µV in photopic ERG	Sensitivity 87.5% Specificity 86%	
	b-wave amplitude=76µV in photopic ERG	Sensitivity 100% Specificity 66%	
	Implicit time of >35 ms in 30 Hz flicker	All patients with iCRVO had implicit time ≥35.0 ms	Kjeka et al., 2013 [155]
	Implicit time of ≥37 ms in 30 Hz flicker	75% of patients with an implicit time of >37 ms developed ocular NV during the follow-up period of one year compared to 7% of CRVO patients with an implicit time of ≤37 ms	Hvarfner et al., 2003 [131]
	Interocular amplitude difference =23 µV in 30 Hz flicker	Sensitivity 100% Specificity 100%	Kuo et al., 2010 [162]
	Interocular amplitude ratio of 60% in 30 Hz flicker	Sensitivity 100% Specificity 100%	
RAPD and ERG combined	≥0.7 log unit RAPD and ≤60% b-wave amplitude	Sensitivity 97-100% Specificity 71%	Hayreh et al., 1990 [123]

Ophthalmo-dynamometry	Central retinal venous pressure > diastolic central retinal arterial pressure	All patients with iCRVO had central retinal venous pressure > diastolic central retinal arterial pressure	McAllister et al., 2014; Jonas & Harder, 2007; Do et al., 2008 [68,141,194]

iCRVO = ischemic central retinal vein occlusion; DA= disc areas; RAPD = relative afferent pupillary defect; NV= neovascularization; CNP= capillary non-perfusion; ND= natural density; ERG= electroretinography; μV= microvolt; ms= millisecond; Hz= Hertz unit.

Table-3: Suggested parameters on structural diagnostic modalities to differentiate between iCRVO and non-iCRVO			
Diagnostic modality	**Parameter**	**Finding**	**Study**
Ophthalmoscopy	Retinal hemorrhage ≥1/4 of posterior retina	Sensitivity 81-84% Specificity 72-74%	Hayreh et al., 2014 [116]
FFA	≥10 DA of retinal CNP (ischemic index≥50%)	*93% of eyes with NVG secondary to iCRVO have ischemic index ≥50% *91% of eyes with retina/disc NV secondary to iCRVO have ischemic index ≥50% *33% and 45% of eyes with ischemic index ≥50% developed NV in retina/disc and NVG, respectively	Magargal et al., 1982 [183]
	10-29 DA of retinal CNP	16% of patients with iCRVO developed anterior segment NV	CVOS, 1997 [6]
	≥75 DA of retinal CNP	52% of patients developed anterior segment NV	
	Ischemic index ≥45% on WA-FFA	All patients with NV (any) had ischemic index ≥45%.	Tsui et al., 2011 [300]

iCRVO = ischemic central retinal vein occlusion; FFA= fundus fluorescein angiography; DA= disc areas; CNP= capillary non-perfusion; NVG= Neovascular glaucoma; NV= neovascularization; WA-FFA= wide-angle fundus fluorescein angiography.

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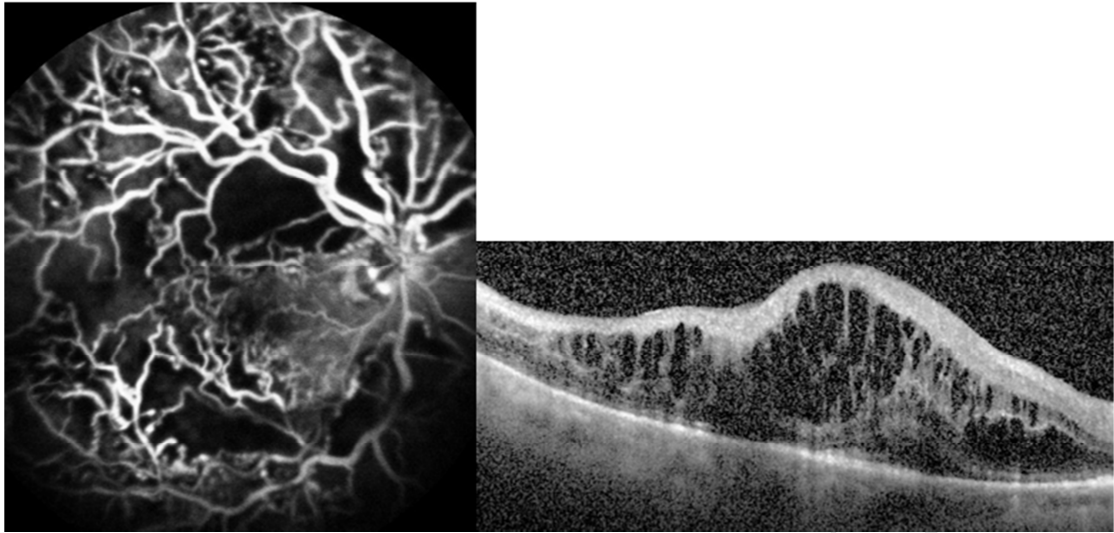
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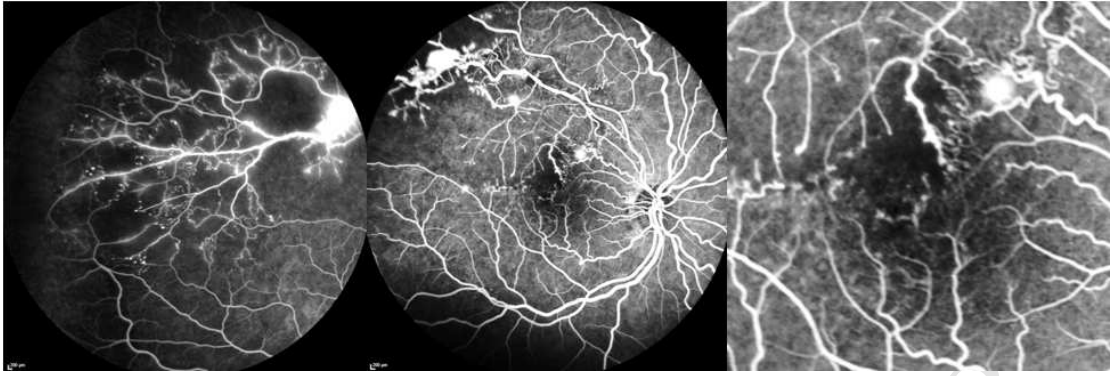
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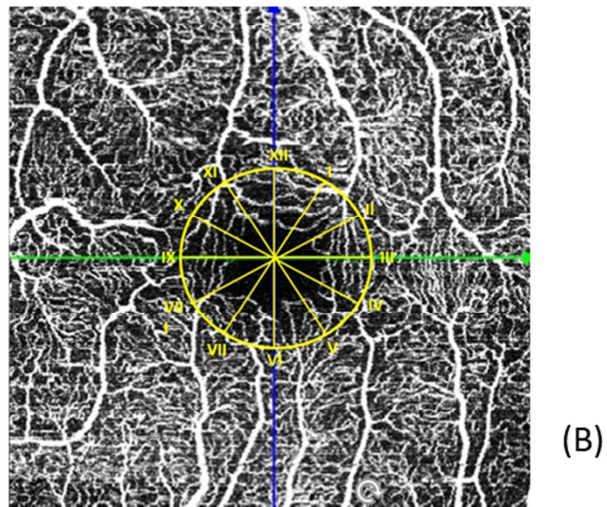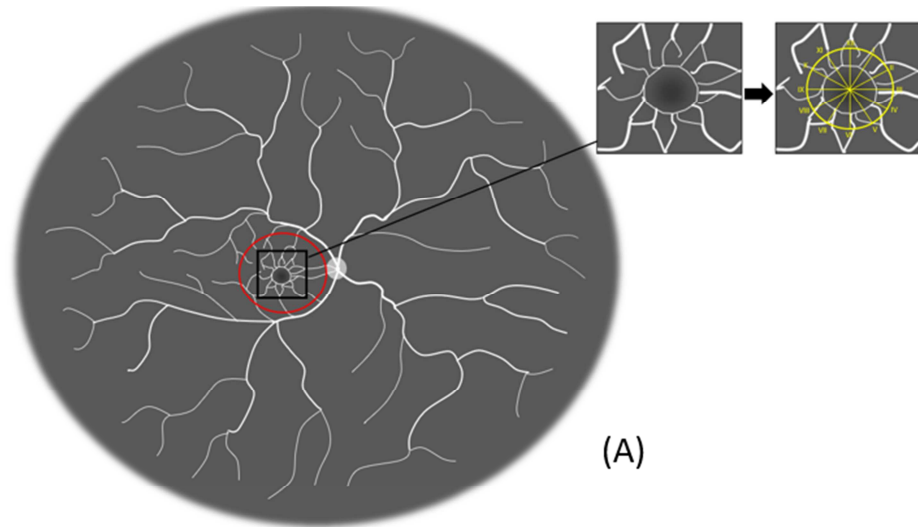
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