The ROYAL COLLEGE of OPHTHALMOLOGISTS

Clinical Guidelines

Retinal Vein Occlusion (RVO) Consultation Document

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1. Key recommendations and Good Practice Points for Implementation

Central retinal vein occlusion (CRVO)

Non-ischaemic CRVO may resolve without any complications. Macular oedema (MO) is the most common complication from CRVO and anti-VEGF treatment is successful at improving vision in eyes with MO secondary to CRVO.

However, 30% of eyes with non-ischaemic CRVO may convert to an ischaemic CRVO over three years. Prompt anti-VEGF therapy does not completely prevent worsening of retinal nonperfusion in eyes with CRVO.[1] Anti-VEGF therapy in eyes with an ischaemic CRVO retains the risk of neovascularisation and will need close monitoring following cessation of anti-VEGF therapy.

Branch retinal vein occlusion (BRVO)

For patients presenting with recent onset mild visual impairment due to MO secondary to BRVO, it may be reasonable to observe the progress of the condition over the first three months of follow-up. However, presentation may be delayed in some patients and in others with significant visual impairment at presentation, only 18 to 41% of eyes improve spontaneously with visual acuity not improving to 6/12 on average, suggesting early treatment may be appropriate in these cases.

Associations and risk factors

The most common associations of Retinal Vein Occlusion (RVO) are related to the raised risk of atherosclerosis and not significantly associated with systemic venous occlusions or their known risk factors. The main associations of RVO can therefore be defined as risk factors for atherosclerosis, and the remainder are conditions that cause hyperviscosity or slow or turbulent flow through retinal veins.

Therefore, diabetes is no more common in patients with RVO than the general population. However, the testing for diabetes at diagnosis of RVO is useful in detecting undiagnosed diabetes. The target HbA1C recommended by NICE for type 2 diabetes is 53 mmol/mol (7.0) (NICE NG28, 2015, updated 2020).

The testing for anti-phospholipid antibodies (aPL) is not recommended for a RVO occurring in isolation of other recognised anti-phospholipid syndrome (APS) clinical associations. There is currently no high quality evidence to support the use of anticoagulation or antiplatelet drugs in the management of RVO.[2] The finding of a thrombophilic abnormality in a patient presenting with a RVO does not alter management options or predict prognosis.

Cardiovascular morbidity and mortality

The systemic conditions for which a patient with RVO may be at greater risk are:

- Stroke: conflicting reports on associations have been noted (see below)[3-6]
- Cardiovascular disease under age 70 was noted in one study[5] but not in another report[7]
- Peripheral venous disease (13/439) 3% pre diagnosis of CRVO.[8]

This does not necessarily mean that CRVO is a risk for these conditions, but rather that RVO and these conditions share underlying risk factors such as hypertension and diabetes. There is no clear evidence that a different therapeutic approach for medical risk factors is warranted following a retinal vein occlusion than would be recommended anyway.

RVO in younger patients (less than 50 years of age)

RVO can occur in young patients with an estimated global prevalence of 0.26% in people age 30-39 years and 0.44% in people age 40-49 years.[28] The need for intravitreal anti-VEGF for macular oedema is less in young patients with CRVO.[63,65] However, at least 20% of patients develop poor visual outcome with severe neovascular complications.[66]

Medical investigations in retinal vein occlusions

The main benefit of medical tests in RVO is to improve health by treating the commonly associated risk factors of atherosclerosis, hypertension, diabetes and lipid abnormalities.

Summary of recommended medical investigations in the eye clinic:

- Medical History
- BP measurement
- Serum glucose estimation
- Request laboratory investigations for FBC and ESR

Further assessment of potential associated conditions, including further medical tests, are probably best performed by the patient's physician who can then organise further management and supportive measures such as smoking cessation.

The decision about whether to continue these oestrogen containing therapies in a woman with retinal vein occlusion should be made on a case by case basis.

Retinal imaging in RVO

- Optical coherence tomography (OCT) is recommended in the diagnosis, monitoring and assessing treatment response of macular oedema secondary to RVO
- Fluorescein angiography (FA)/Optical coherence tomography angiography (OCTA) is recommended to assess retinal nonperfusion to aid the identification of eyes with ischaemic CRVO

Ophthalmological Management of CRVO

- Anti-VEGF agents are the first-line choice for treatment of Macular Oedema due to CRVO.
- Just over a third of patients will require only 3 injections to reach maximum visual acuity (VA) while another third will require 6 consecutive injections. It is recommended to initiate treatment as the posology suggests which is monthly treatment until maximum stable VA is achieved.
- In a PRN regimen, it is recommended that these patients are monitored monthly for optimal visual outcomes.
- a delay in initiating treatment up to six months resulted in fewer visual gains compared to immediate initiation of treatment. It is therefore imperative that patients are initiated on treatment as soon as the diagnosis is established unless the treating physician and/or the patient decide on deferred treatment.
- For patients presenting with a VA of less than 6/96, careful consideration should be given to further therapy in such eyes that do not improve in terms of Snellen visual acuity or OCT central subfield thickness after three loading injections at monthly intervals and treatment is not recommended if no response occurs after six injections. Multiple factors such as degree of macular ischaemia, structural

damage at the fovea and other confounding factors should be taken into account to decide continuation of treatment in this group of patients after initial therapy.

- Intravitreal steroids – NICE TA 229 has recommended the use of Ozurdex in the treatment of MO secondary to CRVO
- Laser photocoagulation There is also no evidence to suggest any benefit from a combination of macular grid laser and intravitreal anti-VEGF or steroids for MO secondary to CRVO.

Management of macular oedema in ischaemic central retinal vein occlusion

- Eyes with >10DA of posterior pole nonperfusion should not be excluded from anti-VEGF therapy.
- Eyes with a presenting vision of 6/96 or worse (eyes that were excluded from clinical trials), anti-VEGF should still be considered if there is presence of significant MO as reasonable improvements in vision may still occur. However, if oedema resolve with no improvement in visual acuity following a trial of anti-VEGF, cessation is recommended after three injections.
- 1-2 monthly observation for neovascularisation is recommended in the first year following cessation of anti-VEGF therapy in eyes with ischaemic CRVO.

Management of ischaemic central retinal vein occlusion and anterior segment neovascularisation

- Monitor Ischaemic CRVO monthly for new vessels of the iris and/ or the angle[9] unless there are particular risk factors.
- Inhibitors of vascular endothelial growth factor (anti-VEGF agents) may be used as adjuvants to pan-retinal photocoagulation in patients with anterior segment neovascularisation secondary to ischaemic CRVO.[10]
- Commence anti-VEGF therapy at the earliest sign of iris or angle new vessels followed by sufficient panretinal photocoagulation either on the same day (prior to anti-VEGF therapy) or within 1-2 weeks.

Management of established neovascular glaucoma

- If the eye has any visual potential, intraocular pressure should be controlled with topical pressure-lowering agents, surgical intervention or cyclo-ablative procedures. In addition, regression of iris new vessels (NVI) and angle new vessels (NVA) seem to offer a long-term chance of maintaining ocular comfort.

Further follow-up in eyes that have significant ischaemia

- monthly follow-up is recommended in the first 6 months and follow-up after six months should be every three months for one year.
- Subsequent follow-up for all patients will depend upon treatment given and complications within the earlier period but will not normally be required after three years in uncomplicated cases.
- The development of disc collaterals + spontaneous resolution of MO indicates a good outcome and should lead to discharge from clinical supervision after 6 months provided no other complications.

Ophthalmological Management of BRVO

- Recommended treatment guideline for MO due to BRVO is that if laser photocoagulation is contemplated, it should be performed in those eyes with MO secondary to BRVO of at least three months' duration with visual acuity of 6/12 or worse and without significant macular haemorrhage and with a fluorescein angiogram showing capillary perfusion in the absence of blood involving the fovea. However, only a minority of patients in clinical practice are eligible for this treatment option based on these recommendations.
- Treatment of neovascularisation:
  - Disc or retinal neovascularisation is an indication for photocoagulation to the ischaemic retina (sector photocoagulation), although available evidence suggests that waiting until vitreous haemorrhage occurs before laser treatment does not adversely affect the visual prognosis.[17]
  - Follow-up visits at three to four monthly intervals are recommended in patients with one quadrant or more retinal ischaemia.
  - Apply sector laser photocoagulation once retinal or optic disc neovascularisation occur.
  - Fluorescein angiography is not usually necessary prior to laser because the area of ischaemia is visible clinically.
- Photocoagulation for retinal neovascularisation in BRVO is applied to the sector of retinal capillary closure. An adequate number of laser spots using a single spot or multisport laser should be applied in the affected sector, one shot width apart with sufficient energy to create a mild grey-white laser discoloration of the retina. A quadrant usually requires at least 500 shots of 500µm diameter.

RVO Service Specifications

- Time from referral from the primary source to initial evaluation and treatment by the ophthalmologist at the eye clinic is not more than 2 – 4 weeks from presentation.
- Minimum clinical services required for effective management
  - Best corrected visual acuity assessments by optometrist or certified VA examiners
  - Colour Fundus photographs and Fundus Fluorescein angiography (FFA) / OCTA by trained technical staff
  - Optical coherence tomography (OCT) with the Spectral domain OCT (SD-OCT) by trained technical staff
  - Treatment initiated within one to two weeks of assessment by the attending ophthalmologist
  - Appropriate facilities for IVT injection
  - Appropriate capacity for follow-up, monitoring and re-treatment

- Referral Pathways:
  - All patients suspected to have RVO by the optometrist, general practitioner, or other health workers should be referred directly to the nearest Eye Centre with pathways set up to allow urgent access.
  - Optometrists may be used for 'screening' or first examination of patients suspected of having RVO.
  - Fast track clinics collecting imaging in the community or hospital can help triage to find those who are symptomatic with reduced vision and centre involving macular oedema.[11]
- Low Vision and Living with RVO:
  - Patients with reduced best-corrected visual acuity secondary to RVO should be offered the access to low vision support and advice at an early stage.
  - Do not to wait until all treatment options have been explored or until an individual's vision deteriorates to a level that merits registration as visually impaired/severely visually impaired before referring an individual to low vision and rehabilitation services.

2. Lay Summary

Retinal vein occlusion occurs when there is an obstruction to the outflow of blood from the retina. This can occur in a branch resulting in a branch retinal vein occlusion or centrally resulting in a central retinal vein occlusion. This condition can occur at any age or gender but is more prevalent in the older age groups. The severity of the impact it can have on vision is a spectrum, with some mild cases with minimal visual disturbances while some can be very significant with marked irreversible damage to the retina and vision loss. This condition can be associated with risk factors such as high blood pressure, high cholesterol and diabetes and management is usually targeting at these risk factors to avoid a further episode or a cardiovascular event to another part of the body.

Macular oedema or fluid leakage within the centre of the retina is a common complication of this condition and can result in poorer vision. This can be improved with treatment and the first line of treatment are injections of a drug into the eye at regular intervals. Some patients can experience growth of new blood vessels in the eye as a complication of this condition and this will require retinal laser treatment to regress the development of these vessels. If left untreated, this can result in worsening of vision and discomfort. Regular monitoring in hospital dis recommended for several years to manage any complication that can arise.

3. Introduction

3.1 Description of the condition

Retinal vein occlusion (RVO) is an obstruction of the retinal venous system by thrombus formation and may involve the central, hemi-central or branch retinal vein. The most common aetiological factor is compression by adjacent atherosclerotic retinal arteries. Other possible causes are external compression or disease of the vein wall e.g., vasculitis.

Central retinal vein occlusion (CRVO) results from thrombosis of the central retinal vein when it passes through the lamina cribrosa.[12,13] It is classically characterised by disc oedema, increased dilatation and tortuosity of all retinal veins, widespread deep and superficial haemorrhages, cotton wool spots, retinal oedema and capillary non-perfusion in all four quadrants of the retina. In less severe forms the disc oedema may be absent. A previous CRVO may show evidence of optic disc and retinal collaterals, a telangiectatic capillary bed and persistent venous dilation and tortuosity, perivenous sheathing, arteriolar narrowing, and macular abnormalities (chronic macular oedema and retinal pigment epithelial changes).

Branch retinal vein occlusion (BRVO) is caused by venous thrombosis at an arteriovenous crossing where an artery and vein share a common vascular sheath.[14,15] It has similar features to CRVO except that they are confined to that portion of the fundus drained by the affected vein.

Hemi-retinal vein occlusion (HRVO) affects either the superior or inferior retinal hemisphere, and the retinal haemorrhages are nearly equal in two altitudinal quadrants (the nasal and temporal aspects) of the involved hemisphere.

The two main complications of RVO are macular oedema and retinal ischaemia leading to iris and retinal neovascularisation.

Macular Oedema (MO): Thrombosis of the retinal veins causes an increase in retinal capillary pressure resulting in increased capillary permeability and leakage of fluid and blood into the retina. Co-existent retinal ischaemia (see below) may exacerbate this process by the production of vascular endothelial growth factor (VEGF) which in turn promotes retinal capillary permeability and leakage into the extracellular space resulting in further development of MO. MO is the most common cause of visual impairment in RVO, followed by foveal ischaemia.

Retinal ischaemia and iris and retinal neovascularisation: Varying degrees of retinal ischaemia due to non-perfusion of retinal capillaries may occur and principally depends on the degree of retinal vein thrombosis. These changes result in increased production of VEGF and other cytokines, which promote new vessel formation principally but not exclusively involving the iris and angle in CRVO and the retina in BRVO. These complications can lead to neovascular glaucoma, vitreous haemorrhage, and tractional retinal detachment with severe visual impairment.

Ischaemic versus non-ischaemic RVO: Both CRVO and BRVO can be broadly classified into ischaemic and non-ischaemic types based on the area of capillary non-perfusion, and this distinction is useful for clinical management. It is arguable if these are two separate entities or just ends of a spectrum. The Central Retinal Vein Occlusion study (CVOS) defined ischaemic CRVO as fluorescein angiographic evidence of more than 10 disc areas (DA) of capillary non-perfusion on seven-field fundus fluorescein angiography.[7,9] However, this definition of >10DA is not appropriate with widefield or ultra-widefield imaging given the larger area imaged and unclear clinical significance of ischaemia in the far periphery. Capillary non-perfusion >10DA in the posterior pole of eyes with CRVO irrespective of imaging modality would suggest a high risk of neovascularisation.[16] An ischaemic index (ratio of capillary non-perfusion/total area visible)

of >45%, total area of nonperfusion >75DA on ultra-widefield angiography or >10DA of posterior pole nonperfusion has been found to correlate with neovascularisation.[16,17] It is also important that a clear distinction is made between macular ischaemia and an ischaemic RVO (i.e. global retinal ischaemia). Furthermore, the definition of an ischaemic CRVO may not simply depend on angiography findings but also other parameters such as the characteristics described below.

Ischaemic CRVO is associated with one or more of the following characteristics: -

1. Poor visual acuity (44% of eyes with vision of <6/60 develop rubeosis [CVOS])[7,9]
2. Relative afferent pupillary defect
3. Presence of multiple dark deep intra-retinal haemorrhages
4. Presence of multiple cotton wool spots
5. Degree of retinal vein dilatation and tortuosity
6. Fluorescein angiography showing greater than 10 disc areas of retinal capillary non-perfusion on 7-field fluorescein angiography (CVOS)[7,9]
7. Electrodiagnostic tests (ERG): reduced b wave amplitude, reduced b:a ratio and prolonged b-wave implicit time on the electroretinogram[18–22]

There is no evidence as to which combination of the above characteristics best defines ischaemic CRVO. It is important to note that up to 30% of eyes with initially non-ischaemic CRVO may convert to ischaemic subtype.[22–25] This is usually heralded by further rapid visual deterioration and requires additional assessment.

The prevalence and incidence of ischaemic BRVO is not fully defined. Ischaemia involving the macula causes visual impairment. However, ischaemia may occur in peripheral areas of the retina and result in retinal neovascularisation and vitreous haemorrhage. Neovascular glaucoma is rare in ischaemic BRVO.

3.2 Population to whom the guideline applies e.g. the age range, gender, clinical description (ICD10) and co-morbidity (ICD10) and any exclusions

This guideline applies to all patients of any age range or gender with a diagnosis of retinal vein occlusion.

The ICD-10 codes are;

- H34.81 Central retinal vein occlusion
- H34.83 Tributary (branch) retinal vein occlusion

3.3 Current practice, and why there is scope for change

Since the publication of the previous edition of The Royal College of Ophthalmologists' (RCOphth) Retinal Vein Occlusion Guideline (2015), advances on retinal imaging including optical coherence tomography (OCT) angiography, ultra-widefield imaging and new clinical studies have expanded our understanding of retinal vein occlusion (RVO) and its management. Increasing evidence of the effectiveness of standard treatment options and comparisons of these therapies have been published. Moreover, evidence on different treatment regimens is also available. The previous guideline (2015) serves as a framework on which additional knowledge has been added to provide an update in the management of RVO.

The new guidelines incorporate established and applicable information and guidance from the previous version with revision. As stated in the previous version, the guidelines are advisory and are not intended as a set of rigid rules, since individual patients require tailored treatment for their circumstances. However, it is hoped that, if used appropriately, the guidelines will lead to a uniformly high standard of management of patients with RVO.

4. Objectives

The aim of the guideline is to provide evidence-based, clinical guidance for the appropriate management of different aspects of RVO. The foundations of the guidelines are based on evidence taken from the literature and published trials of therapies as well as consensus opinion of a representative expert panel convened by the RCOphth with an interest in this condition.

The scope of the guideline is limited to current diagnostic tools, management, service set-up and delivery to facilitate delivery of optimal clinical care pathways and management for patients with RVO.

4.1 Description of the key stakeholders and end users

The guideline is primarily for ophthalmologists; however, they are relevant to other healthcare professionals, service providers and commissioning organisations as well as patient groups. The guideline does not cover the rare, complex, complicated, or unusual cases. It is recommended that readers refer to other relevant sources of information such as summaries of product characteristics (SPCs) for pharmaceutical products as well as the National Institute of Health and Care Excellence (NICE) and General Medical Council (GMC) guidance.

Key stakeholders:

1. Patients with a diagnosis of retinal vein occlusion
2. Ophthalmologists (in particular, medical retina specialists)
3. General Practitioners
4. Optometrists
5. Patient groups
6. Health care commissioners

5. Methodology

5.1 Search Strategy

Medline and Pubmed were used with relevant search terms scanning the database from 30th June 2014 (date of the search period in the previous guidelines) to 31st December 2020. The previous edition of the RCOphth guidelines and NICE single technology appraisals were used as reference sources.

6. Results and summary of findings

6.1 Central Retinal Vein Occlusion

Although some patients with CRVO can experience an improvement in MO and visual acuity, visual acuity generally decreases over time. A systematic review on the natural history of untreated CRVO reported that only a small proportion of patients showed spontaneous improvement in visual acuity and their final visual outcome at 3 – 40 months was not typically greater than 73 ETDRS letters (Snellen equivalent ~6/12). Only 20% of patients who present with an initial visual acuity of 35–65 ETDRS letters (Snellen equivalent 6/60 to 6/18) are likely to improve spontaneously.

Non-ischaemic CRVO may resolve completely without any complications. Follow-up of such cases for at least 18 months is usually recommended but the development of disc collaterals and spontaneous resolution of macular oedema for at least 6 months should allow the discharge of the patient from clinical supervision. However, 30% may convert to an ischaemic CRVO over three years due to an increase in area of non-perfusion. More than 90% of patients with ischaemic CRVO have a final visual acuity of 6/60 or worse.[7,9]

6.2 Branch Retinal Vein Occlusion

Based on the Branch Retinal Vein Occlusion study (BVOS) the prognosis of BRVO is better than CRVO with approximately 50 – 60% of untreated BRVO cases retaining a visual acuity ≥ 6/12 after one year.[26] Therefore, when a patient presents with recent onset mild visual impairment due to MO secondary to BRVO, it may be reasonable to observe the progress of the condition over the first three months of follow-up. However, presentation may be delayed in some patients and in others with significant visual impairment at presentation, only 18 to 41% of eyes improve spontaneously with visual acuity not improving to 6/12 on average, suggesting early treatment may be appropriate in these cases.

However, many patients may not present immediately and only 18 – 41% of eyes with MO due to BRVO at presentation show spontaneous improvement and, on average, visual acuity does not improve above 6/12 in this cohort. Approximately 20% of untreated MO due to BRVO experience significant deterioration of visual acuity over time.[26]

6.3 Bilateral involvement

The majority of RVO cases present as a unilateral condition. However, 5 – 6% present with evidence of bilateral BRVO and 10% of the BRVO patients will have fellow eye involvement over time. Similarly, approximately 10% of CRVO patients present with bilateral involvement at baseline and 5% may have fellow eye involvement over a one year period.[27]

6.4 Epidemiology of Retinal Vein Occlusion

Retinal vein occlusions are a common cause of visual loss in the United Kingdom, and are the second commonest cause of reduced vision due to retinal vascular disease after diabetic retinopathy, with BRVO occurring 2 – 6 times as frequently as CRVO.[26] There is no prevalence or incidence data from England or Wales. Globally, 28 million people are estimated to have RVO with a 10 year cumulative incidence of 1.63%.[28] In Europe, 0.7% of persons age 55 years and older are thought to have RVO.[29] US data reported in 2008 indicate a 15 year incidence of 500 new cases of CRVO per 100,000 population and 1800 BRVO cases per 100,000 population.[30]

The incidence and prevalence of both these conditions increases with age.[28] Australian data suggests that the prevalence of RVO is 0.7% for those younger than 60 years, 1.2% for those 60 – 69 years, 2.1% for those 70 – 79 years and it increases to 4.6% in people aged 80 years or above. No gender or racial differences in prevalence of both these conditions have been reported.

Most patients are unilaterally affected by this condition. Under 10% of CRVO are bilateral at presentation (range 0.4% to 43%). The fellow eye involvement over a one-year period is approximately 5%. Similarly, only 5% – 6% of patients at baseline have BRVO in both eyes at diagnosis with 10% showing bilateral involvement over time.

Visual impairment is more frequent with CRVO than BRVO. Macular oedema (MO) is the leading cause of visual impairment. It is estimated that approximately 11,600 people with BRVO and 5,700 people with CRVO suffer from visual impairment due to MO each year in England and Wales based on an annual incidence of BRVO of 0.12% and CRVO of 0.03% in people aged 45 years or older and 85% of BRVO and 75% of CRVO developing MO within two months of diagnosis while 50% of BRVO and 100% of CRVO experiencing visual impairment due to MO (NICE 2011).

6.5 Aetiology and risk factors of Retinal Vein Occlusions

Retinal vein occlusion is due to thrombosis of retinal veins (central, hemi or branch).[12,13,31] Atherosclerosis of the adjacent central retinal artery possibly compresses the central retinal vein at the lamina cribrosa leading to consequent thrombosis in the venous lumen. Rarely, retrobulbar external compression from thyroid eye disease, orbital tumour, or retrobulbar haemorrhage may be a cause. Whether primary thrombosis plays a role in this condition remains questionable. The clinical appearance is largely related to retinal ischaemia and the effects of elevated concentrations of VEGF in the vitreous and retina. Animals injected with VEGF will develop retinal haemorrhages and the use of anti-VEGF causes retinal haemorrhages to resolve. Branch retinal vein occlusions may relate to the point of arterial venous crossing in the retina.

Associations with developing retinal vein occlusions

The following conditions have variably been reported as associations:

- Hypertension[8,30,32–36]
- Diabetes[8,30(p15),32,33,35,37]
- Hyperlipidaemia[38]
- Hyperhomocysteinaemia
- Blood disorders: high plasma viscosity due to a paraprotein (myeloma ,Waldenstrom's macroglobulinaemia) , raised cell counts (leukaemia, myeloproliferative disorders) and thrombophilic abnormalities (inherited and acquired)
- Systemic inflammatory disorders (Behçets disease, systemic lupus erythematosus polyarteritis nodosa, sarcoidoisis, Wegener's Granulomatosis and Goodpasture's Syndrome)
- Glaucoma[39]
- Shorter axial length
- Retrobulbar external compression

The most common associations of RVO are related to the raised risk of atherosclerosis and not significantly associated with systemic venous occlusions or their known risk factors. The main associations of RVO can therefore be defined as risk factors for atherosclerosis, and the remainder are conditions that cause hyperviscosity or slow or turbulent flow through retinal veins.

The Eye disease case control study compared 258 patients diagnosed with CRVO between 1986 – 1990 in five centres, with 1142 age-matched controls.[33] The controls were recruited a year after the diagnosis of CRVO, from the same eye clinics. This study found an association with increased systemic hypertension, diabetes and glaucoma. These associations were higher with ischaemic CRVO. 65% had hypertension (167/257) compared to 44% of controls (506/1139) odds ratio 2.5 (1.8 – 3.4). Only 2% were started on anti-hypertensive medication at the time of diagnosis. CRVO was less common with moderate alcohol intake. The incidence of diabetes was 16% (43/258) compared to 9% in controls (102/1142); odds ratio two (1.3 – 2.9).

In a study looking at the association of mortality risk with CRVO, 439 patients diagnosed with CRVO in Denmark, between 1976 and 2010, were compared to 2195 age and sex matched controls from the Danish national patient registry alive at the date of diagnosis of CRVO.[34] Co-morbidity was recorded for 10 years pre-diagnosis and over follow-up for five years. CRVO was rare in the general population. Hypertension was found in 68% compared to 55% of controls, odds ratio 2.03(1.48 – 2.78), based on assessing hospital discharge records and drug prescriptions. Diabetes incidence was 16% vs 8.7%, OR 2.08 (1.41 – 3.08). However, it is possible there may have been a selection bias in this study, as the CRVO cases were recruited in the hospital whilst the controls were from the general population.

In the Geneva Study (2010) which evaluated 1267 retinal vein occlusions (CRVO/BRVO) and their response to Ozurdex, hypertension was found in 64% of patients and diabetes in 12%.[40] Their average age was 65. This is in keeping with the rates found in the aforementioned studies. In a recent metanalaysis on diabetes and risk of retinal vein occlusion, it was concluded that diabetes was significantly associated with CRVO but not with BRVO.[41]

The incidence of hypertension is common in the population; 1in 4 adults in England (31% of men; 26% of women) 2015. (NICE NG136). Indeed, the incidence of hypertension in persons over 65 years of age in the UK (NICE CG127, 2011) and in the USA is currently approximately 65%.[42] The United States (US) National Health and Nutrition Examination survey of 2009 – 2010 showed that the age-specific and age-adjusted prevalence of hypertension among adults aged 18 and over was 6% in age group 18 – 39 years, 30.4% in 40 – 59 years, and 66.7% in people aged 60 years or above.[43] The guidelines on diagnosing and managing hypertension are summarised in the NICE guideline NG136 2019. Hypertension in Adults: diagnosis and management.

The current incidence of diabetes in the population seems to be as common as in the reported cases of vein occlusions. From NICE (NICE NG28) (updated 2020) on type 2 diabetes management, it was reported that 3.2 million people in the UK had diabetes with 90% being type 2. The UK 2013 statistics has reported an overall prevalence of diabetes of 6% and 6.7% in England and Wales respectively.[44] In the United States, the National Diabetes Statistics report 2020 estimated 1 in 10 Americans had diabetes and diabetes was present in 26.8% in people aged over 65 years.[45] Therefore, diabetes is no more common in patients with RVO than the general population. However, the testing for diabetes at diagnosis of RVO is useful in detecting undiagnosed diabetes. The target HbA1C recommended by NICE for type 2 diabetes is 53 mmol/mol (7.0) (NICE NG28, 2015, updated 2020).

In a population study in South Korea with 46,259 participants with RVO and a control arm of 138,777 participants, 14,727 cases of dementia occurred.[46] RVO was associated with an increased risk of subsequent all cause dementia, Alzheimer's disease and vascular dementia in both hypertensive and non-hypertensive individuals.[46]

6.6 The relation of RVO to systematic vein occlusions and the role of testing for venous occlusions risk factors

The main risk factors for systemic venous thromboembolism (VTE) are: age, immobilisation, surgery, cancer, pregnancy and oestrogen containing oral contraceptives and HRT. There is no good evidence that these are risk factors for RVO, however, conditions that cause systemic inflammation or hyperviscosity increase the risk of VTE and can rarely be associated with a retinal vein occlusion.

An individual may have an increased risk of VTE due to an inherited or acquired thrombophilia. The British Committee for Standards in Haematology (BCSH) Clinical Guidelines for testing for heritable thrombophilia (2010) and the Unusual Site VTE BCSH guidelines (2012) concluded that such testing was not appropriate for retinal vein occlusions.[47,48] A systematic review in 2017 evaluated the evidence for thrombophilia investigation in patients presenting with RVO and given the lack of high quality evidence concluded systematic thrombophilia screening of patients presenting with RVO could not be recommended.[49] A recent meta-analysis in 2020 pooled the prevalence reported in 95 studies in adults with RVO and RAO for Factor V Leiden (FVL) and Prothrombin (F-II) G20210A mutations, MTHFR C677T and PAI 4G polymorphisms, Antithrombin III (AT-III), Protein C (PC) and Protein S (PS) activity deficiencies, hyperhomocysteinemia and antiphospholipid (APL) antibodies.[50] A similar prevalence of all the inherited and acquired thrombophilias was found in patients with RVO compared to healthy subjects in keeping with these factors not being of primary importance in the pathogenesis of RVO.[50]

Acquired thrombophilia includes antiphospholipid syndrome (APS), myeloproliferative disorders and paroxysmal nocturnal haemoglobinuria (PNH). APS is an acquired autoimmune disorder associated with thrombosis (arterial, venous or microvascular) and/ or defined pregnancy morbidity. Although a number of other possible clinical associations have been reported RVO is not recognised as a clinical event in the consensus statement on classification criteria.[51] Guidelines on the diagnosis and management of APS in the UK[52] detail the laboratory testing criteria required for the diagnosis of APS which require persistence of test abnormalities on repeat testing >12 weeks apart. Antibodies may be detected as a lupus anticoagulant (LA) using coagulation based assays (e.g. DRVVT) or solid phase ELISA tests for IgG anti-phospholipid antibodies. For the latter the specificity, isotype and titre of the antibodies are important with only IgG antibodies considered to be relevant for thrombosis risk. Sample collection and preparation can affect the detection of LA. The diagnosis of APS therefore depends on a thorough assessment of the clinical history, consideration of alternative causes of thrombosis or pregnancy morbidity and review of the laboratory data in the light of knowledge of the limitations of the assays. Antiphospholipid antibodies (aPL) are a common incidental finding e.g. in the Leiden thrombophilia study, a population-based case control study of VTE, LA was present in 0.9% of unaffected controls (compared to 3.1% of cases), and anti-b2GPI in 3.4% of controls (compared to 7.5% of patients).[53] In a larger study, 178 asymptomatic carriers of aPL were followed up for 36 months and no episode of thrombosis was detected.[54] A diagnosis of APS can only be made in the context of recognised clinical features and persistent laboratory test abnormalities and influences the therapeutic management decisions on duration of anticoagulation and use of anti-platelet agents to reduce the risk of recurrent clinical events. Although a meta-analysis of 11 case control studies in 2015 reported an association between anticardiolipin Antibodies (ACA) but not LA with RVO this finding was not reproduced in the recent larger metanalysis by Romiti et al 2020; which pooled data on 2130 patients from 24 studies.[50,55] The testing for aPL is not recommended for a RVO occurring in isolation of other recognised APS clinical associations.

There is currently no high quality evidence to support the use of anticoagulation or antiplatelet drugs in the management of RVO.[2] The finding of a thrombophilic abnormality in a patient presenting with a RVO does not alter management options or predict prognosis.

6.7 Cardiovascular morbidity and mortality

Not surprisingly given the association with hypertension and diabetes some studies have found a higher incidence of cardiovascular and cerebrovascular morbidity and mortality in RVO patients compared to controls. However, this has not been found in all studies.

The systemic conditions for which a patient with RVO may be at greater risk are:

- Stroke: conflicting reports on associations have been noted (see below)[3-6]
- Cardiovascular disease under age 70 was noted in one study5 but not in another report[7]
- Peripheral venous disease (13/439) 3% pre diagnosis of CRVO.[8]

This does not necessarily mean that CRVO is a risk for these conditions, but rather that RVO and these conditions share underlying risk factors such as hypertension and diabetes. There is no clear evidence that a different therapeutic approach for medical risk factors is warranted following a retinal vein occlusion than would be recommended anyway.

6.8 Is RVO a predictor for the future development of stroke?

Tsaloumas and associates reported that RVO did not increase the rate of stroke development in a hospital-based study on 549 RVO patients after a mean follow-up period of 9.08 years.[4] These findings were confirmed in a retrospective population based study in Taiwan on 350 RVO versus 2100 controls.[5] However, Cugati et al found that men with RVO are associated with a non-significant 2.3-fold higher risk of cerebrovascular mortality for all ages in a pooled cohort of two-population based studies.[6] Similarly, a population-based study utilizing pooled data from the Atherosclerosis Risk in Communities Study and the Cardiovascular Health Study reported that carotid artery plaques are more common in patients with RVO; however, this association was not noted in another population-based study. In the study by Bertelson et al (2014) the incidence of stroke was higher both before and after the diagnosis of CRVO.[6,8,56] However, in a meta-analysis of 5 publications published in the Journal of the American Heart Association 2016, both CRVO (RR.1.90, 95%CI:0.64-1.34) and BRVO (RR:1.79,95%CI:1.18-2.72) at baseline conferred a greater incidence of stroke.[57]

6.9 Is RVO associated with increased mortality?

Reports on this subject are conflicting too. Bertelsen et al (2014) found a higher overall increased mortality compared to controls for CRVO (5.9 deaths/100 person years compared to 4.3 deaths/100 person years [HR, 1.45:95% CI,1.19 – 1.76]).[8] However, when the data was adjusted for overall occurrence of cardiovascular disorders including hypertension, peripheral vascular disease, ischaemic heart disease, myocardial infarction, congestive cardiac failure, cerebrovascular disease and diabetes, the mortality rate was comparable to that in the control population (HR 1.19;95% CI,0.96 – 1.46).[8]

Using the same methodology, this finding of no specific increase in mortality was also found for BRVO.58 Participants with BRVO at baseline did not have an increased 8-year risk of mortality due to ischaemic heart disease in the Beaver Dam study.[58] A population based study reported that RVO did not predict acute myocardial infarction.[58] Similarly, other reports show that RVO is not associated with cerebrovascular mortality.[32,59] However, Cugati et al (2007) found that men with RVO were associated with a non-significant 2.3-fold higher risk of cerebrovascular mortality for all ages in a pooled cohort of two-population based studies.[6] In another population-based study (Beijing Eye Study), RVO was significantly associated with an

increased overall mortality rate in subjects aged below 69 years.[60] Based on the current evidence, careful cardiovascular assessment and treatment of cardiovascular risk factors by the patient's physician are advocated in young male patients with RVO.[61]

6.10 Distinct clinical entities of retinal vein occlusion

Hemisphere vein occlusion

The risk of rubeosis in ischaemic hemi-central vein occlusion is greater than that of BRVO but less than that of CRVO.[23] The risk of disc neovascularisation appears greater for hemispheric vein occlusion than either ischaemic CRVO or BRVO.[62] The management of hemispheric vein occlusion is similar to that described for branch retinal vein occlusion.

RVO in younger patients (less than 50 years of age)

RVO can occur in young patients with an estimated global prevalence of 0.26% in people age 30-39 years and 0.44% in people age 40-49 years.[28] The causation of RVO in the younger person is still unclear in most cases. In a cohort study of 69 patients age <50 with CRVO, common comorbidities include hypertension (44%), dyslipidaemia (38%) and diabetes mellitus (23%).[63] A role for dehydration in such cases has been suggested but remains unproven.[64] Central retinal vein occlusion in this age group has been thought to have a more benign outcome in a greater proportion of patients, with spontaneous regression of the central retinal venous occlusive event being more common. The need for intravitreal anti-VEGF for macular oedema is less in young patients with CRVO.[63,65] However, at least 20% of patients develop poor visual outcome with severe neovascular complications.[66]

6.11 Medical investigations in retinal vein occlusions

In general, the aims of investigations in a medical condition are to manage causative factors that might improve the condition, prevent progression, or prevent recurrence in the same eye or in the other eye, and to reduce the risk to overall health. Apart from the rarely associated hyperviscosity conditions, there is little evidence that the natural history of a RVO will be influenced or a further RVO prevented, and the main benefit of medical tests in RVO is to improve health by treating the commonly associated risk factors of atherosclerosis, hypertension, diabetes and lipid abnormalities.

Summary of recommended medical investigations in the eye clinic:

- Medical History
- BP measurement
- Serum glucose estimation
- Request laboratory investigations for FBC and ESR

Testing the BP, serum glucose, FBC and ESR will detect associations with retinal vein occlusions that require urgent action such as severe hypertension, uncontrolled diabetes or rarely blood conditions such as leukaemia. A raised ESR may represent an inflammatory condition or a blood disorder such as myeloma.

Further assessment of potential associated conditions, including further medical tests, are probably best performed by the patient's physician who can then organise further management and supportive measures such as smoking cessation. For example, hypertension and diabetes are common and NICE guidance for assessment and management should be followed such as ambulatory BP measurements, which are not easily performed from an eye clinic; testing the lipid profile may require a fasting test.

The history, ocular examination and initial test results may direct further investigations. For example, raised white blood cells could point to leukaemia or a lymphoproliferative disorder, a raised ESR the presence of a paraprotein or a vasculitis and questions about symptoms such as night sweats, a physical examination for lymphadenopathy and immunoglobulin electrophoresis may be indicated.

Bilateral presentation or any sign of a vascular disturbance in the other eye, such as a few dot haemorrhages should increase suspicion of an underlying systemic condition.

The British Society of Haematology does not recommend routine thrombophilia testing for retinal vein occlusions.[47,48] Testing for acquired thrombophilia in an isolated retinal vein occlusion is also not recommended. (See section 5).

It is recommended that oestrogen-containing hormone replacement therapy and oral contraceptives not be commenced in those women with a history of retinal vein occlusion. However, the continued use in a patient who develops RVO does not appear to be associated with a higher rate of recurrence. The decision about whether to continue these oestrogen containing therapies in a woman with retinal vein occlusion should be made on a case by case basis.

6.12 Retinal imaging in RVO

Optical Coherence Tomography (OCT)

OCT is a widely used imaging modality providing quick and useful imaging of the macula. In RVO, OCT is recommended in the diagnosis, monitoring and assessing treatment response of macular oedema secondary to RVO. Features commonly seen are intraretinal fluid and subretinal fluid with an average central subfield thickness of 665-694µm in CRVO and 555-559µm in BRVO.[67–69] Increase in disorganization of the retinal inner layers (DRIL) and ellipsoid zone disruption is correlated with poorer visual outcomes following anti-VEGF therapy which were reported across several studies.[70–75]

Optical Coherence Tomography-Angiography (OCTA)

OCTA is a non-invasive imaging modality independent of intravenous contrast that can provide depth resolving information on retinal perfusion. Current widefield OCTA modalities using a 12mmX12mm field or a montage of multiple 12mmX12mm fields provides a significant coverage of the posterior pole and mid-periphery (montage). OCTA provides comparable measurements of capillary non-perfusion and foveal avascular zone when compared with traditional fluorescein angiography.[76,77] Widefield OCTA, specifically a montage of multiple 12mmX12mm scans is also useful in detection of retinal neovascularisation.[78]

Fluorescein Angiography (FA)

The use of OCTA where available has replaced FA in the assessment of macular ischaemia or even posterior pole non-perfusion when widefield OCTA is used. However, the FA provides information on transit, flow, vessel staining and leakage which is not evident on OCTA, thus, still useful in the assessment of RVO. Typically, the FA appearance of an acute CRVO will manifest reduced arterio-venous transit and late venous staining. This is useful in differentiating CRVO with ocular ischaemic syndrome (OIS), whereby, a reduced transit is also evident along with a commonly unilateral presentation, however, the late arterial staining and peripheral microaneurysms present in OIS is not seen in CRVO. FA is also useful in the diagnosis of a macular BRVO with macular oedema with identification of the affected vein with corresponding vascular changes – tortuous, narrowed, focally dilated vessels and capillary non-perfusion.[79]

Ultra-widefied fluorescein angiography (UWFA) exposes changes seen in the periphery. The clinical significance of capillary non-perfusion in the periphery is unclear. Despite a larger area imaged, >10DA of posterior pole non-perfusion is associated with a larger total area of nonperfusion and an increase risk of neovascularisation.[16] The mean total area of capillary non-perfusion on UWFA is 34DA and predominantly involves the temporal retina (75% of eyes).[80]

6.13 Ophthalmological management of CRVO

Macular oedema

Anti-VEGF

Anti-VEGF agents are the first-line choice for treatment of MO due to CRVO. The three widely used anti-VEGF agents are ranibizumab (Lucentis, Novartis), aflibercept (Eylea, Bayer) and bevacizumab (Avastin, Roche). The visual outcomes and mean number of injections in pivotal clinical trials are summarised in Table 1 and Table 2.

Ranibizumab

The pan-VEGF-A blocker, ranibizumab is EMA approved and recommended by NICE (NICE TA238, May 2013) for the treatment of visual impairment due to MO secondary to RVO. Ranibizumab is a humanized recombinant monoclonal antibody fragment that selectively binds to human VEGF-A and prevents it from binding to its receptors. The dose of ranibizumab in adults is 0.5mg/0.05ml given as a single intravitreal injection. The interval between two injections is at least 4 weeks. The posology for Lucentis summarises that treatment is initiated with monthly injections until maximum visual acuity is achieved and/or no signs of disease activity, with three or more consecutive injections may be needed. Monitoring and treatment intervals are at the discretion of the clinician and a treat and extend regimen can be considered.

Aflibercept

The pan-VEGF-A, VEGF-B and placental growth factor (PlGF) blocker, aflibercept, is recommended for use in managing macular oedema secondary to CRVO with NICE issuing TA305 in February 2014. Aflibercept is a fusion protein consisting of portions of human VEGF (Vascular Endothelial Growth Factor) receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1. The dose of aflibercept is 2mg/0.05ml and the interval between two doses is at least 4 weeks. The posology for aflibercept in RVO is similar to the Lucentis (see above).

Bevacizumab

Bevacizumab (Avastin, Roche) has a concentration of 25mg/ml and 100mg in each 4ml vial. Avastin is not formulated for intravitreal use. However, increasing data support the fact that multiple intravitreal bevacizumab injections reduce MO due to CRVO.[81,82] Bevacizumab remains an off-label drug for intravitreal use.

Treatment regimen

Several treatment regimens have been used which includes a varied loading dose (3-6 monthly injections) followed by a fixed monthly, PRN or treat and extend regimen. The number of injections required to initiate treatment is unclear with superior results seen in trials with 6 monthly injections versus trials with 4 monthly mandated injections.[67,83] However, these results are the mean values and may reflect the increasing number of patients who respond following repeated injections. This is reported in CRYSTAL, whereby the loading dose is individualised, stable VA was achieved in 37% after 3 monthly injections, 14.3% after 4 monthly injections, 6.4% after 5 monthly injections, and 9.2% after 6 monthly injections. Therefore, just over a third of patients will require only 3 injections to reach maximum VA while another third will require 6 consecutive injections. It is recommended to initiate treatment as the posology suggests which is monthly treatment until maximum stable VA is achieved.

In a PRN regimen, it is recommended that these patients are monitored monthly for optimal visual outcomes. In the second year, visual acuity gains obtained with monthly monitoring in year one are unlikely to be sustained if quarterly monitoring is undertaken as shown in the HORIZON and GALILEO trials. Eight weekly monitoring in the COPERNICUS trial also showed a mean decline of four letters from that achieved in year one. This data indicates that there is a subgroup of patients who require monthly monitoring to achieve and maintain maximal visual benefit. The decline in vision gains seen in the PRN phase of CRUISE led to the SHORE study which was a 15 month study comparing visual acuity gains in a PRN treatment and a monthly treatment following a 7 consecutive monthly treatments.[84] The SHORE study did not find a significant difference in vision gains between the two arms at 15 months but a significantly lower number of injections in the PRN cohort.[84] Comparison between a monthly and treat and extend protocol in patients who had a good response after 6 monthly injections of aflibercept in the SCORE2 trial revealed no significant difference in vision gains in the arms at 12 months but significantly less injections in the treat and extend arm.[85] Therefore, the three treatment regimens (fixed monthly injections, PRN, and treat and extend) following a loading phase provide similar visual outcomes. The risk of monthly injections in a fixed monthly treatment regimen and the requirement for monthly appointments in the PRN regimen leaves the treat and extend regimen as the preferred option.

Interestingly, CRYSTAL reported 9.8% of patients required only the three loading injections and 6.2% require treatment every month in the first year revealing the spectrum of the required treatment in CRVO.[86] It is important to state that a treat and extend regimen may unnecessarily treat almost 10% of patients while evidence of recurrence of activity did not harbour an inferior outcome provided prompt treatment is applied (within a month). Therefore, it is not unreasonable to initially extend by 2-4 weeks until recurrence is identified. Furthermore, in the PRN phase in clinical trials, the mean number of injections continues to decrease between Month 6-12 and Month 12-24. Once an interval is identified, it is reasonable to maintain the treatment intervals and only extend after a 6 month period.

Poor response

Despite excellent visual outcomes in clinical trials, significant vision loss was still observed with treatment. The proportion of vision loss of >15 letters at 6 months was 5.3% (COPERNICUS-aflibercept), 1.0% (GALILEO-aflibercept) and 2.3% (CRUISE-ranibizumab).[87–89] In SCORE2, 8.6% of patients receiving six monthly aflibercept injections, were deemed to have a poor response which was defined as visual acuity less than 58 letters or visual acuity improvement of fewer than 5 letters from baseline, and spectral-domain optical coherence tomography (SD-OCT)with 1 or more of CST 300µm or greater.[90] In SCORE2, 22.5% of patients receiving six monthly bevacizumab injections were deemed to have a poor response, the defined criteria of which is mentioned above.[90]

Long-term outcomes

The RETAIN Study included patients with CRVO and BRVO in a prospective follow-up of a subset of patients from two phase three trials of ranibizumab in RVO.[91] The mean follow-up was 49.7 months for CRVO patients, where 14 of 32 patients (44%) had oedema resolution (defined as no intraretinal fluid for 6 months or more since the last injection), with 71% receiving their last injection within two years of treatment initiation. However, in unresolved patients, a mean number of 5.9 injections of ranibizumab were given in year 4. In eyes with resolved disease had greater improvement in BCVA compared to baseline (25.2 vs. 4.3 letters; p= 0.002).[91] On a PRN dosing regimen with a review at least every three months and a mean of two injections, 53.1% gained BCVA of 15 letters or more, and 43.8% of patients had a final BCVA of 20/40 or better at 48 months.

Effect of duration of CRVO prior to anti-VEGF treatment

Most participants in the CRUISE trial (71.2%) had a duration of MO of less than three months and approximately 55% of participants in the aflibercept trials had less than two months duration. Sub-group analysis of all the anti-VEGF trials to date indicates that the visual outcome is best in participants with a shorter duration of MO. In the aflibercept trials, the proportion of participants who gained at least 15 letters at week 24 was higher in those with CRVO of less than two months duration. It is therefore essential that patients are referred and treated promptly. The CRYSTAL study highlighted the disadvantages of delayed treatment with eyes treated within 3 months faring better compared to eyes with >9 months from diagnosis.[86]

The CRUISE and LEAVO study included participants with CRVO diagnosed in the previous 12 months whilst COPERNICUS and GALILEO included CRVO of less than nine months duration.[87,92,93] It is unlikely for more long standing CRVO cases to present to medical retina clinics at present due to an established referral system for this condition. Nevertheless, the effect of these agents in chronic MO of more than 12 months duration remains unclear. However, treatment with anti-VEGF may be initiated in these patients if the treating retinal specialist expects an improvement or stabilization of VA based on his/her judgment. The change in visual acuity after three loading injections should help decide if further anti-VEGF treatment is worthwhile. The studies also show that a delay in initiating treatment up to six months resulted in fewer visual gains compared to immediate initiation of treatment. It is therefore imperative that patients are initiated on treatment as soon as the diagnosis is established unless the treating physician and/or the patient decide on deferred treatment.

Poor presenting VA

The lower limit of BCVA at entry of LEAVO, CRUISE, GALILEO and COPERNICUS was 24 letters (Snellen 6/96). Therefore, the dosing regimen, number of injections required and the visual outcome in patients presenting with less than 24 letters remain unclear. Anecdotal clinical experience, however, indicates that eyes with Snellen VA<6/96 do well with treatment as long as there is no gross afferent pupillary defect. Careful consideration should be given to further therapy in such eyes that do not improve in terms of Snellen visual acuity or OCT central subfield thickness after three loading injections at monthly intervals and treatment is not recommended if no response occurs after six injections.

Approximately 20% of the patients in the CRUISE, GALILEO and COPERNICUS trials had a visual acuity of Snellen 6/60 to 6/96. A greater gain of visual acuity is expected in this group due to the floor effect as shown in the aflibercept trials. However, the final visual acuity of patients in this category and the impact of the final visual acuity on the patient's quality of vision remain unclear. Multiple factors such as degree of macular ischaemia, structural damage at the fovea and other confounding factors should be taken into account to decide continuation of treatment in this group of patients after initial therapy.

Summary of anti-VEGF trials in treating macular oedema secondary to CRVO

Table 1: Visual outcomes of patients receiving intravitreal anti-VEGF for macular oedema due to central retinal vein occlusion in randomised clinical trials

Study	Study Arms	Baseline BCVA, letters	Mean gain in BCVA, letters				Proportion with ≥15 ETDRS letter gain, %			
			6m	12m	18m	24m	6m	12m	18m	24m
CRUISE [88,94]	0.5mg Ranibizumab	48.1	14.9	13.9			47.7	50.8		
	Sham + PRN 0.5mg Ranibizumab after 6 months	49.2	0.8	7.3			16.9	33.1		
HORIZON [95] (extension from CRUISE- change in VA based on CRUISE baseline)	0.5 Ranibizumab			16.2		12.0				45.1
	Sham + PRN 0.5 Ranibizumab			9.4		7.6				38.3
CRYSTAL[86,96]	0.5mg Ranibizumab	53.0		12.3		12.1		49.2		49.2
GALILEO [89,93,97]	2mg Aflibercept	53.6	18.0	16.9	13.7		60.2	60.2	57.3	
	Sham + PRN Aflibercept after 12m	50.9	3.3	3.8	6.2		22.1	32.4	29.4	
COPERNICUS [87,98,99]	2mg Aflibercept	50.7	17.3	16.2		13.0	56.1	55.3		49.1
	Sham + 2mg Aflibercept after 6m	48.9	-4.0	3.8		1.5	12.3	30.1		23.2
LEAVO[67]	0.5mg Ranibizumab	53.6				12.5				47
	2mg Aflibercept	54.1				15.1				52
	1.25mg Bevacizumab	54.4				9.8				45
SCORE [283(p2)]	Afliberc ept	50.3	18.9				65.1			
	Bevacizumab	50.4	18.6				61.3			

Table 2: Mean number of injections for patients receiving intravitreal anti-VEGF for macular oedema due to central retinal vein occlusion in randomised clinical trials

Study	Study Arms	Treatment criteria	Mean number of injections in the first year	Mean number of injections in the second year
CRUISE/ HORIZON [88,95]	0.5mg Ranibizumab	6 monthly treatments + PRN	3.3 (6-12m)	3.5
	Sham + PRN		3.7 (6-12m)	2.9
CRYSTAL[86,96]	0.5mg Ranibizumab	Monthly injections until maximum stable VA for 3 visits (minimum of 3) + PRN treatment until maximum stable VA for 3 visits	8.1 (0-12m)	13.1 (0-24m)
GALILEO [89,97]	2mg Aflibercept	6 monthly treatments + PRN	2.5 (6-12m)	1.3 (12-18m)
	Sham + PRN Aflibercept after 12m	PRN		1.7 (12-18m)
COPERNICUS [87,99]	2mg Aflibercept	6 monthly treatments + PRN	2.7 (6-12m)	3.3 (12-24m)
	Sham + 2mg Aflibercept after 6m	PRN	3.9 (6-12m)	2.1 (12-24m)
LEAVO[67]	0.5mg Ranibizumab	4 monthly treatments + PRN	11.8 (0-24m)	
	2mg Aflibercept		10.0 (0-24m)	
	1.25mg Bevacizumab		11.5 (0-24m)	

Intravitreal steroids

Intravitreal 0.7mg dexamethasone (Ozurdex) was analysed in the GENEVA study programme.[40] Following a single intravitreal injection, the percentage of eyes with ≥ 15 letter gain in BCVA was significantly higher compared with sham at days 30 to 90 with a peak effect at 60 days. Subgroup analyses of the BRVO and CRVO subjects showed a significantly greater number achieved ≥ 15 letter gain from 30 to 90 days than sham treated eyes. In terms of safety, raised IOP peaked at month two (3.2% of patients had an IOP>35 mmHg), but declined significantly by month three and was close to 0% by month six, with 19% of patients requiring an IOP-lowering agent at month six and 0.7% of patients requiring any IOP-lowering surgical procedures. Similarly, rates of cataract progression were low with 7% progression at month six, compared to 4% in the sham group.[40]

The results further indicate that eyes treated earlier had a better chance of visual acuity gain, and that those treated later (i.e. controls that were subsequently treated) never achieved the final visual acuity gains of those treated promptly. Based on the GENEVA study programme, OZURDEX has received FDA and EU approval for the 0.7 mg preparation, and is licensed in the UK for the treatment of adult patients with MO following CRVO.[40] NICE TA 229 has recommended the use of Ozurdex in the treatment of MO secondary to CRVO.

Following intravitreal Ozurdex treatment, improvement in vision has been noted to be as early as day 7 but only achieving its peak benefit at day 60. The median duration of vision gain following intravitreal dexamethasone was approximately 2-3 months suggesting a duration of benefit that is less than expected and possibly warranting shorter treatment intervals.[100] In SCORE2, poor responders to monthly aflibercept that were switched to intravitreal Ozurdex did not manifest a significant improvement 6 months post-treatment, however, the numbers were small to conclude a lack of improvement.[90] In a retrospective case series, a switch to ozurdex after anti-VEGF treatment failure resulted in significant vision gains at 30 days.[101] Again, caution should be exercised with interpretation of studies with no control arm and/or small numbers.

As for intravitreal triamcinolone acetonide, evidence from the SCORE study indicates that it may produce anatomical and functional improvement of MO related to CRVO but the effects are short-lived.[102] Repeated IVTA may not necessarily improve vision.[102] This treatment is rarely offered to patients today and not recommended given superior options that are both licensed and approved for use in the UK. It is important to appreciate further that the preparation of triamcinolone used for intravitreal injections in the SCORE Study is unpreserved (TRIVARIS, Allergan), and different from the preparation freely available in the UK (Kenalog, Squibb), which is recommended for intra-articular injection.

Comparison between different intravitreal therapies

Intravitreal ranibizumab, aflibercept and bevacizumab have all proven efficacy in managing macular oedema secondary to CRVO. Comparisons between the three treatments is difficult when studies report individual cohort outcomes whereby variations in treatment protocol, eligibility criteria, treatment duration can affect the magnitude of visual acuity gains. The LEAVO study was a multicentre, prospective, randomised and noninferiority trial comparing the three intravitreal therapies for macular oedema secondary to CRVO and performed in 44 NHS sites in the UK.[67] Eligibility criteria includes CRVO-related macular oedema of less than 12months' duration with best corrected visual acuity 19 and 78 letters and OCT central subfield thickness (CST) of 320μm or greater. Participants (n=463) were randomised to ranibizumab, aflibercept or bevacizumab and received 4 monthly injections followed by a PRN treatment over a total of 100 weeks. Comparisons were made with ranibizumab as during the trial conception, ranibizumab was the only approved drug for use in CRVO in the UK. Mean visual acuity gains at 100 weeks were 12.5 letters for ranibizumab, 15.1 letters for aflibercept and 9.8 letters for bevacizumab. Aflibercept was found to be non-inferior but not superior to ranibizumab and bevacizumab was not noninferior to ranibizumab. The proportion of patients achieving >15 letter gains were similar, 47%, 52% and 45% for ranibizumab, aflibercept and bevacizumab respectively.[67]

SCORE2 investigated whether bevacizumab was noninferior to aflibercept for the treatment of macular oedema secondary to CRVO and HRVO.83 Participants (n=362) were randomised to receive 4-weekly aflibercept or bevacizumab for 6 months with the primary outcome at month-6. Bevacizumab was noninferior to aflibercept with comparable visual acuity gains of 18.9 letters in the aflibercept arm and 18.6 letters in the bevacizumab arm. The proportion of patients achieving >15 letter gains were similar at 65.1% and 61.3% for aflibercept and bevacizumab respectively.83 In SCORE2, 22.5% of patients receiving six monthly bevacizumab injections were deemed to have a poor response, the defined criteria of which is mentioned above.90 Of these, a switch to intravitreal aflibercept resulted in significant visual acuity gains of approximately 10 letters.90 However, caution needs to be taken given the small numbers involved and lack of a control group.

COMRADE-C investigated the efficacy of intravitreal dexamethasone (Ozurdex) and ranibizumab was studied in treated macular oedema secondary to CRVO. Patients randomised to a minimum of 3 monthly ranibizumab followed by a PRN regimen versus a single intravitreal ozurdex injection.[103] No difference in visual acuity gains were noted at month 1 and month 2, however, from month 3 to month 6, there was a consistent difference in favour of ranibizumab. This reflects the visual acuity gains following intravitreal ozurdex averaging 2-3 months.[100]

Laser photocoagulation

Macular oedema following CRVO results from leakage of perifoveal capillaries into the macular area and is typically associated with visual loss. There was no proven treatment for this condition until 10 years ago. The CVOS study failed to indicate benefit from grid treatment, although a trend in favour of treatment was observed in younger patients.[104] There is also no evidence to suggest any benefit from a combination of macular grid laser and intravitreal anti-VEGF or steroids for MO secondary to CRVO.

Ischaemic central retinal vein occlusion

Patients with ischaemic CRVO are at risk of neovascular glaucoma for which laser photocoagulation is beneficial. This risk of iris neovascularisation is higher if the area of retinal ischaemia (retinal non-perfusion as determined by FFA) is >10 disc diameters CVOS).[7,9] With the use of ultra-widefield fluorescein angiography (UWFA), a larger area is imaged and the significance of which in the determination of an ischaemic CRVO is unclear. Posterior pole capillary nonperfusion >10DA and >75DA of capillary nonperfusion on UWFA was found to be associated with an increased incidence of neovascularisation.[16] In a LEAVO substudy, despite prompt and regular intravitreal anti-VEGF therapy, significant increase in capillary nonperfusion on ultra-widefield angiography can still occur.[80]

Management of macular oedema in ischaemic central retinal vein occlusion

Most clinical trials excluded patients with poor baseline visual acuities making strong conclusions on the efficacy of anti-VEGF in ischaemic CRVO difficult. However, GALILEO (13.6%) and COPERNICUS (15%) included eyes with >10DA of capillary nonperfusion and yet in this cohort, significant vision gains were obtained.[87,89,105] In the RAVE study, eyes with at least 3 of the 4 high-risk criteria: best-corrected visual acuity (BCVA) ≤6/60, loss of the 1-2e isopter on Goldmann visual field, RAPD being ≥0.9 log units determined with neutral density filters, and electroretinogram (ERG) B-wave reduction to ≤60% of the corresponding A-wave were included and reported excellent vision gains with anti-VEGF therapy.[106] Therefore, eyes with >10DA of nonperfusion should not be excluded from anti-VEGF therapy. As for eyes with a presenting vision of 6/96 or worse (eyes that were excluded from clinical trials) with marked ischaemia on angiography, anti-VEGF may still be considered as significant improvements in vision may still occur. It is important to mention that should oedema resolve with no improvement in visual acuity following a trial of anti-VEGF, cessation is recommended after three injections. It is important in these cases to appreciate that anti-VEGF may mask the development of neovascularisation as neovascular complications in ischaemic CRVO is not ameliorated with anti-VEGF therapy and only delayed.[106] In an analysis of 222 eyes with MO secondary to CRVO, 4.5%

developed neovascularisation with the median interval from most recent intravitreal anti-VEGF therapy to observation of neovascularisation reported to be 9.6 months.[107] Therefore, close observation (1-2 monthly) is recommended in the first year following cessation of anti-VEGF therapy in eyes with ischaemic CRVO. It has also been reported that progression of capillary nonperfusion can occur while on regular intravitreal therapy and in some cases, the progression is not reflected in a sudden change in visual acuity, occurring almost 'silently'.[80] Caution must be taken when anti-VEGF therapy is ceased and angiography or OCTA may be helpful to reassess the extent of ischaemia. Advancing age and a history of glaucoma are risk factors for progression of capillary nonperfusion.[80]

Management of ischaemic central retinal vein occlusion and anterior segment neovascularisation
Panretinal photocoagulation (PRP) remains the mainstay of treatment when iris new vessels (NVI) or angle new vessels (NVA) are visible. Ischaemic CRVO should ideally be monitored monthly for new vessels of the iris and/ or the angle.[9] However, as this is not logistically possible in most centres, 6-weekly reviews may be sufficient, unless there are particular risk factors. Prophylactic PRP can also be considered especially in patients with >10DA of capillary nonperfusion in the posterior pole or >75DA of capillary nonperfusion on UWFA, as 80% of eyes with this level of nonperfusion develop neovascularisation.[16] Inhibitors of vascular endothelial growth factor (anti-VEGF agents) such as ranibizumab, aflibercept and bevacizumab have anti-angiogenic properties and may be used as adjuvants to pan-retinal photocoagulation in patients with anterior segment neovascularisation secondary to ischaemic CRVO.[10] It is advocated to commence anti-VEGF therapy at the earliest sign of iris or angle new vessels followed by sufficient panretinal photocoagulation either on the same day (prior to anti-VEGF therapy) or within 1-2 weeks.

Management of posterior segment neovascularisation
This is an uncommon complication following ischaemic central retinal vein occlusion in eyes which have not developed neovascular glaucoma or who have been successfully treated with panretinal photocoagulation for anterior segment neovascularisation. Panretinal photocoagulation may be useful in preventing vitreous haemorrhage.

Pan-retinal Photocoagulation Technique
Pan-retinal photocoagulation for CRVO with NVI or NVA requires a significant number of laser shots delivered adequately to cover the ischaemic retina to ensure regression of NVI and /or NVA over time. Either single spot or multi-spot lasers may be used. Treatment is usually placed in the periphery avoiding areas of retinal haemorrhage. Some cases require further treatment if the iris neovascularisation fails to regress.[9] Caution must be taken to ensure sufficient laser treatment is administered in eyes with neovascularisation that were pre-treated with anti-VEGF as regression from sufficient PRP cannot be ascertained.

Management of established neovascular glaucoma
The aim of management of this condition in a blind eye is to keep the eye pain free. This is usually achieved by topical steroids and atropine. However, if the eye has any visual potential, intraocular pressure should be controlled with topical pressure-lowering agents, surgical intervention or cyclo-ablative procedures. In addition, regression of NVI and NVA seem to offer a long-term chance of maintaining ocular comfort.

Intravitreal and intracameral anti-VEGF agents have been shown to cause regression of iris new vessels and decrease angle obstruction. Comparative case series indicate that iris new vessels regress faster after intravitreal bevacizumab with PRP than with PRP alone. The reports also suggest that bevacizumab may reduce the need for surgical interventions and may also serve as a useful adjunct to filtering surgery.[108,109]

Recommendations for Further Follow-up
In eyes that have significant ischaemia (> 10DA posterior pole nonperfusion) and anti-VEGF therapy not initiated or required, monthly follow-up is recommended in the first 6 months and follow-up after six months should be every three months for one year. In non-ischaemic eyes initial follow-up every three

months for six months is advised. Subsequent follow-up for all patients will depend upon treatment given and complications within the earlier period but will not normally be required after three years in uncomplicated cases. The development of disc collaterals +/- spontaneous resolution of MO indicates a good outcome and should lead to discharge from clinical supervision after 6 months provided no other complications. However, data available on the treatment of MO with anti-VEGF agents indicates that MO may recur for several years and therefore follow-up beyond current recommendations may be required in a proportion of patients to ensure long term maintenance of stabilized visual acuity gains.

Experimental treatments

Peripheral retinal laser to augment effects of anti-VEGF therapy for macular oedema

The concept of applying targeted peripheral retinal laser in CRVO to improve visual acuity outcomes and reduce the injection frequency of anti-VEGF therapy were investigated in the RELATE and WAVE trials.[110,111] In the CRVO cohort of the RELATE trial, there were no significant difference in the visual acuities of the ranibizumab arm and the laser+ranibizumab arm at all time points, week 48, week 96 and week 144.[110] It is worth mentioning that there was an initial decrease in visual acuity which corresponded with an increase in central subfield thickness following laser therapy which later improved. The mean number of injections was not reduced with scatter laser, in fact, the mean number of injections at week 144 was higher in the laser+ranibizumab arm compared to the ranibizumab only arm, 17.9 v 12.4, p= 0.05.[110]

The WAVE study, which was a 12 month, prospective, randomised trial including patients with both CRVO and BRVO found similar outcomes.[111] The mean visual acuity gains were 10.7 letters in the ranibizumab only arm and 14.9 letters in the laser+ranibizumab arm, with no significant difference identified, p=0.46.[111] The mean number of injections in the PRN phase was 3.7 in ranibizumab monotherapy arm and 3.1 in the combined laser and ranibizumab arm, again with no significant difference identified.[111]

Laser Chorio-retinal anastomosis (L-CRA)

McAllister and colleagues evaluated the effectiveness of a laser-induced chorioretinal anastomosis (L-CRA) as a treatment for non-ischemic CRVO and observed that visual acuity improved significantly in eyes in which successful anatomosis were created.[112] In a more recent publication using a solid-state laser photocoagulator equipped with a special mode that can be activated to deliver power of up to 5 W at 532 nm, together with custom temporal and spatial settings, a success rate of 71% was achieved in creating an anastomosis.[113] However, chorioretinal anastomosis remains an experimental treatment. There are significant complications associated with the procedure which includes closure of the distal segment of the vein resulting in a wedge area of nonperfusion (12%), new vessel development (17%) although almost half regressed spontaneously, choroidal neovascularisation, retinal and subretinal fibrosis or traction, and vitreous haemorrhage.[113-115] In 2018, McAllister and colleagues published a randomised trial investigating L-CRA + ranibizumab versus ranibizumab alone for patients with macular oedema secondary to CRVO.[116] A successful L-CRA was created in 83% of patients in the L-CRA+ranibizumab arm.[116] In the PRN phase of the study, month 7-month 24, the total number of injections required were 3.2 in the combination group and 7.1 in the ranibizumab group, difference of 3.9; 95% CI, 2.7-5.1; P < .001. The mean gain in visual acuities at month 24 were identical between both groups, +16 letters.[116] The complication rate in the combination group (L-CRA+ranibizumab) in this study was not insignificant, 14% requiring a vitrectomy and 17% developing neovascularisation of which 50% regressed spontaneously.[116]

6.14 Ophthalmological management of BRVO

The diagnosis of BRVO is clinical, as described above. In doubtful cases, especially small BRVO, fluorescein angiography and/or OCTA may be indicated to confirm the diagnosis. Fluorescein angiography is particularly useful in determining the extent of macular oedema and ischaemia, as well as peripheral ischaemia. Macular oedema and neovascularisation of the retina or disc are the two major complications that may require therapy. Retinal neovascularisation occurs in 36% of eyes with >5 DD.[26]

Treatment of macular oedema

Aflibercept (NICE TA409 2016), ranibizumab (TA283 2013), and Ozurdex (NICE TA229 2011) are licensed and approved by NICE for treatment for macular oedema for BRVO. Table 3 summarises the clinical trial data.

Aflibercept and ranibizumab are the first line of treatment. Ozurdex is used as second line in poor responders and those requiring frequent injections. Laser used to be the first line of treatment and in the NICE TAGs for ranibizumab and Ozurdex these injections were only recommended if grid laser was not effective or was not suitable due to the amount of blood in the eye. In the NICE TAG for aflibercept prior laser was not required and the BRIGHTER trial showed that additional laser to ranibizumab did not improve the outcome or reduce the number of injections. In this trial, at 24 months, intravitreal ranibizumab with or without macular laser achieved far superior vision gains compared to eyes receiving macular laser only (17.3/15.5 vs. 11.6 letters; P < 0.0001).[117]

Observation for persistent centre involving macular oedema (>3 months) due to a BRVO is not recommended as there is not good evidence for vison improvement and delay in treatment with anti-VEGF may lead to worse outcomes.

6.14.1 Intravitreal anti-VEGF therapy

The posology for ranibizumab is now the same for all conditions with 4 weekly injections until maximum benefit is obtained. The posology for aflibercept varies with condition but also starts with monthly injections. Increasingly treat and extend is being used for retinal vein occlusions.

Ranibizumab (Lucentis, Novartis) given in two doses (0.3mg and 0.5mg) every month for 6 months, was compared with sham, in the BRAVO study.[92] At six months, the mean gain in VA was +16.6 and +18.3 letters (0.3 and 0.5 mg respectively) compared to +7.3 letters in the sham injection group. Sixty-one percent of the ranibizumab 0.5mg group achieved a 15 letter gain versus 29% in the sham treated group. However, from months three to five a single application of rescue laser photocoagulation was also allowed in all study arms, if haemorrhages had cleared sufficiently to allow safe application of laser and the following criteria were met: Snellen equivalent BCVA ≤20/40 or mean central subfield thickness ≥250µm and compared with the visit three months before the current visit, the patient had a gain of <5 letters in BCVA or a decrease of <50µm in mean central subfield thickness. Based on these criteria, approximately 20% of patients in both ranibizumab arms received adjunctive laser, versus 55% in the sham injection arm. Following the first six months, all patients were enrolled into an open-label extension for an additional six months and the overall 12 months' results suggest that the visual gain established in the first six months can be retained with a slightly less intensive pro re nata (PRN) therapy with ranibizumab (an average of 5.7 injections in the first 6 months, vs. 2.7 injections in the second PRN six month phase).[118]

Ranibizumab 0.5mg (Lucentis) for MO secondary to BRVO was subsequently endorsed via a NICE TA283 in May 2013. The TA stated that ranibizumab should be considered if laser has failed or has been deemed an unsuitable treatment.

Further to BRAVO the open label extension of the HORIZON trial looked at 304 previous BRAVO patients with MO secondary to BRVO to assess the long-term safety and efficacy of ranibizumab treatment.[92] Patients entered the trial after one year in BRAVO and were enrolled for a further 12 months in HORIZON.[95] Patients were seen at least every three months and given an intravitreal ranibizumab 0.5 mg if pre-specified retreatment criteria met. Patients were eligible to receive an intravitreal injection of 0.5 mg ranibizumab if visual acuity was less than or equal to 20/40 or center subfield thickness was ≥250 μm. Patients with BRVO were eligible for rescue grid laser therapy if BCVA was ≤20/40 (6/12) caused by MO. The mean change from baseline BCVA at 12 months was 0.9 in the sham/0.5mg, -2.3 in the 03/0.5mg ranibizumab and -0.7 in the 0.5mg groups respectively. There were no new adverse events identified.[92] As such the long term administration of ranibizumab in a prn regimen was well tolerated and efficacious in patients with MO secondary to BRVO. The more recent RETAIN Study included 34 patients with BRVO in a prospective follow-up of a subset of patients from two phase three trials of ranibizumab in RVO.[91] Over a mean follow-up of 49.0 months, 17 of 34 BRVO eyes (50%) had resolution of their oedema (defined as no intraretinal fluid for six months or more after the last injection). The last injection was given within two years of treatment initiation in 76%. The mean number of injections required in unresolved patients in year four was 3.2. In eyes where the oedema had resolved, a mean improvement in BCVA of 25.9 letters was achieved versus 17.1 letters (p= 0.09) in eyes with unresolved oedema. This shows that the long-term outcomes of BRVO eyes treated with ranibizumab was excellent, although about half of them required continuing treatment.[91]

In the BRIGHTER trial, patients with macular oedema secondary to BRVO were randomised to intravitreal ranibizumab alone, intravitreal ranibizumab+laser and laser alone. Mean visual acuity gains at 6 months were similar (14.8 letters) in the ranibizumab and ranibizumab+laser suggested no added benefit of combined therapy to intravitreal therapy alone. In eyes only treated with macular laser, mean vision gain was 6.0 letters.[119] This was sustained in the 24 months result of the BRIGHTER trial whereby visual acuity gains with macular laser+ ranibizumab (+15.4) was not superior to intravireal ranibizumab only (+15.0) and did not result in a reduction in the number of injections (11.4 v 11.3).[117,119]

Aflibercept (Eylea, Bayer) In the VIBRANT Study.[69] A total of 183 subjects with treatment naïve MO due to BRVO with sufficient clearing of macular haemorrhage to allow laser treatment at baseline and best corrected visual acuity of 24 – 73 ETDRS letters were randomized to four weekly aflibercept versus macular laser. At six months, 53% of subjects gained 15 letters after a mean of 5.7 injections compared to 27% in the laser arm treated with a mean of 1.7 sessions of macular laser. The mean gain in best-corrected visual acuity was 17 ETDRS letters versus 6.9 ETDRS in the laser arm. The functional outcomes mirrored the significantly more reduction in mean central retinal thickness in the aflibercept arm (-280.5μm) compared to the laser arm (-128.8μm). The benefits seen were sustained in the 12 month outcomes, 57.1% achieving >15 letter gains with intravitreal aflibercept alone and mean visual acuity gains of 17.1 letters. The macular laser arm received intravitreal aflibercept after 6 months, however, did not manage to attain the gains seen in the group randomised to intravitreal aflibercept from the start, 41.1% >15 letter gain and mean gain of 12.2 letters at 12 months.[120]

Bevacizumab. Data support the fact that multiple intravitreal bevacizumab injections reduce MO secondary to BRVO including those that had failed previous laser treatment. The most common treatment regimen is two to three injections over the first five to six months.[121,122] However, further randomized, controlled trials are required to assess long-term safety and efficacy of intravitreal bevacizumab.

Comparison between different intravitreal therapies

Comparisons between anti-VEGF therapies for macular oedema secondary to BRVO were performed in the MARVEL study between ranibizumab and bevacizumab. The difference between bevacizumab and ranibizumab was not significant at 6 months, -2.5 letters (95% CI -8.0 to +5.0; p=0.74).[123]

Comparison between vision gains with intravitreal Ozurdex and intravitreal ranibizumab was investigated in the COMRADE-B study. Findings were similar with the COMRADE-C study whereby no difference in vision gains were noted in the first 3 months after which eyes receiving intravitreal ranibizumab were better which reflects the duration of action of the Ozurdex implant.[124]

6.14.2 Intravitreal steroids

Steroids are largely used as a second line treatment for patients who are needing a lot of anti-VEGF treatment as the injection interval can be longer. They are best used in pseudophakes who do not have a pressure rise from steroids.

Intravitreal triamcinolone acetonide (IVTA): The long-term safety and efficacy of IVTA (using preservative-free triamcinolone) was evaluated in the Standard Care Versus Corticosteroid for Retinal Vein Occlusion Study (SCORE) that showed that this treatment is not beneficial for this condition.[125]

The GENEVA study that evaluated safety and efficacy of an intravitreal implant of dexamethasone (Ozurdex; Allergan Inc., Irvine, California, USA) in participants with MO secondary to retinal vein occlusion showed that the outcome of this drug in MO due to BRVO was better than in the control participants.[40] In the GENEVA study programme, Ozurdex (0.7mg) and an alternative dose of dexamethasone in an implant (0.35mg) was compared to a sham injection in patients with CRVO and BRVO in two parallel multicentre studies. Re-treatment was possible 6 months after the first injection under pre-specified re-treatment criteria. The first trial did not meet its original primary end-point, namely proportion of eyes gaining 15 letters ETDRS BCVA. The two trials were analysed together and the primary outcome measure for all patients was time to achieve a ≥ 15 letter gain. The percentage of eyes with ≥ 15 letter gain in BCVA was significantly higher in both implant groups compared with sham at days 30 to 90 with a peak effect at 60 days (29%). Subgroup analyses of the BRVO and CRVO subjects showed a significantly greater number achieved ≥ 15 letter gain from 30 to 90 days than sham treated eyes, and that sham treated eyes in the BRVO subgroup were more likely to improve spontaneously than similarly managed CRVO eyes. Anatomically, improvements in MO were seen with OCT. In terms of safety, raised IOP peaked at month two (3.2% of patients had an IOP>35 mmHg), but declined significantly by month three. Nineteen percent of patients required an IOP lowering agent at month six and 0.7% of patients required IOP lowering surgical procedures. Cataract incidence and progression is a significant complication of Ozurdex therapy.[40]

Based on the GENEVA study programme, Ozurdex received FDA and EU approval for the 0.7 mg preparation, and is licensed in the UK for the treatment of adult patients with MO following either BRVO or CRVO.[61]

6.14.3 Laser photocoagulation

In the BVOS study, the average improvement in VA in the laser arm after three years of follow-up was 1.3 lines. The BVOS also reported that 40% of treated eyes (n=43) had worse than 20/40 visual acuity at three years, and 12% of treated eyes had 20/200 or worse visual acuity at three years highlighting the need for better treatment options. Today, the recommended treatment guideline for MO due to BRVO is that if laser photocoagulation is contemplated, it should be performed in those eyes with MO secondary to BRVO of at least three months' duration with visual acuity of 6/12 or worse and without significant macular haemorrhage and with a fluorescein angiogram showing capillary perfusion in the absence of blood involving the fovea. However, only a minority of patients in clinical practice are eligible for this treatment

option based on these recommendations. Furthermore, laser therapy is typically further delayed three to six months after the onset of BRVO to allow for spontaneous improvement to occur (30%) and for macular haemorrhage to lessen to permit appropriate treatment.

This may further compromise visual potential in eyes with persistent MO.[126] If laser therapy is planned, fluorescein angiography should ideally be carried out prior to this therapy usually at > 3 months if visual acuity is 6/12 or less. This has two functions. Firstly, it identifies the leaking capillaries and secondly will indicate the degree of macula ischaemia, which may limit the value of photocoagulation. It will also help to avoid laser treatment to collateral vessels. Those with severe visual loss (less than 6/60 vision) and those in whom symptoms have been present for more than one year are unlikely to benefit from the treatment. Laser photocoagulation using a 50 to 100um spots size for MO requires mild photocoagulation spots only, i.e. faint grey discoloration of the retina only The power setting required will vary from patient to patient and should be adjusted accordingly. An average of between 20 to 100 applications (depending on the area of vascular leakage) are required in a grid pattern to the areas of vascular leakage but avoiding the foveal avascular zone and any surrounding areas of capillary closure. Collaterals should be avoided.

6.14.4 Observation

A systematic review of the natural history of BRVO reported that visual acuity is moderately poor at baseline (Snellen <6/12). Although visual improvement is more prevalent in BRVO than CRVO, few studies reported improvement beyond 6/12.27 The Branch Vein Occlusion Study (BVOS) was a multicentre, prospective, randomized trial designed to study the natural history and effect of laser treatment in this condition. This study demonstrated that, after three years of follow-up and based on available data on 43 participants, 28 (63%) of laser-treated eyes had improved ≥2 lines of vision , compared with 13 (37%) out of 35 untreated eyes that remained in the study for 36 months.[126]

Summary of visual outcomes in the various randomized clinical trials evaluating therapies in macular oedema due to BRVO

Table 1: Visual outcomes of patients receiving intravitreal anti-VEGF for macular oedema due to central retinal vein occlusion in randomised clinical trials

Study	Study Arms (n)	Baseline BCVA	Mean gain in BCVA			Proportion with ≥15 ETDRS letter gain		
			in 6 months	in 12 months	in 36 months	at 6 months	at 12 months	at 36 months
BVOS	Observation (n=35)				+0.23 line			
	Laser (n=43)				+1.33 line			
SCORE	1mg IVTA (n=121)	58.2		5.7	4.4		25.6	25
	4mg IVTA (n=125)	56.1		4.2	8.0		27.2	50
	Laser (n=121)	56.8		4.0	12.9		28.9	48
GENEVA	0.7mg Ozurdex (n=427)	54.3				41		
	Sham (n=426)	53.9				23		
BRAVO	0.3mg Ranibizumab (n=134)	56.0	16.6	16.4		51.2	56	
	0.5mg Ranibizumab (n=131)	54.0	18.3	18.3		61.1	60	
	Sham (n=132)	54.7	7.3	12.1		28.8	44	
VIBRANT	2mg Aflibercept (n=85)	58.6	17	17.1		52.7	57.1	
	Laser (n=83)	57.7	6.9				41	
BRIGHTER	0.5mg Ranibizumab (n=183)	59.5	14.8			45		
	0.5mg Ranibizumab + Laser (n=180)	56.6	14.8			47.2		
	Laser (n=92)	56.5	6.0			27.8		

6.14.5 Treatment of neovascularisation

Disc or retinal neovascularisation is an indication for photocoagulation to the ischaemic retina (sector photocoagulation), although available evidence suggests that waiting until vitreous haemorrhage occurs before laser treatment does not adversely affect the visual prognosis.[17] New vessels occur only when there is at least a quadrant of capillary closure and commonly after six months following the occlusion.

Follow-up visits at three to four monthly intervals are recommended in patients with one quadrant or more retinal ischaemia. It is recommended that sector laser photocoagulation is applied once retinal or optic disc neovascularisation occur. Fluorescein angiography is not usually necessary prior to laser because the area of ischaemia is visible clinically.

Photocoagulation for retinal neovascularisation in BRVO is applied to the sector of retinal capillary closure. An adequate number of laser spots using a single spot or multisport laser should be applied in the affected sector, one shot width apart with sufficient energy to create a mild grey-white laser discoloration of the retina. A quadrant usually requires at least 500 shots of 500µm diameter.

6.14.6 Experimental Treatments

An RCT comparing arteriovenous sheathotomy and IVTA showed similar benefits.127 Based on these results and the known complications rate of vitreo-retinal procedures, this procedure is not recommended at present.[128]

7. Treatment Algorithms

7.1 Treatment algorithm for CRVO

Treatment of risk factors (to be managed by patient's physician).

Ophthalmic management

Baseline

1. Visual acuity measurement, RAPD, OCT, IOP, and gonioscopy (if ischaemic CRVO suspected).
2. Colour fundus photographs and fluorescein angiography should be performed when the diagnosis is uncertain. Angiography (FA or wfOCTA) is recommended to assess the extent of retinal nonperfusion in suspected ischaemic CRVO cases and this can either be done at baseline or at a later stage if anti-VEGF therapy is commenced. Prophylactic PRP should be considered and discussed in eyes with >10DA of posterior pole nonperfusion.
3. If no iris or angle NV and OCT evidence of MO:
    a) If visual acuity is 6/96 or better, commence intravitreal anti-VEGF
    b) If visual acuity is less than 6/96, the potential for significant improvement in visual acuity is minimal and the risk of ocular neovascularisation is high. However, eyes with VA< 6/96 may be offered treatment as some of these eyes may respond. These patients should be watched for NVI/NVA
    c) If visual acuity is better than 6/12, it is not unreasonable to observe the patient for spontaneous resolution as per the judgment of the treating ophthalmologist.

Choice of agent

Ranibizumab and aflibercept are the two anti-VEGF agents recommended by NICE for MO due to CRVO. Ozurdex, a dexamathasone implant is also recommended by NICE for this condition but is now used as a second-line agent, if anti-VEGF is contraindicated (recent cardiovascular event), or a preferred option for a patient who do not favour monthly injections. There is no visual acuity or central macular thickness restriction in the commencement of treatment with any of these agents.

Treatment

At each follow-up visit, visual acuity, macular thickness and IOP should be assessed, and the presence of neovascularisation assessed.

If ranibizumab or aflibercept are the first line of treatment, monthly intravitreal injections are initiated until maximum stable visual acuity is achieved. If no improvement in visual acuity over the course of the first three injections is observed, cessation of treatment may be considered, and it is recommended after six injections.

Patients who achieve visual acuity stability can be managed either with a treat and extend regimen or a PRN regimen. Patients on the treat and extend regimen may be extended by 2-4 weeks longer than the prior interval if the vision remains stable and no recurrence of MO. The intervals can be shortened if there is loss of visual acuity due to MO secondary to CRVO. Once this interval to recurrence is identified, it is advisable to maintain on this interval for a 6-month period before extending again. Patients on a PRN regimen should be monitored at monthly (or bi-monthly) intervals and treatment resumed when there is loss of visual acuity due to MO secondary to CRVO.

If Ozurdex is the first line of treatment, re-treatment may be required at four to six monthly intervals until visual stability is obtained. The occasional patient may require treatment at three months. However, more frequent and repeated treatments with Ozurdex increase the risk of adverse events and these should be discussed with the patient. Patients should be monitored for raised intraocular pressure (IOP) which peaks at Day 60 and formation or progression of cataract. Intravitreal Ozurdex does not protect or mask neovascularisation thus eyes judged to be ischaemic will still require monthly assessments.

Stopping treatment

Consider stopping ranibizumab and aflibercept therapy if after three consecutive monthly treatments, visual acuity has not improved and CMT has not reduced from baseline. Reduction in MO without VA improvement or deterioration (i.e. stable VA) may be accepted as a favourable, but suboptimal outcome. Stopping ranibizumab and aflibercept therapy is recommended if after six consecutive monthly treatments, visual acuity has not improved by at least five letters and CMT has not reduced from baseline. However, if anti-VEGF is commenced in an eye with very poor presenting vision to assess visual potential, and there is no improvement after three loading doses, treatment can be stopped. Consider FA or wfOCTA at this stage if it has not been done to clarify if the visual acuity is poor due to central macular ischaemia alone or widespread retinal ischaemia. If the latter, consider prophylactic PRP. In eyes with >10DA of posterior pole nonperfusion, upon cessation of anti-VEGF therapy, 1-2 monthly reviews are recommended in the first year.

Switching agents

If an anti-VEGF agent is stopped due to lack of efficacy, there are no randomised controlled trials that provide evidence that switching to another anti-VEGF agent may be effective. However, given our experience with switching anti-VEGF agents in neovascular age related macular degeneration, it may be worthwhile switching to another anti-VEGF agent and further monthly injections for three months may be given to assess the efficacy of the switch. In SCORE2, there was a favourable improvement in vision following a switch to aflibercept from bevacizumab in poor responders.[90]

There is a good rationale to switch from Ozurdex to an anti-VEGF agent and vice versa as the different mode of actions of these agents may aid in resolution of MO. However, the long-term outcomes of sequential or combination treatment of anti-VEGF agents and steroids remain unclear.

Follow-up/discharge

- *Non-ischaemic CRVO*

Follow-up every 3 months is recommended in the first 6 months in eyes not requiring treatment. Discharge from hospital eye services can be considered after a minimum of 18 months if no intervention is required or 18 months from the last intravitreal therapy.

- *In ischaemic CRVO or eyes with >10DA of posterior pole nonperfusion*

Monthly monitoring is recommended for 6 months and subsequently every 3 months for a year if anti-VEGF therapy is not commenced. This can be extended in the second and third year. In ischaemic CRVO eyes that received anti-VEGF therapy, 1-2 monthly reviews are recommended in the first year. Follow-up is recommended for 3 years from the last intervention, if any.

Anterior segment neovascularisation

- *If iris or angle neovascularisation occurs and the anterior chamber angle is open*

Urgent intravitreal anti-VEGF is recommended with PRP within the same day (prior to anti-VEGF treatment) or within two weeks initially. PRP plus intravitreal bevacizumab (off license) can be repeated if NVI/NVA persist.

- *If iris or angle NV are present with a closed angle and raised intraocular pressure*

Urgent PRP is recommended with cyclodiode laser therapy / tube shunt surgery. The latter is preferable if the angle closure is established. If the intraocular pressure is normal or normalizes with the above therapy, intravitreal bevacizumab can be considered. If the intraocular pressure is significantly elevated it should be managed as above with topical and medical management in addition. Caution is advised if bevacizumab or any anti-VEGF agent is considered in the presence of raised intraocular pressure as this can be exacerbated in the short-term. If vitreous haemorrhage precludes a view of the fundus, transcleral diode therapy and retinal cryotherapy can be used. An early specialist glaucoma opinion should be sought.

7.2 Treatment algorithm for BRVO

A. Treatment of risk factors by patient's physician.

B. Ophthalmic management of BRVO

Baseline assessment

Measure visual acuity, OCT, colour fundus photography. FFA can help assess the degree of ischaemia as can OCTA but maybe more useful to assess reasons for poor vision after initial anti-VEGF treatment, to distinguish new vessels from collaterals or if laser is planned for new vessels.

Treatment

For a BRVO with centre involving oedema start anti-VEGF injections. For a macular BRVO with no oedema follow-up with repeat OCT can be performed. For a non macular involving BRVO follow-up may or may not be required depending on the degree of ischaemia.

Alternatives to anti-VEGF are Ozurdex or grid laser. Ozurdex is best used as a second line agent if frequent injections are being required and are a problem but additional follow-up will still be required for pressure checks. Grid laser is an option but the results are not likely to be as good as anti-VEGF treatment.

Posology for ranibizumab and aflibercept are largely the same for BRVO and CRVO:

- Posology for ranibizumab:

The recommended dose for Lucentis is 0.5 mg given as a single intravitreal injection. This corresponds to an injection volume of 0.05 ml. The interval between two doses injected into the same eye should be at least four weeks. Treatment is initiated with one injection per month until maximum visual acuity is achieved and/or there are no signs of disease activity i.e. no change in visual acuity and in other signs and symptoms of the disease under continued treatment. In patients with wet AMD, DME and RVO, initially, three or more consecutive, monthly injections may be needed. Thereafter, monitoring and treatment intervals should be determined by the physician and should be based on disease activity, as assessed by visual acuity and/or anatomical parameters.

Monitoring for disease activity may include clinical examination, functional testing or imaging techniques

(e.g. optical coherence tomography or fluorescein angiography).

- Posology for aflibercept:

The recommended dose for Eylea is 2 mg aflibercept equivalent to 50 microlitres. After the initial injection, treatment is given monthly. The interval between two doses should not be shorter than one month. If visual and anatomic outcomes indicate that the patient is not benefiting from continued treatment, Eylea should be discontinued. Monthly treatment continues until maximum visual acuity is achieved and/or there are no signs of disease activity. Three or more consecutive, monthly injections may be needed.

Treatment may then be continued with a treat-and-extend regimen with gradually increased treatment intervals to maintain stable visual and/or anatomic outcomes, however there are insufficient data to conclude on the length of these intervals. If visual and/or anatomic outcomes deteriorate, the treatment interval should be shortened accordingly.

The monitoring and treatment schedule should be determined by the treating physician based on the individual patient's response.

Monitoring for disease activity may include clinical examination, functional testing or imaging techniques (e.g. optical coherence tomography or fluorescein angiography).

ISCHAEMIC BRVO

a) Watch carefully for NV

b) If NVE — consider sector laser photocoagulation applied to all ischaemic quadrants. Intravitreal anti-VEGF treatment (off-license) may also be given in combination with laser.

c) Follow-up at three monthly intervals for up to 24 months.

8. RVO Service Provision

8.1 RVO Service Specifications

Early access

It is recommended that the time from referral from the primary source to initial evaluation and treatment by the ophthalmologist at the eye clinic is not more than 2 – 4 weeks from presentation.

Minimum clinical services required for effective management

These include:

- Best corrected visual acuity assessments by optometrist or certified VA examiners
- Colour Fundus photographs and Fundus Fluorescein angiography (FFA) / OCTA by trained technical staff
- Optical coherence tomography (OCT) with the SD-OCT by trained technical staff
- Treatment initiated within one to two weeks of assessment by the attending ophthalmologist
- Appropriate facilities for IVT injection
- Appropriate capacity for follow-up, monitoring and re-treatment

RVO Referral Pathways

All patients suspected to have RVO by the optometrist, general practitioner, or other health workers should be referred directly to the nearest Eye Centre with pathways set up to allow urgent access. Optometrists may be used for 'screening' or first examination of patients suspected of having RVO. Fast track clinics collecting imaging in the community or hospital can help triage to find those who are symptomatic with reduced vision and centre involving macular oedema.[11]

Low Vision and Living with RVO

It is known that the sudden onset of visual loss whether unilateral or bilateral results in significant distress. BRVO and CRVO are reported to be associated with a decreased vision-related quality of life as measured by the VFQ-25.[129,130] The decrease in VFQ-25 scores is related to the degree of visual loss in the better-seeing eye and the overall systemic health of the patient.[129,130] Patients with either central or branch retinal vein occlusion with macular oedema have significant impact on their quality of life, and were willing to undergo potentially invasive treatment.[131,132]

Patients with reduced BCVA secondary to RVO should be offered the opportunity of accessing low vision support and advice at an early stage. Advice and use of task lighting and magnifiers reduce the early impact of sight loss and the risk of falls. It is important not to wait until all treatment options have been explored or until an individual's vision deteriorates to a level that merits registration as visually impaired/ severely visually impaired before referring an individual to low vision and rehabilitation services.

It is easier to introduce the patient to low vision services at an earlier than later stage of the disease when individual can learn how to use their remaining vision more effectively, retaining independence and confidence.

9. Audit and service evaluation

9.1 Efficacy vs effectiveness

RCTs provide the gold standard evidence of the of the efficacy of a treatment but of a relatively small number of patients who have fulfilled the inclusion requirements of the study over a relatively short time. Real world evidence (RWE) can provide data on much larger numbers of patients with broader baseline characteristics over longer periods. Increasingly large data sets are being collected such as the UK EMR user group (using Medisoft); Fight Retinal Blindness, Vestrum; Iris registry.[133-139] Evidence for alternative treatment regimens can be generated, such as treat and extend that can go on to be tested in RCTs. In time after the licence of a treatment following a randomised trial the posology of a treatment may change based on further evidence from additional RCTs but also large RWE reports, such as the Luminous data base for ranibizumab.[140]

Caution needs to be taken when assessing the outcomes of RWE, such as comparing outcomes between medications, as treatment decisions are not randomised, adherence to treatment can be poor and methods of assessing visual acuity is variable. Nevertheless, the ability to measure outcomes of a service is important, as the full benefit of a treatment will only be obtained if treatment can be given in line with best evidence and maintained over time.

9.2 Suggestions for service evaluation measures

- **Completeness of data** can be an issue especially if different data sources are used such as case notes and EMR or two different EMR systems): recording of diagnosis; baseline visual acuity and at each visit; recording of OCT CMT, procedures and complications.
- **Time to first treatment from referral**
- **Proportion of patients given their first three injections four weeks apart (for ant-VEGF)**
- **Proportion of patients remaining under follow-up over time**
- **Documented evidence of reason why a patient is no longer under follow-up**
- **Number of injections over a year**
- **Changes in visual acuity over time:** Median VA maybe better than mean for this as significant fluctuation in vision can occur such as with the development of a vitreous haemorrhage or cataract, or the removal of these, which can skew results, depending on sample size.
- **Complication rates:** especially endophthalmitis

10. Suggestions for ongoing research

Trials of newer drugs are ongoing specifically brolucizumab for macular oedema secondary to central retinal vein occlusion (RAVEN) and the use of faricimab for retinal vein occlusion. The surgical treatments for RVO currently remain experimental. Innovative therapies in the treatment of ischaemic RVOs, where current therapies are ineffective, may allow visual preservation or restoration.

11. Guideline Development Group

11.1 Membership

Chair:
Prof Sobha Sivaprasad, Moorfields Eye Hospital, London

Members:

- Mr Luke Nicholson, Moorfields Eye Hospital, London
- Mr Winfried Amoaku, Nottingham University Hospital, Nottingham
- Mr James Talks, Royal Victoria Infirmary, Newcastle upon Tyne
- Dr Katherine Talks, Royal Victoria Infirmary, Newcastle upon

11.2 Declaration of interest

- Prof Sobha Sivaprasad has received an honorarium for advisory board meetings and speaker fees from Allergan, Boehringer Ingleheim, Novartis, Bayer, Optos, Heidelberg Engineering, Oxurion, Ophthea, Oculis, Apellis and Roche. Been awarded institutional research grants by Novartis, Bayer, Allergan, Boehringer Ingleheim. Received support from industry towards publication for the AURA and RELIGHT, and research grants from Research Grants: Novartis, Bayer, Allergan, Boehringer Ingleheim.
- Mr Luke Nicholson has received speaker fees from Allergan and Bayer.
- Mr Winfried Amoaku has received research funding from Allergan, Bausch and Lomb, Novartis and Pfizer, is on an Advisory Board for Alcon, Allergan, Novartis, Bayer, Alimera, Roche and Thrombogenics, has received educational travel grants from Bayer, Novartis and Pfizer, speaker honoraria from Alimera, Allergan, Bausch and Lomb, Bayer, Novartis and Pfizer. He has been involved with Pharma-sponsored Clinical Trials: Allergan, Bausch and Lomb, Novartis, Pfizer2009 – 14. Clinical Trials: i) National CI (and PI, Nottingham) Pfizer. Case-Crossover Study of PDE5 Inhibitor as factor in AION; ii) PI- Novartis. REPAIR Phase 2, Protocol CRFB002AGB10. Multicentre; iii) PI- Novartis. COMRADE B and C. Phase 3, Protocol CRFB002 EDE17 and CRFB002 EDE18. Multicentre trial ranibizumab vrs dexamethasone in BRVO and CRVO; iv) PI- Phase 4 Observational Constance. He is also a member of the Macular Society Scientific Committee.
- Mr James Talks has attended Advisory Boards for Bayer, Novartis, Alimera and Allergan. He has participated in Pharma-sponsored Clinical Trials for Bayer, Novartis, Roche and Boehringer Ingelheim. He has also received educational travel grants from Bayer.
- Dr Katherine Talks has received educational travel grants from CSL-Behring, Pfizer & Sobi.

12. References

1. Nicholson L, Vazquez-Alfageme C, Sen P, et al. The clinical relevance of ultra-widefield angiography findings in patients with central retinal vein occlusion and macular oedema receiving anti-VEGF therapy. *Eye Lond Engl*. Published online May 25, 2021. doi:10.1038/s41433-021-01553-7

2. Ageno W, Beyer-Westendorf J, Garcia DA, Lazo-Langner A, McBane RD, Paciaroni M. Guidance for the management of venous thrombosis in unusual sites. *J Thromb Thrombolysis*. 2016;41(1):129-143. doi:10.1007/s11239-015-1308-1

3. Werther W, Chu L, Holekamp N, Do DV, Rubio RG. Myocardial infarction and cerebrovascular accident in patients with retinal vein occlusion. *Arch Ophthalmol Chic Ill 1960*. 2011;129(3):326-331. doi:10.1001/archophthalmol.2011.2

4. Tsaloumas MD, Kirwan J, Vinall H, et al. Nine year follow-up study of morbidity and mortality in retinal vein occlusion. *Eye Lond Engl*. 2000;14(Pt 6):821-827. doi:10.1038/eye.2000.230

5. Ho J, Liou S-W, Lin H-C. Retinal vein occlusion and the risk of stroke development: a five-year follow-up study. *Am J Ophthalmol*. 2009;147(2):283-290.e2. doi:10.1016/j.ajo.2008.08.006

6. Cugati S, Wang JJ, Knudtson MD, et al. Retinal vein occlusion and vascular mortality: pooled data analysis of 2 population-based cohorts. *Ophthalmology*. 2007;114(3):520-524. doi:10.1016/j.ophtha.2006.06.061

7. Natural history and clinical management of central retinal vein occlusion. The Central Vein Occlusion Study Group. *Arch Ophthalmol Chic Ill 1960*. 1997;115(4):486-491.

8. Bertelsen M, Linneberg A, Christoffersen N, Vorum H, Gade E, Larsen M. Mortality in patients with central retinal vein occlusion. *Ophthalmology*. 2014;121(3):637-642. doi:10.1016/j.ophtha.2013.07.025

9. A randomized clinical trial of early panretinal photocoagulation for ischemic central vein occlusion. The Central Vein Occlusion Study Group N report. *Ophthalmology*. 1995;102(10):1434-1444.

10. Davidorf FH, Mouser JG, Derick RJ. Rapid improvement of rubeosis iridis from a single bevacizumab (Avastin) injection. *Retina Phila Pa*. 2006;26(3):354-356. doi:10.1097/00006982-200603000-00017

11. Lee JX, Manjunath V, Talks SJ. Expanding the role of medical retina virtual clinics using multimodal ultra-widefield and optical coherence tomography imaging. *Clin Ophthalmol Auckl NZ*. 2018;12:2337-2345. doi:10.2147/OPTH.S181108

12. Green WR, Chan CC, Hutchins GM, Terry JM. Central retinal vein occlusion: a prospective histopathologic study of 29 eyes in 28 cases. *Retina Phila Pa*. 1981;1(1):27-55.

13. Green WR. Retina. In Spencer WH (Ed): Ophthalmic pathology. An Atlas and Textbook. 3rd Ed. Philadephia. WB Saunders. 1985; p589.

14. Hockley DJ, Tripathi RC, Ashton N. Experimental retinal branch vein occlusion in the monkey. Histopathological and ultrastructural studies. *Trans Ophthalmol Soc U K*. 1976;96(2):202-209.

15. Orth DH, Patz A. Retinal branch vein occlusion. *Surv Ophthalmol*. 1978;22(6):357-376.

16. Nicholson L, Vazquez-Alfageme C, Patrao NV, et al. Retinal Nonperfusion in the Posterior Pole Is Associated With Increased Risk of Neovascularization in Central Retinal Vein Occlusion. *Am J Ophthalmol*. 2017;182:118-125. doi:10.1016/j.ajo.2017.07.015

17. Tsui I, Kaines A, Havunjian MA, et al. Ischemic index and neovascularization in central retinal vein occlusion. *Retina Phila Pa*. 2011;31(1):105-110. doi:10.1097/IAE.0b013e3181e36c6d

18. Sabates R, Hirose T, McMeel JW. Electroretinography in the prognosis and classification of central retinal vein occlusion. *Arch Ophthalmol Chic Ill 1960*. 1983;101(2):232-235. doi:10.1001/archopht.1983.01040010234010

19. Hayreh SS, Klugman MR, Podhajsky P, Kolder HE. Electroretinography in central retinal vein occlusion. Correlation of electroretinographic changes with pupillary abnormalities. *Graefes Arch Clin Exp Ophthalmol Albrecht Von Graefes Arch Klin Exp Ophthalmol.* 1989;227(6):549-561. doi:10.1007/BF02169451

20. Breton ME, Quinn GE, Keene SS, Dahmen JC, Brucker AJ. Electroretinogram parameters at presentation as predictors of rubeosis in central retinal vein occlusion patients. *Ophthalmology.* 1989;96(9):1343-1352. doi:10.1016/s0161-6420(89)32742-4

21. Kaye SB, Harding SP. Early electroretinography in unilateral central retinal vein occlusion as a predictor of rubeosis iridis. *Arch Ophthalmol Chic Ill 1960*. 1988;106(3):353-356. doi:10.1001/archopht.1988.01060130379026

22. Bresnick GH. Following up patients with central retinal vein occlusion. *Arch Ophthalmol Chic Ill 1960*. 1988;106(3):324-326. doi:10.1001/archopht.1988.01060130350018

23. Hayreh SS, Rojas P, Podhajsky P, Montague P, Woolson RF. Ocular neovascularization with retinal vascular occlusion-III. Incidence of ocular neovascularization with retinal vein occlusion. *Ophthalmology*. 1983;90(5):488-506.

24. Quinlan PM, Elman MJ, Bhatt AK, Mardesich P, Enger C. The natural course of central retinal vein occlusion. *Am J Ophthalmol*. 1990;110(2):118-123. doi:10.1016/s0002-9394(14)76979-x

25. Minturn J, Brown GC. Progression of nonischemic central retinal vein obstruction to the ischemic variant. *Ophthalmology*. 1986;93(9):1158-1162.

26. Argon laser scatter photocoagulation for prevention of neovascularization and vitreous hemorrhage in branch vein occlusion. A randomized clinical trial. Branch Vein Occlusion Study Group. *Arch Ophthalmol Chic Ill 1960*. 1986;104(1):34-41. doi:10.1001/archopht.1986.01050130044017

27. Rogers S, McIntosh RL, Cheung N, et al. The prevalence of retinal vein occlusion: pooled data from population studies from the United States, Europe, Asia, and Australia. *Ophthalmology*. 2010;117(2):313-319.e1. doi:10.1016/j.ophtha.2009.07.017

28. Song P, Xu Y, Zha M, Zhang Y, Rudan I. Global epidemiology of retinal vein occlusion: a systematic review and meta-analysis of prevalence, incidence, and risk factors. *J Glob Health*. 2019;9(1):010427. doi:10.7189/jogh.09.010427

29. Li JQ, Terheyden JH, Welchowski T, et al. Prevalence of Retinal Vein Occlusion in Europe: A Systematic Review and Meta-Analysis. *Ophthalmol J Int Ophtalmol Int J Ophthalmol Z Augenheilkd*. 2019;241(4):183-189. doi:10.1159/000494224

30. Klein R, Moss SE, Meuer SM, Klein BEK. The 15-year cumulative incidence of retinal vein occlusion: the Beaver Dam Eye Study. *Arch Ophthalmol Chic Ill 1960*. 2008;126(4):513-518. doi:10.1001/archopht.126.4.513

31. Frangieh GT, Green WR, Barraquer-Somers E, Finkelstein D. Histopathologic study of nine branch retinal vein occlusions. *Arch Ophthalmol Chic Ill 1960*. 1982;100(7):1132-1140. doi:10.1001/archopht.1982.01030040110020

32. Elman MJ, Bhatt AK, Quinlan PM, Enger C. The risk for systemic vascular diseases and mortality in patients with central retinal vein occlusion. *Ophthalmology*. 1990;97(11):1543-1548. doi:10.1016/s0161-6420(90)32379-5

33. Risk factors for central retinal vein occlusion. The Eye Disease Case-Control Study Group. *Arch Ophthalmol Chic Ill 1960*. 1996;114(5):545-554.

34. Koizumi H, Ferrara DC, Bruè C, Spaide RF. Central retinal vein occlusion case-control study. *Am J Ophthalmol*. 2007;144(6):858-863. doi:10.1016/j.ajo.2007.07.036

35. Rath EZ, Frank RN, Shin DH, Kim C. Risk factors for retinal vein occlusions. A case-control study. *Ophthalmology*. 1992;99(4):509-514. doi:10.1016/s0161-6420(92)31940-2

36. Dodson PM, Galton DJ, Hamilton AM, Blach RK. Retinal vein occlusion and the prevalence of lipoprotein abnormalities. *Br J Ophthalmol*. 1982;66(3):161-164. doi:10.1136/bjo.66.3.161

37. Shahsuvaryan ML, Melkonyan AK. Central retinal vein occlusion risk profile: a case-control study. *Eur J Ophthalmol*. 2003;13(5):445-452. doi:10.1177/112067210301300505

38. Wang YX, Zhang JS, You QS, Xu L, Jonas JB. Ocular diseases and 10-year mortality: the Beijing Eye Study 2001/2011. *Acta Ophthalmol (Copenh)*. 2014;92(6):e424-428. doi:10.1111/aos.12370

39. Yin X, Li J, Zhang B, Lu P. Association of glaucoma with risk of retinal vein occlusion: A meta-analysis. *Acta Ophthalmol (Copenh)*. 2019;97(7):652-659. doi:10.1111/aos.14141

40. Haller JA, Bandello F, Belfort R, et al. Dexamethasone intravitreal implant in patients with macular edema related to branch or central retinal vein occlusion twelve-month study results. *Ophthalmology*. 2011;118(12):2453-2460. doi:10.1016/j.ophtha.2011.05.014

41. Wang Y, Wu S, Wen F, Cao Q. Diabetes mellitus as a risk factor for retinal vein occlusion: A meta-analysis. *Medicine (Baltimore)*. 2020;99(9):e19319. doi:10.1097/MD.0000000000019319

42. National Clinical Guideline Centre (UK). *Hypertension: The Clinical Management of Primary Hypertension in Adults: Update of Clinical Guidelines 18 and 34*. Royal College of Physicians (UK); 2011. Accessed July 21, 2020. http://www.ncbi.nlm.nih.gov/books/NBK83274/

43. www.cdc.gov/nchs/nhanes/search/nhanes09_10.aspx. US National Health and Nutrition Examination survey (NHNES) of 2009-20Hypertension. Accessed 19 Sept 2014.

44. http://www.diabetes.org.uk/About_us/What-we-say/Statistics/Diabetes-in-the-UK-2013-Key-statistics-on-diabetes. Diabetes in the UK in 2013: Key Statistics in diabetes. Accessed 19 Sept 2014.

45. www.cdc.gov/diabetes/pubs/statsreport14.htm. US National diabetes statistics report 2014. Accessed 19 Sept 2014.

46. Nam GE, Han K, Park SH, Cho KH, Song SJ. Retinal Vein Occlusion and the Risk of Dementia: A Nationwide Cohort Study. *Am J Ophthalmol*. 2021;221:181-189. doi:10.1016/j.ajo.2020.07.050

47. Tait C, Baglin T, Watson H, et al. Guidelines on the investigation and management of venous thrombosis at unusual sites. *Br J Haemato*l. 2012;159(1):28-38. doi:10.1111/j.1365-2141.2012.09249.x

48. Baglin T, Gray E, Greaves M, et al. Clinical guidelines for testing for heritable thrombophilia. *Br J Haematol*. 2010;149(2):209-220. doi:10.1111/j.1365-2141.2009.08022.x

49. Kirkegaard K, Heegaard S, Hvas A-M. No evidence for thrombophilia in patients with retinal venous occlusion: a systematic GRADE-based review. *Acta Ophthalmol (Copenh*). 2017;95(1):12-19. doi:10.1111/aos.13214

50. Romiti GF, Corica B, Borgi M, et al. Inherited and acquired thrombophilia in adults with retinal vascular occlusion: A systematic review and meta-analysis. *J Thromb Haemost JTH*. 2020;18(12):3249-3266. doi:10.1111/jth.15068

51. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost JTH*. 2006;4(2):295-306. doi:10.1111/j.1538-7836.2006.01753.x

52. Keeling D, Mackie I, Moore GW, Greer IA, Greaves M, British Committee for Standards in Haematology. Guidelines on the investigation and management of antiphospholipid syndrome. *Br J Haematol*. 2012;157(1):47-58. doi:10.1111/j.1365-2141.2012.09037.x

53. de Groot PG, Lutters B, Derksen RHWM, Lisman T, Meijers JCM, Rosendaal FR. Lupus anticoagulants and the risk of a first episode of deep venous thrombosis. *J Thromb Haemost JTH*. 2005;3(9):1993-1997. doi:10.1111/j.1538-7836.2005.01485.x

54. Girón-González JA, García del Río E, Rodríguez C, Rodríguez-Martorell J, Serrano A. Antiphospholipid syndrome and asymptomatic carriers of antiphospholipid antibody: prospective analysis of 404 individuals. *J Rheumatol*. 2004;31(8):1560-1567.

55. Zhu W, Wu Y, Xu M, et al. Antiphospholipid Antibody and Risk of Retinal Vein Occlusion: A Systematic Review and Meta-Analysis. *PLoS ONE*. 2015;10(4). doi:10.1371/journal.pone.0122814

56. Cheung N, Klein R, Wang JJ, et al. Traditional and novel cardiovascular risk factors for retinal vein occlusion: the multiethnic study of atherosclerosis. *Invest Ophthalmol Vis Sci*. 2008;49(10):4297-4302. doi:10.1167/iovs.08-1826

57. Li M, Hu X, Huang J, Tan Y, Yang B, Tang Z. Impact of Retinal Vein Occlusion on Stroke Incidence: A Meta-Analysis. *J Am Heart Assoc*. 2016;5(12). doi:10.1161/JAHA.116.004703

58. Klein R, Klein BE, Moss SE, Meuer SM. The epidemiology of retinal vein occlusion: the Beaver Dam Eye Study. *Trans Am Ophthalmol Soc*. 2000;98:133-141; discussion 141-143.

59. Mansour AM, Walsh JB, Henkind P. Mortality and morbidity in patients with central retinal vein occlusion. *Ophthalmol J Int Ophtalmol Int J Ophthalmol Z Augenheilkd*. 1992;204(4):199-203. doi:10.1159/000310294

60. Xu L, Liu WW, Wang YX, Yang H, Jonas JB. Retinal vein occlusions and mortality: the Beijing Eye Study. *Am J Ophthalmol*. 2007;144(6):972-973. doi:10.1016/j.ajo.2007.07.015

61. Priluck IA, Robertson DM, Hollenhorst RW. Long-term follow-up of occlusion of the central retinal vein in young adults. *Am J Ophthalmol.* 1980;90(2):190-202. doi:10.1016/s0002-9394(14)74853-6

62. Hayreh SS, Hayreh MS. Hemi-central retinal vein occulsion. Pathogenesis, clinical features, and natural history. *Arch Ophthalmol Chic Ill 1960*. 1980;98(9):1600-1609. doi:10.1001/archopht.1980.01020040452011

63. Koh Y-Y, Lai C-C, Wu W-C, et al. Baseline clinical features predict visual outcome in young patients with central retinal vein occlusion. *Graefes Arch Clin Exp Ophthalmol Albrecht Von Graefes Arch Klin Exp Ophthalmol.* 2020;258(7):1367-1377. doi:10.1007/s00417-020-04679-8

64. Moisseiev E, Sagiv O, Lazar M. Intense exercise causing central retinal vein occlusion in a young patient: case report and review of the literature. *Case Rep Ophthalmol*. 2014;5(1):116-120. doi:10.1159/000360904

65. Rothman AL, Thomas AS, Khan K, Fekrat S. CENTRAL RETINAL VEIN OCCLUSION IN YOUNG INDIVIDUALS: A Comparison of Risk Factors and Clinical Outcomes. *Retina Phila Pa*. 2019;39(10):1917-1924. doi:10.1097/IAE.0000000000002278

66. Fong AC, Schatz H. Central retinal vein occlusion in young adults. *Surv Ophthalmol*. 1993;37(6):393-417. doi:10.1016/0039-6257(93)90138-w

67. Hykin P, Prevost AT, Vasconcelos JC, et al. Clinical Effectiveness of Intravitreal Therapy With Ranibizumab vs Aflibercept vs Bevacizumab for Macular Edema Secondary to Central Retinal Vein Occlusion: A Randomized Clinical Trial. *JAMA Ophthalmol*. Published online August 29, 2019. doi:10.1001/jamaophthalmol.2019.3305

68. Scott IU, VanVeldhuisen PC, Oden NL, et al. Baseline predictors of visual acuity and retinal thickness outcomes in patients with retinal vein occlusion: Standard Care Versus COrticosteroid for REtinal Vein Occlusion Study report 10. *Ophthalmology*. 2011;118(2):345-352. doi:10.1016/j.ophtha.2010.06.034

69. Campochiaro PA, Clark WL, Boyer DS, et al. Intravitreal aflibercept for macular edema following branch retinal vein occlusion: the 24-week results of the VIBRANT study. *Ophthalmology*. 2015;122(3):538-544. doi:10.1016/j.ophtha.2014.08.031

70. Chan EW, Eldeeb M, Sun V, et al. Disorganization of Retinal Inner Layers and Ellipsoid Zone Disruption Predict Visual Outcomes in Central Retinal Vein Occlusion. *Ophthalmol Retina*. 2019;3(1):83-92. doi:10.1016/j.oret.2018.07.008

71. Berry D, Thomas AS, Fekrat S, Grewal DS. Association of Disorganization of Retinal Inner Layers with Ischemic Index and Visual Acuity in Central Retinal Vein Occlusion. *Ophthalmol Retina*. 2018;2(11):1125-1132. doi:10.1016/j.oret.2018.04.019

72. Etheridge T, Blodi B, Oden N, et al. Spectral Domain Optical Coherence Tomography Predictors of Visual Acuity in the Study of COmparative Treatments for REtinal Vein Occlusion 2 (SCORE2). *Ophthalmol Retina*. Published online December 26, 2020. doi:10.1016/j.oret.2020.12.016

73. Babiuch AS, Han M, Conti FF, Wai K, Silva FQ, Singh RP. Association of Disorganization of Retinal Inner Layers With Visual Acuity Response to Anti-Vascular Endothelial Growth Factor Therapy for Macular Edema Secondary to Retinal Vein Occlusion. *JAMA Ophthalmol*. 2019;137(1):38-46. doi:10.1001/jamaophthalmol.2018.4484

74. Mimouni M, Segev O, Dori D, Geffen N, Flores V, Segal O. Disorganization of the Retinal Inner Layers as a Predictor of Visual Acuity in Eyes With Macular Edema Secondary to Vein Occlusion. *Am J Ophthalmol*. 2017;182:160-167. doi:10.1016/j.ajo.2017.08.005

75. Sen P, Gurudas S, Ramu J. Predictors of visual acuity outcomes following anti-VEGF treatment for macular edema secondary to central retinal vein occlusion. Ophthalmol Retina. (in press).

76. Werner JU, Böhm F, Lang GE, Dreyhaupt J, Lang GK, Enders C. Comparison of foveal avascular zone between optical coherence tomography angiography and fluorescein angiography in patients with retinal vein occlusion. *PloS One*. 2019;14(6):e0217849. doi:10.1371/journal.pone.0217849

77. Nobre Cardoso J, Keane PA, Sim DA, et al. Systematic Evaluation of Optical Coherence Tomography Angiography in Retinal Vein Occlusion. *Am J Ophthalmol*. 2016;163:93-107.e6. doi:10.1016/j.ajo.2015.11.025

78. Huemer J, Khalid H, Wagner SK, et al. Phenotyping of retinal neovascularization in ischemic retinal vein occlusion using wide field OCT angiography. *Eye Lond Engl*. Published online November 30, 2020. doi:10.1038/s41433-020-01317-9

79. Novais EA, Waheed NK. Optical Coherence Tomography Angiography of Retinal Vein Occlusion. *Dev Ophthalmol*. 2016;56:132-138. doi:10.1159/000442805 Nicholson L, Vazquez-Alfageme C, Sen P, Patrao NV, Peto T, Yang Y, Sivaprasad S, Hykin PG. The clinical relevance of ultra-widefield angiography findings in patients with central retinal vein occlusion and macular oedema receiving anti-VEGF therapy. Eye (Lond). 2021 May 25.

81. Gado AS, Macky TA. Dexamethasone intravitreous implant versus bevacizumab for central retinal vein occlusion-related macular oedema: a prospective randomized comparison. *Clin Experiment Ophthalmol*. 2014;42(7):650-655. doi:10.1111/ceo.12311

82. Epstein DL, Algvere PV, von Wendt G, Seregard S, Kvanta A. Benefit from bevacizumab for macular edema in central retinal vein occlusion: twelve-month results of a prospective, randomized study. *Ophthalmology*. 2012;119(12):2587-2591. doi:10.1016/j.ophtha.2012.06.037

83. Scott IU, VanVeldhuisen PC, Ip MS, et al. Effect of Bevacizumab vs Aflibercept on Visual Acuity Among Patients With Macular Edema Due to Central Retinal Vein Occlusion: The SCORE2 Randomized Clinical Trial. *JAMA*. 2017;317(20):2072-2087. doi:10.1001/jama.2017.4568

84. Campochiaro PA, Wykoff CC, Singer M, et al. Monthly versus as-needed ranibizumab injections in patients with retinal vein occlusion: the SHORE study. *Ophthalmology*. 2014;121(12):2432-2442. doi:10.1016/j.ophtha.2014.06.011

85. Scott IU, VanVeldhuisen PC, Ip MS, et al. Comparison of Monthly vs Treat-and-Extend Regimens for Individuals With Macular Edema Who Respond Well to Anti-Vascular Endothelial Growth Factor Medications: Secondary Outcomes From the SCORE2 Randomized Clinical Trial. *JAMA Ophthalmol.* 2018;136(4):337-345. doi:10.1001/jamaophthalmol.2017.6843

86. Larsen M, Waldstein SM, Boscia F, et al. Individualized Ranibizumab Regimen Driven by Stabilization Criteria for Central Retinal Vein Occlusion: Twelve-Month Results of the CRYSTAL Study. *Ophthalmology.* 2016;123(5):1101-1111. doi:10.1016/j.ophtha.2016.01.011

87. Brown DM, Heier JS, Clark WL, et al. Intravitreal aflibercept injection for macular edema secondary to central retinal vein occlusion: 1-year results from the phase 3 COPERNICUS study. *Am J Ophthalmol.* 2013;155(3):429-437.e7. doi:10.1016/j.ajo.2012.09.026

88. Campochiaro PA, Brown DM, Awh CC, et al. Sustained benefits from ranibizumab for macular edema following central retinal vein occlusion: twelve-month outcomes of a phase III study. *Ophthalmology.* 2011;118(10):2041-2049. doi:10.1016/j.ophtha.2011.02.038

89. Korobelnik J-F, Holz FG, Roider J, et al. Intravitreal Aflibercept Injection for Macular Edema Resulting from Central Retinal Vein Occlusion: One-Year Results of the Phase 3 GALILEO Study. *Ophthalmology.* 2014;121(1):202-208. doi:10.1016/j.ophtha.2013.08.012

90. Ip MS, Oden NL, Scott IU, et al. Month 12 Outcomes After Treatment Change at Month 6 Among Poor Responders to Aflibercept or Bevacizumab in Eyes With Macular Edema Secondary to Central or Hemiretinal Vein Occlusion: A Secondary Analysis of the SCORE2 Study. *JAMA Ophthalmol.* 2019;137(3):281-287. doi:10.1001/jamaophthalmol.2018.6111

91. Campochiaro PA, Sophie R, Pearlman J, et al. Long-term outcomes in patients with retinal vein occlusion treated with ranibizumab: the RETAIN study. *Ophthalmology.* 2014;121(1):209-219. doi:10.1016/j.ophtha.2013.08.038

92. Brown DM, Campochiaro PA, Bhisitkul RB, et al. Sustained benefits from ranibizumab for macular edema following branch retinal vein occlusion: 12-month outcomes of a phase III study. *Ophthalmology.* 2011;118(8):1594-1602. doi:10.1016/j.ophtha.2011.02.022

93. Holz FG, Roider J, Ogura Y, et al. VEGF Trap-Eye for macular oedema secondary to central retinal vein occlusion: 6-month results of the phase III GALILEO study. *Br J Ophthalmol.* 2013;97(3):278-284. doi:10.1136/bjophthalmol-2012-301504

94. Brown DM, Campochiaro PA, Singh RP, et al. Ranibizumab for macular edema following central retinal vein occlusion: six-month primary end point results of a phase III study. *Ophthalmology.* 2010;117(6):1124-1133.e1. doi:10.1016/j.ophtha.2010.02.022

95. Heier JS, Campochiaro PA, Yau L, et al. Ranibizumab for macular edema due to retinal vein occlusions: long-term follow-up in the HORIZON trial. *Ophthalmology.* 2012;119(4):802-809. doi:10.1016/j.ophtha.2011.12.005

96. Larsen M, Waldstein SM, Priglinger S, et al. Sustained Benefits from Ranibizumab for Central Retinal Vein Occlusion with Macular Edema: 24-Month Results of the CRYSTAL Study. *Ophthalmol Retina.* 2018;2(2):134-142. doi:10.1016/j.oret.2017.05.016

97. Ogura Y, Roider J, Korobelnik J-F, et al. Intravitreal aflibercept for macular edema secondary to central retinal vein occlusion: 18-month results of the phase 3 GALILEO study. *Am J Ophthalmol.* 2014;158(5):1032-1038. doi:10.1016/j.ajo.2014.07.027

98. Boyer D, Heier J, Brown DM, et al. Vascular endothelial growth factor Trap-Eye for macular edema secondary to central retinal vein occlusion: six-month results of the phase 3 COPERNICUS study. *Ophthalmology.* 2012;119(5):1024-1032. doi:10.1016/j.ophtha.2012.01.042

99. Heier JS, Clark WL, Boyer DS, et al. Intravitreal aflibercept injection for macular edema due to central retinal vein occlusion: two-year results from the COPERNICUS study. *Ophthalmology.* 2014;121(7):1414-1420.e1. doi:10.1016/j.ophtha.2014.01.027

100. Kuppermann BD, Haller JA, Bandello F, et al. Onset and duration of visual acuity improvement after dexamethasone intravitreal implant in eyes with macular edema due to retinal vein occlusion. *Retina Phila Pa*. 2014;34(9):1743-1749. doi:10.1097/IAE.0000000000000167

101. Yap TE, Husein S, Miralles de Imperial-Ollero JA, Colizzi B, Cordeiro MF, Younis S. The efficacy of dexamethasone implants following anti-VEGF failure for macular oedema in retinal vein occlusion. *Eur J Ophthalmol*. Published online December 27, 2020:1120672120978355. doi:10.1177/1120672120978355

102. Ip MS, Scott IU, VanVeldhuisen PC, et al. A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with observation to treat vision loss associated with macular edema secondary to central retinal vein occlusion: the Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) study report 5. *Arch Ophthalmol Chic Ill 1960*. 2009;127(9):1101-1114. doi:10.1001/archophthalmol.2009.234

103. Hoerauf H, Feltgen N, Weiss C, et al. Clinical Efficacy and Safety of Ranibizumab Versus Dexamethasone for Central Retinal Vein Occlusion (COMRADE C): A European Label Study. *Am J Ophthalmol*. 2016;169:258-267. doi:10.1016/j.ajo.2016.04.020

104. Evaluation of grid pattern photocoagulation for macular edema in central vein occlusion. The Central Vein Occlusion Study Group M report. *Ophthalmology*. 1995;102(10):1425-1433.

105. Feltgen N, Ogura Y, Boscia F, et al. Impact of Baseline Retinal Nonperfusion and Macular Retinal Capillary Nonperfusion on Outcomes in the COPERNICUS and GALILEO Studies. *Ophthalmol Retina.* 2019;3(7):553-560. doi:10.1016/j.oret.2019.02.010

106. Brown DM, Wykoff CC, Wong TP, et al. Ranibizumab in preproliferative (ischemic) central retinal vein occlusion: the rubeosis anti-VEGF (RAVE) trial. *Retina Phila Pa.* 2014;34(9):1728-1735. doi:10.1097/IAE.0000000000000191

107. Hogg HDJ, Talks SJ, Pearce M, Simplicio SD. Real-World Visual and Neovascularisation Outcomes from anti-VEGF in Central Retinal Vein Occlusion. *Ophthalmic Epidemiol*. 2021;28(1):70-76. doi:10.1080/09286586.2020.1792937

108. Beutel J, Peters S, Lüke M, et al. Bevacizumab as adjuvant for neovascular glaucoma. *Acta Ophthalmol (Copenh)*. 2010;88(1):103-109. doi:10.1111/j.1755-3768.2008.01355.x

109. Cornish KS, Ramamurthi S, Saidkasimova S, Ramaesh K. Intravitreal bevacizumab and augmented trabeculectomy for neovascular glaucoma in young diabetic patients. *Eye Lond Engl*. 2009;23(4):979-981. doi:10.1038/eye.2008.113

110. Campochiaro PA, Hafiz G, Mir TA, et al. Scatter Photocoagulation Does Not Reduce Macular Edema or Treatment Burden in Patients with Retinal Vein Occlusion: The RELATE Trial. *Ophthalmology*. 2015;122(7):1426-1437. doi:10.1016/j.ophtha.2015.04.006

111. Wykoff CC, Ou WC, Wang R, et al. Peripheral Laser for Recalcitrant Macular Edema Owing to Retinal Vein Occlusion: The WAVE Trial. *Ophthalmology*. 2017;124(6):919-921. doi:10.1016/j.ophtha.2017.01.049

112. McAllister IL, Gillies ME, Smithies LA, et al. The Central Retinal Vein Bypass Study: a trial of laser-induced chorioretinal venous anastomosis for central retinal vein occlusion. *Ophthalmology*. 2010;117(5):954-965. doi:10.1016/j.ophtha.2009.10.026

113. McAllister IL, Smithies LA, Previn V. TECHNIQUE OF LASER CHORIORETINAL ANASTOMOSIS CREATION IN CENTRAL RETINAL VEIN OCCLUSION AND SUCCESS RATE WITH A NEW PHOTOCOAGULATOR SYSTEM. *Retina Phila Pa*. 2016;36(10):1971-1978. doi:10.1097/IAE.0000000000001025

114. Luttrull JK. Epiretinal membrane and traction retinal detachment complicating laser-induced chorioretinal venous anastomosis. *Am J Ophthalmol*. 1997;123(5):698-699. doi:10.1016/s0002-9394(14)71088-8

115. Browning DJ, Rotberg MH. Vitreous Hemorrhage complicating laser-induced chorioretinal anastomosis for central retinal vein occlusion. *Am J Ophthalmol*. 1996;122(4):588-589. doi:10.1016/s0002-9394(14)72128-2

116. McAllister IL, Smithies LA, Chen FK, Mackey DA, Sanfilippo PG. Two-Year Efficacy of Ranibizumab Plus Laser-Induced Chorioretinal Anastomosis vs Ranibizumab Monotherapy for Central Retinal Vein Occlusion: A Randomized Clinical Trial. *JAMA Ophthalmol*. 2018;136(12):1391-1397. doi:10.1001/jamaophthalmol.2018.4973

117. Tadayoni R, Waldstein SM, Boscia F, et al. Sustained Benefits of Ranibizumab with or without Laser in Branch Retinal Vein Occlusion: 24-Month Results of the BRIGHTER Study. *Ophthalmology*. 2017;124(12):1778-1787. doi:10.1016/j.ophtha.2017.06.027

118. Murakami T, Takagi H, Ohashi H, et al. Role of posterior vitreous detachment induced by intravitreal tissue plasminogen activator in macular edema with central retinal vein occlusion. *Retina Phila Pa*. 2007;27(8):1031-1037. doi:10.1097/IAE.0b013e318074bc39

119. Tadayoni R, Waldstein SM, Boscia F, et al. Individualized Stabilization Criteria-Driven Ranibizumab versus Laser in Branch Retinal Vein Occlusion: Six-Month Results of BRIGHTER. Ophthalmology. 2016;123(6):1332-1344. doi:10.1016/j.ophtha.2016.02.030

120. Clark WL, Boyer DS, Heier JS, et al. Intravitreal Aflibercept for Macular Edema Following Branch Retinal Vein Occlusion: 52-Week Results of the VIBRANT Study. *Ophthalmology*. 2016;123(2):330-336. doi:10.1016/j.ophtha.2015.09.035

121. Prager F, Michels S, Kriechbaum K, et al. Intravitreal bevacizumab (Avastin) for macular oedema secondary to retinal vein occlusion: 12-month results of a prospective clinical trial. *Br J Ophthalmol*. 2009;93(4):452-456. doi:10.1136/bjo.2008.141085

122. Moradian S, Faghihi H, Sadeghi B, et al. Intravitreal bevacizumab vs. sham treatment in acute branch retinal vein occlusion with macular edema: results at 3 months (Report 1). *Graefes Arch Clin Exp Ophthalmol Albrecht Von Graefes Arch Klin Exp Ophthalmol*. 2011;249(2):193-200. doi:10.1007/s00417-010-1440-8

123. Narayanan R, Panchal B, Das T, et al. A randomised, double-masked, controlled study of the efficacy and safety of intravitreal bevacizumab versus ranibizumab in the treatment of macular oedema due to branch retinal vein occlusion: MARVEL Report No. 1. *Br J Ophthalmol*. 2015;99(7):954-959. doi:10.1136/bjophthalmol-2014-306543

124. Hattenbach L-O, Feltgen N, Bertelmann T, et al. Head-to-head comparison of ranibizumab PRN versus single-dose dexamethasone for branch retinal vein occlusion (COMRADE-B). *Acta Ophthalmol (Copenh)*. 2018;96(1):e10-e18. doi:10.1111/aos.13381

125. Scott IU, Ip MS, VanVeldhuisen PC, et al. A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with standard care to treat vision loss associated with macular Edema secondary to branch retinal vein occlusion: the Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) study report 6. *Arch Ophthalmol Chic Ill 1960*. 2009;127(9):1115-1128. doi:10.1001/archophthalmol.2009.233

126. Miller SD. Argon laser photocoagulation for macular edema in branch vein occlusion. *Am J Ophthalmol*. 1985;99(2):218-219.

127. Chung EJ, Lee H, Koh HJ. Arteriovenous crossing sheathotomy versus intravitreal triamcinolone acetonide injection for treatment of macular edema associated with branch retinal vein occlusion. *Graefes Arch Clin Exp Ophthalmol Albrecht Von Graefes Arch Klin Exp Ophthalmol.* 2008;246(7):967-974. doi:10.1007/s00417-008-0830-7

128. NICE Interventional Procedure Guidance IPG3Arteriovenous crossing sheathotomy for branch retinal vein occlusion. http://guidance.nice.org.uk/IPG3issued 24 March 2010. Accessed 15 June 20.

129. Awdeh RM, Elsing SH, Deramo VA, Stinnett S, Lee PP, Fekrat S. Vision-related quality of life in persons with unilateral branch retinal vein occlusion using the 25-item National Eye Institute Visual Function Questionnaire. *Br J Ophthalmol.* 2010;94(3):319-323. doi:10.1136/bjo.2007.135913

130. Deramo VA, Cox TA, Syed AB, Lee PP, Fekrat S. Vision-related quality of life in people with central retinal vein occlusion using the 25-item National Eye Institute Visual Function Questionnaire. *Arch Ophthalmol Chic Ill 1960*. 2003;121(9):1297-1302. doi:10.1001/archopht.121.9.1297

131. Chang MA, Fine HF, Bass E, et al. Patients' preferences in choosing therapy for retinal vein occlusions. *Retina Phila Pa*. 2007;27(6):789-797. doi:10.1097/IAE.0b013e31802c0a34

132. Sakuma H, Azukzawa M, Higuchi R. Patients' satisfaction after trans-Tenon injection of retrobulbar triamcinolone for macular edema. Jap J Clin Ophthalmol 2005; 59:1337 – 1340.

133. Finger RP, Daien V, Talks JS, et al. A novel tool to assess the quality of RWE to guide the management of retinal disease. *Acta Ophthalmol (Copenh)*. Published online December 28, 2020. doi:10.1111/aos.14698

134. Okada M, Mitchell P, Finger RP, et al. Nonadherence or Nonpersistence to Intravitreal Injection Therapy for Neovascular Age-Related Macular Degeneration: A Mixed-Methods Systematic Review. *Ophthalmology*. 2021;128(2):234-247. doi:10.1016/j.ophtha.2020.07.060

135. Talks J, Daien V, Finger RP, et al. The use of real-world evidence for evaluating anti-vascular endothelial growth factor treatment of neovascular age-related macular degeneration. *Surv Ophthalmol*. 2019;64(5):707-719. doi:10.1016/j.survophthal.2019.02.008

136. Daien V, Eldem BM, Talks JS, et al. Real-world data in retinal diseases treated with anti-vascular endothelial growth factor (anti-VEGF) therapy - a systematic approach to identify and characterize data sources. *BMC Ophthalmol.* 2019;19(1):206. doi:10.1186/s12886-019-1208-9

137. Gale R, Gill C, Pikoula M, et al. Multicentre study of 4626 patients assesses the effectiveness, safety and burden of two categories of treatments for central retinal vein occlusion: intravitreal anti-vascular endothelial growth factor injections and intravitreal Ozurdex injections. *Br J Ophthalmol.* Published online September 22, 2020. doi:10.1136/bjophthalmol-2020-317306

138. Gale R, Pikoula M, Lee AY, et al. Real world evidence on 5661 patients treated for macular oedema secondary to branch retinal vein occlusion with intravitreal anti-vascular endothelial growth factor, intravitreal dexamethasone or macular laser. *Br J Ophthalmol.* Published online June 12, 2020. doi:10.1136/bjophthalmol-2020-315836

139. Ciulla T, Pollack JS, Williams DF. Visual acuity outcomes and anti-VEGF therapy intensity in macular oedema due to retinal vein occlusion: a real-world analysis of 15 613 patient eyes. *Br J Ophthalmol.* Published online October 14, 2020. doi:10.1136/bjophthalmol-2020-317337

140. Pearce I, Clemens A, Brent MH, et al. Real-world outcomes with ranibizumab in branch retinal vein occlusion: The prospective, global, LUMINOUS study. *PloS One*. 2020;15(6):e0234739. doi:10.1371/journal.pone.0234739