Retinal Vein Occlusion

Background
Retinal vein occlusion (RVO) is a common cause of visual loss. It is an obstruction of the retinal venous system by thrombus formation and may involve the central, hemi-central or branch retinal vein. Thrombus formation may be the primary cause but other possible causes are external compression or disease of the vein wall e.g. vasculitis. Retinal vein occlusions are the second commonest cause of reduced vision due to retinal vascular disease, with BRVO occurring 2-3 times as common as CRVO. In the Australian population study, the incidence was 0.7% at 49-60yrs and 4.6% at 80yrs. It is currently estimated from pooled data from 15 population studies that there are about 520 new cases per million population of RVO. These include 442 and 80 per million of BRVO and CRVO respectively.

AETIOLOGY AND RISK FACTORS
Retinal vein occlusion is due to thrombosis within retinal veins (central, hemi or branch) although it remains unclear whether it is a primary or secondary effect. Established cardiovascular risk factors are the predominant medical associations for both central and branch vein occlusions and are summarised below.

Systemic vascular/atherosclerotic risk factors in RVO
Study design, patient characteristics, and risk factor definitions are seldom standardized across the various published papers in the literature. However, accounting for this it remains probable that systemic hypertension is the strongest independent risk factor associated with all types of RVO especially in the older (over 50 years) age group. Uncontrolled or newly diagnosed hypertension is common in this group, and recurrence of RVO in the same or fellow eye is also noted when hypertension is poorly controlled. In their meta-analysis of 21 studies, O’Mahoney et al12 report a significant association between hypertension and both CRVO (pooled odds ratio [OR = 3.8] and BRVO [pooled OR 3.0]. Accepting an inconsistent definition of hyperlipidemia across studies they also found hyperlipidemia to be twice as common in RVO cases (both CRVO and BRVO) compared to controls (pooled OR 2.5). Some studies also report hypertension and hyperlipidemia as independent risk factors for RVO12. The association of diabetes mellitus with RVO is weaker and has not been found to be consistent across all studies9-12. Its association with CRVO may be stronger than with BRVO10.

Hematological disorders and other systemic conditions.
Conditions that lead to increased blood viscosity such as myeloproliferative disorders are uncommon but known to be associated with CRVO. Similarly, a number of rare systemic inflammatory disorders causing systemic vasculitis (such as Behçet’s disease and polyarteritis nodosa) also cause retinal vasculitis leading to RVO, especially in the younger age group. The cause and management of the RVO here is closely linked to the underlying systemic disease and its management. Over recent years there has been great interest in the potential role of thrombophilia in the development of RVO and in particular CRVO. Thrombophilia refers to the propensity to develop thrombosis (usually venous) due to an abnormality in the coagulation system. This can be congenital (e.g., Factor V Leiden, hyperhomocysteinemia or protein C, protein S and antithrombin deficiencies) or acquired (e.g., antiphospholipid syndrome), and its importance is potentially greater in the younger age group. However, Fegan’s review on CRVO and thrombophilia16 suggested that there was a lack of consistency between studies in showing a valid association between CRVO and protein C, protein S and antithrombin III deficiency, and factor V Leiden/activated protein C resistance. These natural anticoagulants are very labile with fluctuating physiological levels. It is recommended that they should be measured on at least two separate samples and if found abnormal confirm with a third estimation. Most studies used single measurements and varying types of assays. The studies also lacked the statistical power to show a true difference either due to small sample size or lack of a suitable control group. In the antiphospholipid syndrome (APS) antibodies to phospholipid activate the coagulation cascade leading to both arterial and venous thrombosis. Tests can be done to either detect the antibody (using the anticardiolipin antibody assay) or its effect on coagulation using a test for lupus anticoagulant. Up to 8% of patients with APS have ocular manifestations and 4 of 8 studies reviewed by Fegan16 showed a significant association of APS in CRVO. Further studies are required to determine the strength of association between APS and RVO. Homocysteine is a naturally occurring amino acid not found in protein. There are many causes for hyperhomo-cysteinemia (including rare enzyme deficiencies leading to homocystinuria) which predisposes to both arterial and venous thrombosis.16 Several studies have questioned the validity of carrying out exhaustive tests for thrombophilia in RVO in the absence of a suggestive...
medical history. However their results have shown notable evidence of an association of hyperhomocysteinemia with CRVO sufficient to recommend the benefit of checking for hyperhomocysteinemia, which is correctable with folate acid and vitamins B6 and B12 supplements.15-16 On current evidence it would be reasonable to not recommend general thrombophilia screening for all patients with RVO, but to reserve it for older patients with a past history of thromboembolic events and in young patients without any other general risk factors.

**Glucoma/ocular hypertension**

The association between RVO (CRVO in particular) and glaucoma/ocular hypertension has been widely reported with the Eye Disease Case-Control Study reporting an adjusted OR of 5.4 in CRVO for a history of glaucoma. The pathophysiology of this association is unclear, although deformation of the lamina cribrosa in glaucoma may distort the central retinal vein as it exits the eye.

**Familial RVO**

Familial clustering of RVO (CRVO in particular) has been reported but these reports have been few in number. It is interesting that such cases are more often bilateral, with a younger age at onset than sporadic cases. More data from existing and future familial clusters is required to establish if there is a genetic cause in these cases.

**CLINICAL FEATURES OF CRVO**

**Non-Ischemic CRVO**

Non-ischemic CRVO is the most common type, accounting for about 75%. Presentation is with sudden, unilateral blurred vision. Mild to moderate loss of acuity, usually 20/200 or better, and an absent or mild relative afferent pupillary defect (RAPD), characterize these patients. Fundoscopy shows tortuosity and dilatation of all branches of the central retinal vein, dot/blot and flame-shaped hemorrhages, throughout all four quadrants and most numerous in the periphery, and optic disc and macular edema. Blood levels are often seen within the large retinal cysts in the foveolar area. Some cotton-wool patches, particularly in hypertensive patients, may be present. Transient retinal vessel wall sheathing may occur.

The acute signs resolve over 6-12 months, with disc collaterals and pigmentary changes at the macula as residual findings. In a clearly non-ischemic occlusion, initial follow-up should take place after 3 months. Conversion to ischemic CRVO occurs in 15% of cases within 4 months and 34% within 3 years.

**A- Nonischaemic CRVO with minimal retinal hemorrhages, B- Ischemic CRVO with extensive retinal hemorrhages**

**Ischemic CRVO**

Ischemic CRVO is characterized by rapid onset venous obstruction resulting in decreased retinal perfusion, capillary closure and retinal hypoxia. Patients with severe central retinal vein obstruction typically have severe visual loss, usually less than 20/200; a marked afferent pupillary defect; severe tortuosity and engorgement of all branches of the central retinal vein, extensive deep blot and flame-shaped hemorrhages involving the peripheral retina and posterior pole, severe disc edema and hyperemia. This may lead to profound vascular leakage, rubeosis iridis and raised intraocular pressure. The prognosis is extremely poor due to macular ischemia. Rubeosis iridis develops in about 50% of eyes, usually between 2 and 4 months (100-day glaucoma), and there is a high risk of neovascular glaucoma. Retinal neovascularization occurs in about 5% of eyes. Where possible, patients with ischemic CRVO should be seen monthly for 6 months to detect the onset of anterior segment neovascularization. Subsequent review should usually be for up to 2 years to detect significant ischemia and macular oedema.

Natural history data from the CVOS study19,20 and a systematic literature review8 demonstrated that visual outcome of CRVO depends on the visual acuity at presentation. Eyes with initial visual acuity of 20/40 (6/12) or better have a better prognosis for retaining good vision than those with worse vision. Only 20% of eyes with initial visual acuity of 20/50-20/200 (6/15 -6/60) improve spontaneously to 20/50 (6/15) while 80% of patients with baseline vision worse than 20/200 (6/60) remain at this level or worsen. Furthermore, the longer the duration of macular oedema, the more the structural damage at the fovea so it is justifiable that early treatment be initiated.

**CLINICAL FEATURES OF BRVO**

Major BRVO can be asymptomatic or with visual blurring usually involving the sector of visual field corresponding to the area of the retina involved. In macular BRVO, there is always a central visual disturbance with normal peripheral vision. Acute BRVO presents characteristic clinical features with flame-shaped, dot and blot hemorrhage, soft and hard exudates, retinal edema, and dilated, tortuous vein in a segmental distribution. Signs of old occlusion are vascular sheathing and venous collaterals. The diagnosis is based on clinical examination under slit lamp and fundoscopy in artificial mydriasis, VA is of great importance for future visual prognosis. BRVO often leads to retinal non-perfusion zones in the occlusion area. Fluorescein angiography is particularly useful in determining the extent of ME and ischemia, although the ischemic areas are often obscured by the presence of intraretinal hemorrhage. Retinal neovascularization occurs in 36% of eyes with an area of non-perfusion greater than 5 disc diameter.
Natural history data from an evidence-based systematic review of 24 studies by Rogers et al. indicated that VA was moderately poor (worse than 6/12) at presentation, and that although there may be some improvement in the follow-up period, such improvement was limited such that the average improvement did not result in VA better than 6/12. Macular oedema may develop in 5 to 15% of eyes over a 1-year period; however, of the eyes that had macular oedema at presentation, 18 to 40% may show some resolution. Approximately 20% of untreated eyes experienced significant vision deterioration over time. In the BVOS5, approximately 50% of untreated eyes with BRVO retain vision of 6/12 or better whilst 25% will have vision of <6/60.5. Fellow eye involvement by BRVO may occur in 10% of cases over time.

**Clinical evaluation**

The minimum assessments required before commencing treatments for CRVO include:

Clinical examination including
a. Best corrected visual acuity (BCVA)
b. Pupillary reactions- the presence of a brisk afferent papillary defect (APD)
c. IOP
d. Gonioscopy
e. Slit lamp biomicroscopy of the anterior segment and fundus

**Retinal Imaging**

a. Colour fundus photographs (Whenever possible)
b. Optical coherent tomography (OCT)
c. Fundus fluorescein angiography (FFA) where the interpretation is not confounded by the presence of marked intraretinal haemorrhage or can be based on clinical judgement.

Electro-retinography: Is useful to differentiate nonischaemic CRVO from Ischaemic CRVO. Nonischemic RVO have normal b wave amplitude and b/a wave ratio. Ischemic type usually have reduced b wave amplitude and b/a wave ratio.23,24

The minimum assessments required before commencing treatments for BRVO include:
- Clinical examination including
  a. Best corrected visual acuity (BCVA)
  b. Pupillary reactions- the presence of a brisk afferent papillary defect (APD)
  c. IOP
  d. Gonioscopy if clinically indicated
  e. Slit lamp biomicroscopy of the anterior segment and fundus

**Retinal Imaging**

a. Colour fundus photographs (whenever possible)
b. Optical coherent tomography (OCT)
c. Fundus fluorescein angiography (FFA) where the interpretation is not confounded by the presence of marked intraretinal haemorrhage or as per clinical judgement.

**FFA IN RVO**

FFA in RVO shows dilatation and tortuosity of affected veins with retinal hemorrhages, cotton wool spots and edema in the areas of drainage. In all eyes there is a delay in the filling of the retinal circulation, dilated capillaries, microaneurysms and telangiectastic changes. Blocked fluorescence of the underlying retinal circulation occur if extensive intraretinal hemorrhages are present especially in the early part of the disease and therefore FFA may not reveal useful information.

![Fig 4; FFA of BRVO with segmental capillary nonperfusion and macular ischaemia](image4.png)

![Fig 7; Spectral domain OCT of macula in vein occlusion with cystoid macular edema and subfoveal detachment](image7.png)

![Fig 5; FFA of CRVO. A- early phase showing the delay in AV transit of the dye, B- late phase showing diffuse leakage of the dye from the vessels.](image5.png)
CRVO is said to be perfused if capillary non-perfusion is less than 10 disc areas and non-perfused if capillary non-perfusion is more than 10 disc areas. BRVO is said to be perfused if capillary non-perfusion is less than 5 disc areas and non-perfused if capillary non-perfusion is more than 5 disc areas. Another main role of FFA is evaluation of macular edema. Macular edema can be of perfused type, if there is an intact parafoveal capillary network in arteriovenous phase followed by late accumulation of dye involving the foveal center, non-perfused if there are areas of parafoveal and perifoveal capillary non-perfusion with no accumulation of dye seen in late phase. In other cases a mixed picture with combination of capillary dilatation and leakage, areas of capillary non-perfusion in the parafoveal region, with late phase showing some degree of accumulation of dye. Late staining and leakage from affected veins also occurs. Retinal capillary obliteration is a progressive phenomenon and it takes 3-4 weeks to obliterate; if FFA is done early, perfectly normal capillaries may be seen, despite retinal ischemia and may lead to wrong diagnosis of non-ischemic variety.

OCT in RVO
OCT delineates macular changes at a stage when fundus biomicroscopy and fluorescein angiography are not very informative. The various anatomical patterns of structural changes appreciated better on OCT are SRD, CME, epiretinal membrane, lamellar holes and subhyaloid or preretinal hemorrhages. OCT examination shows CME, if there were hyporeflective intraretinal cavities in cross sectional scans radiating from centre of macula and SRD, if there is retinal elevation over a nonreflective cavity with minimal shadowing of underlying tissues or if posterior surface of the retina is elevated above the retinal pigment epithelium. Non-ischemic maculae show an early and more rapid decline in macular thickness compared with ischemic occlusions. OCT is also useful to quantify macular edema and helps in follow up of patients with macular edema, in assessing treatment response especially to intravitreal pharmacotherapy and in explaining poor outcomes and has been part of all the recent trials in the management of macular edema of vein occlusions.

MANAGEMENT
There are two aims in the management of retinal vein occlusion: the identification of modifiable risk factors and their medical management and the recognition and management of sight-threatening complications.

Central retinal vein occlusion (CRVO)
The main management problem is to differentiate ischaemic from non-ischaemic central retinal vein occlusion. Patients with ischaemic CRVO are at risk of neovascular glaucoma. This risk of iris neovascularisation is higher if the area of retinal ischaemia (retinal non-perfusion as determined by FFA) is >10 disc diameters. Ischaemic central retinal vein occlusion is associated with one or more of the following characteristics:
1. Poor visual acuity (44% of eyes with vision of <6/60 develop rubeosis)
2. Relative afferent pupillary defect
3. Presence of multiple dark deep intra-retinal haemorrhage
4. Presence of multiple cotton wool spots
5. Fluorescein angiography showing greater than 10 disc areas of retinal capillary non-perfusion (CVOS)
6. Electrodiagnostic tests (ERG): reduced b wave amplitude, reduced b:a ratio and prolonged b-wave implicit time
7. Degree of retinal vein dilatation and tortuosity
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 patients with initially non-ischaemic central retinal vein occlusion will develop ischaemic transformation. This is usually heralded by further rapid visual deterioration and requires further assessment. CRVO especially of the non-ischaemic type needs to be differentiated from the ocular ischaemic syndrome and other simulating retinopathies.

Medical Investigations for Patients Presenting with Retinal Vein Occlusion
ALL PATIENTS
Full blood count
ESR
Peripheral smear
Random blood glucose (in non diabetics), FBS/PPBS,HBAIC (In known diabetics)
Lipid profile
ECG+ECHO heart
Carotid Doppler study
MORE SPECIALISED TESTS ACCORDING TO CLINICAL INDICATION
Thrombophilia screen
Medical Management

Medical management should be targeted at three areas:

1. Restoring venous patency

Clinical & Diagnostic Work-up: This is applicable in a limited number of cases. Patients with ‘incipient’ retinal vein occlusion (consisting of the presence of dilated retinal veins and few widely scattered haemorrhages without any macular oedema in patients who are either asymptomatic or have transient episodes of blurring in the affected eye and may have slight increase in retinal circulation time on fluorescein angiography) should have medical investigation for underlying systemic risk factors and treatment urgently as there is the potential to prevent progression, or to reverse the existing occlusion.

The medical therapies explored to improve retinal venous flow include:

- **Anti-coagulants**: heparin

- **Fibrinolytic agents**: streptokinase, tissue plasminogen activator (intravitreal or systemic)

- **Anti-platelet drugs**: aspirin, prostacyclin, ticlopidine

These would seem to be logical treatments, but results from trials using heparin, streptokinase and warfarin have been disappointing with limited evidence of benefit owing to adverse effects of retinal and vitreous haemorrhage. Aspirin is not recommended for primary prevention of cardiovascular events. If aspirin is used in primary prevention, the balance of benefits and risks should be considered for each individual, particularly the presence of risk factors. Given that there is insufficient evidence to suggest that RVO is a risk factor for stroke or vascular mortality, the role of aspirin in RVO remains equivocal.

**Haemodilution**: The effects of haemodilution have been inconsistent in completed control trials in RVO and the treatment may have adverse effects on the patients’ general well-being.

2. Ameliorate cardiovascular morbidity and mortality associated with retinal vein occlusion

Manage underlying risk factors: Although reports on the association of RVO with cardiovascular morbidity and mortality are conflicting, it is crucial that all cardiovascular risk factors be identified and treated in patients with RVO. Cardiovascular risk factors identified in patients with retinal vein occlusion should be managed according to the Joint British recommendations on prevention of coronary heart disease and the recent updates on the management of hypertension and the use of statins. Patients with rarer underlying conditions such as myeloma and inflammatory disorders should be referred and managed by appropriate specialists.

3. To prevent the recurrence of retinal vein occlusion

Several series have demonstrated that recurrence of retinal vein occlusion may occur in the affected eye or in the fellow eye in up to 15% of patients over a five year follow up period. Rates vary according to studies in differing countries from 9 to 15%. In view of the poor potential visual outcome of patients with recurrent retinal vein occlusion, this aspect has been studied, but not in controlled trials. Available data supports the concept that recurrence of retinal vein occlusion may be reduced by medical treatments of underlying cardiovascular risk factors.

**CRVO Study**

Group M—Macular Edema: Macular grid photocoagulation was effective in reducing angiographic evidence of macular edema but did not improve visual acuity in eyes with reduced vision due to macular edema from CVO.

Group N—Panretinal Photocoagulation for Nonischemic CVO: Prophylactic panretinal photocoagulation did not prevent the development of iris neovascularization in eyes with 10 or more disc areas of retinal capillary nonperfusion confirmed by fluorescein angiography. Rather, results of this randomized clinical trial demonstrate that it is safe to wait for the development of early iris neovascularization and then apply panretinal photocoagulation.

Group I—Indeterminate: Eyes with such extensive intraretinal hemorrhage that it is not possible to determine the retinal capillary perfusion status act as if they are ischemic or nonperfused.

**Management of nonischaemic central retinal vein occlusion**

An initial evaluation of risk factors and the appropriate treatment of the present risks must proceed alongside management of the ocular findings. These patients are managed conservatively till significant macular edema or features of ischaemic CRVO occur.

A useful algorithm is as follows.
Fig 8; Patient with non ischaemic CRVO with good vision at presentation with good natural resolution over 6 months

1. If VA is better than 6/12 + OCT <250 microns, observe at monthly intervals for worsening in vision, increase in macular thickness, increase in IOP and onset of neovascularisation.
2. If VA is 6/12 or worse + OCT ≥250 microns (Stratus, or equivalent) consider pharmacotherapy with Ozurdex or anti-VEGF agents which is unlicensed but has robust evidence.
3. However, the presence of a brisk APD associated with VA<6/96 indicates potentially poor treatment outcomes.
   a. As such no treatment would be recommended for such cases. Watch for NVI/NVA, and treat as ischaemic CRVO

Subsequent Follow-Up
1. Depending on baseline VA, OCT & FFA findings, and initial treatment options, monitoring will be required at varying frequencies during the first 6 months.
   a. Assessments at each visit include VA, IOP, gonioscopy, fundoscopy, and OCT
   b. From month 6 to 18 months, monitoring at monthly or 3 monthly, depending on the particular treatment of choice

Re-treatment Criteria
1. Based on the results of the clinical trials, treatment may be repeated unless
   a. VA>6/7.5 (84 letters on LogMAR) OR
   b. Central Retina Thickness (CRT) on OCT<250 microns OR
   c. Treatment is discontinued at the clinician’s discretion (See below)
2. Re-treatment with dexamethasone implant (OZURDEX) should take place at 4 to 6 month intervals. There is only limited case report data to support dosing intervals less than 6 monthly.
3. Based on the CRUISE study, consider following the monthly injection schedule for the first 6-12 months, and the PRN re-treatment criteria from the study should be used as the basis for a PRN dosing regimen.

Management of ischaemic central retinal vein occlusion and anterior segment neovascularisation
An initial evaluation of risk factors and the appropriate treatment of the present risks must proceed alongside management of the ocular findings. The evidence supports the use of laser pan-retinal photocoagulation (PRP) when iris new vessels (INV) or angle new vessels (ANV) are visible. Recent evidence indicates that intravitreal anti-VEGF agents in combination with PRP results in dramatic regression of the INV/ANV. ICRVO should be monitored monthly for new vessels iris and/ or angle. Repeat anti-VEGF and PRP are advocated in case of recurrence of new vessels. In some patients, it may not be logistically possible to review these patients monthly, 2-3 monthly reviews may be sufficient, unless there are particular risk factors. Particular individualized arrangements need to be made for these patients. In circumstances when regular follow-up is impractical, prophylactic treatment with PRP and anti-VEGF agent may be appropriate. However, none of the available or commonly used anti-VEGF agents (bevacizumab, ranibizumab, pegaptanib) currently have regulatory approval for such an indication.

There is no proven protective effect of intravitreal triamcinolone acetone on anterior segment neovascularisation and it may exacerbate any pre-existing neovascular glaucoma. This treatment option is not recommended.

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 for rubeosis by laser. There is anecdotal evidence that new vessels may be managed with a combination of anti-VEGF and PRP. Pan-retinal photocoagulation for CRVO with INV or ANV requires 1500 – 2000 of 500-micron burns at the retina. This is best applied with 0.05-0.1 second applications one burn width apart with sufficient energy to produce a pale burn in the retina. Treatment is usually placed in the periphery avoiding areas of retinal haemorrhage. Some cases require further treatment if the iris neovascularisation fails to regress. The pan-VEGF A blockers, ranibizumab and bevacizumab have been shown
to cause regression of new vessels of the iris, angle and retina when given intravitreally at the dose of 0.5mg/0.05ml and 1.25mg/0.05ml respectively. However, the effect is transient and recurrence of new vessels is common so repeated treatment, typically every six weeks with these agents supplemented with PRP may be required.

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, cyclo-ablative procedures or filtering surgery. Intravitreal and intracameral bevacizumab has 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 serve as a useful adjunct to filtering surgery.

Management of macular edema in CRVO
Macular oedema following central retinal vein occlusion results from leakage of perifoveal capillaries. It results in visual loss. Randomised controlled trials have failed to indicate benefit with grid laser photocoagulation, although a trend in favour of treatment has been observed in younger patients. Although there was significant reduction in the severity of macular oedema in treated eyes compared to controls there was no visual acuity benefit.

Triamcinolone acetonide: The rationale for the use of intravitreal triamcinolone acetonide (IVTA) to treat macular oedema is that corticosteroids reduce retinal capillary permeability and inhibit the expression of the VEGF gene and the metabolic pathway of VEGF. Evidence for the use of a specific preparation of triamcinolone in CRVO is from the SCORE-CRVO Study (SCORE Study Report 5). In this study, a

**Fig 9; FFA of patient with ischaemic CRVO**
A; with new vessels disc and elsewhere, B; lasered eye with persistent NVD and macular ischaemia

**Fig 10; Patient with CRVO and macular edema treated with ozurdex implant (implant is seen in the fundus photo)**
A; baseline OCT with severe CME and Submacular detachment, B; dry fovea at 4 months follow up
preservative-free form of triamcinolone (TRIVARIS, Allergan) given at different doses, 1mg and 4mg, at four monthly intervals and with pre-defined retreatment criteria, was compared to observation. Results showed that bothdoses of IVTA produced both anatomical and functional improvement of macular oedema due to CRVO, compared to observation. However, at month 12, the 1mg dose had a better safety profile compared to the 4mg dose in terms of a lower incidence of raised intraocular pressure (IOP) ≥35mmHg (5% vs. 8%), incidence of cataract formation or progression (26% vs. 33%, cf. 18% for observation) and need for cataract surgery (0% vs. 4%).

**Dexamethasone Biodegradable Implant:** The rationale for the use of intravitreal dexamethasone to treat macular oedema is similar to that of IVTA, although dexamethasone has been shown to be a more potent corticosteroid that IVTA but also is able to reduce retinal capillary permeability and inhibit the expression of the VEGF gene and the metabolic pathway of VEGF. However, dexamethasone when injected intravitreally in its free form, has a short half-life that limits its clinical utility as an injectable suspension. A pre-filled applicator single-use, sustained release biodegradable implant containing 0.7mg of dexamethasone (OZURDEX, Allergan) has been studied in the GENEVA study programme. In this study, OZURDEX and an alternative dose of dexamethasone implant (0.35mg) were compared to a sham injection, in patients with CRVO and BRVO in 2 parallel multicentre studies and published together as the GENEVA study. 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. 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 similar managed CRVO eyes. Anatomically, improvements in macular oedema as seen by OCT were also seen. In terms of safety, raised IOP peaked again at month 2 (3.2% of patients had an IOP>35 mmHg), but declined significantly by month 3 and was close to 0% by month 6, with 19% of patients requiring an IOP lowering agent at month 6 and 0.7% of patients requiring any IOP lowering surgical procedures. Similarly, rates of cataract progression were low with 7% progression at month 6, compared to 4% in the sham group. Based on the GENEVA study programme, OZURDEX has received approval for the treatment of macular oedema following either BRVO or CRVO. A post hoc analysis suggested that eyes treated within 90 days of CMO being present were more likely to improve than eyes commencing treatment after this time point.

**Ranibizumab:** The pan-VEGF blocker, ranibizumab (LUCENTIS, Novartis) when given in 2 doses (0.3mg and 0.5mg) every month for 6 months, in the CRUISE Trial, was shown to produce a 3-line gain of visual acuity and corresponding anatomical response. The mean gain in VA was 12.7 and 14.9 letters respectively with the 0.3 and 0.5 mg compared to the sham treated group at 6 months. Following the first 6 months, all patients were enrolled into an open-label extension for an additional 6 months and the overall 12 months results suggest that the visual gain established in the first 6 months can be retained with a slightly less intensive pro re nata (PRN) therapy with ranibizumab (an average of 5.6 injections in 1st 6 months, vs. 3.3 injections in 2nd PRN 6 month phase). Early treatment may be preferable as confirmed from the earlier smaller observational studies and a sham controlled study.

**Bevacizumab:** The pan-VEGF blocker, bevacizumab is unlicensed for intraocular use. Several case series (without controls) indicate that approximately 50% of subjects with non-ischaemic CRVO improve 2 or more lines with intravitreal bevacizumab, whilst 90% of eyes showed vision stabilization by 12 months. The reported follow-up periods are short and so the treatment regimen and the response to treatment in the long-run remain unclear.

**Pegaptanib:** A phase II trial, and prospective case series indicate that intravitreal 0.3mg pegaptanib sodium when given every 6 weekly for 6 months improved the visual acuity by approximately 7 letters at 6 months. The reported follow-up periods are short and so the treatment regimen and the response to treatment in the long-run remain unclear.

### Recommendations for Further Follow-up

Follow-up after the initial 6 months of treatment will depend upon initiation of anti-VEGF agent or steroid treatment for macular oedema but will normally be required for up to 2 years in uncomplicated cases. The eyes should be monitored for ischaemia (> 10DD non-perfusion) and for occurrence/recurrence of macular oedema. The development of disc collaterals +/- resolution of the macular oedema should lead to discharge from clinical supervision.

### Experimental treatments in CRVO

Chorio-retinal anastomosis (C-RA) was recently evaluated in a small (n=113) randomised clinical trial. Of patients in whom the C-RA was patent (76%), VA improved by a mean of 11.7 letters compared to controls. Side effects included neovascularisation at the site of the anastomosis in 18% and vitrectomy was required in 9%, due to macular traction or non-resolving vitreous haemorrhage. The procedure requires a special high power laser and significant operator experience. It is only recommended in the context of prospective data collection by an ophthalmologist specifically trained in its
Intravitreal Drug trials in CRVO

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<td>SCORE</td>
<td>Preservative free IVTA 1 mg</td>
<td>4 monthly injection</td>
<td>Atleast 3 month old CRVO Nonischaemic 20/40-20/400 vision CFT &gt; 250 mic No ERM/ VMT</td>
<td>Atleast 25% improved by 15 letters</td>
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<td></td>
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<td>5% glaucoma 26% cataract</td>
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<td>CRUISE</td>
<td>Lucentis 0.5 mg</td>
<td>Monthly injection for 6 months</td>
<td>Atleast 3 month old CRVO Nonischaemic 20/40-20/400 vision CFT &gt; 250 mic No ERM/ VMT</td>
<td>48% improved by 3 lines or more</td>
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<td>Average Vision gain of 14 letters</td>
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<td>GENEVA</td>
<td>Oxurdex 0.7 mg</td>
<td>Single injection</td>
<td>At least 6 wk old CRVO 20/50-20/200 vision CFT &gt; 300 mic Nn ERM/VMT</td>
<td>Atleast 25% improved by 15 letters</td>
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use. An Australian review of the technique concluded that there was only level IV evidence available.\(^6\) The procedure was therefore classified as experimental, with potential to cause serious side effects. Other studies have reported significant complications associated with the procedure e.g. choroidal neovascularisation\(^6\), retinal and subretinal fibrosis or traction\(^6\)\(^4\)\(^5\), and vitreous haemorrhage.\(^6\)

Trials of other treatments such as radial optic neurotomy (RON) with pars plana vitrectomy, and thrombolytic therapies are under way.\(^6\)\(^6\)\(^7\) RON is essentially a procedure in which a radial incision is made in the nasal segment of the scleral ring in order to decompress the presumed pressure within this compartment so as to relieve pressure on the CRV. These, however, are only experimental at present and are, therefore, not recommended except as part of clinical trials.

**BRVO STUDY\(^5\),\(^6\)**
- Focal laser for perfused macular edema with vision 6/12 or worse; useful.
- Sector photocoagulation for BRVO if new vessels or vitreous hemorrhage seen.
- No role for prophylactic sector photocoagulation

**Branch Retinal Vein Occlusion**
The diagnosis of branch retinal vein occlusion is clinical, as described before. In doubtful cases, especially small BRVO, fluorescein angiography may be indicated to confirm the diagnosis. Fluorescein angiography is particularly useful in determining the extent of macular oedema and ischaemia. In the BVOS, approximately 50% of untreated eyes with BRVO retain vision of 6/12 or better whilst 25% will have vision of <6/60. Macular oedema and neovascularisation of the retina or disc are the two major complications which may require therapy. Retinal neovascularisation occurs in 36% of eyes with >5 DD, and 62% with >4DD area of non-perfusion, as reported in 2 independent studies.\(^6\)\(^6\)

**NonIschaemic BRVO**

Management of macular oedema secondary to BRVO with no or minimal evidence of macular ischaemia

1. If patients with macular oedema secondary to BRVO are seen within 3 months of onset of BRVO, consider pharmacotherapy with Ozurdex which is licensed or Ranibizumab which is unlicensed but has robust clinical evidence of efficacy.
2. If patients are seen after 3 months from onset of BRVO, consider laser photocoagulation or pharmacotherapy with Ozurdex which is licensed or Ranibizumab which is unlicensed but has robust clinical evidence of efficacy.

Management in eyes with evidence of marked macular ischaemia

No immediate treatment is recommended. Watch for conversion of the RVO to ischaemic type and subsequent neovascularisation

**Re-treatment criteria**
1. Based on the results of the clinical trials, treatment may be repeated unless.
   a. VA>6/7.5 (84 letters on LogMAR) OR
   b. Central Retina Thickness (CRT) on OCT<250 microns
   c. Treatment should be discontinued (See below)
2. Re-treatment with dexamethasone implant (OZURDEX) should take place with 4-6 months after first treatment.
3. Re-treatment with ranibizumab injections should occur monthly for the first 6 months followed by a PRN schedule based on re-treatment criteria from the BRAVO study.
4. Re-treatment with modified Grid Laser Photocoagulation should be considered at 4 monthly intervals

Ischaemic BRVO
1. Watch carefully for NV
2. Perform 3 Monthly follow, especially if the area of retinal ischaemia is > 4DD, and treatment is not required for macular oedema.
3. If NVE occurs, there is limited anecdotal evidence for the use of intravitreal bevacizumab in such cases and its use would be considered unlicensed, e.g.
   a. PRP+-/intravitreal bevacizumab 4-6 weekly until quiescent.
   b. bevacizumab
4. Follow-up 3 monthly to up to 12 months. Subsequent follow-up will be guided by the clinical findings and on-going treatment.

Fig 11; FFA of a patient with ischaemic BRVO
A; macular ischaemia, B; new vessels elsewhere

Treatment of neovascularisation in BRVO
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.6,69 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 3- 4 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 neovascularisation is applied to the sector of retinal capillary closure.6 500-micron burns at the retina are used and are applied in a scatter pattern to the affected sector, one burn width apart are appropriate with sufficient energy to create a gentle burn. A quadrant usually requires 400-500 burns.

Laser treatment of macular oedema in BRVO
Randomised clinical studies in the laser treatment of macular oedema have demonstrated that a grid pattern of photocoagulation in the distribution of leaking capillaries is beneficial but it is recommended only after a period of three to six months following the initial event and following absorption of the majority of haemorrhage6,70.

Fluorescein angiography should 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 photocoagulation70. It will also help to avoid laser to collaterals.

The optimal technique to administer laser photocoagulation for macular oedema requires gentle burns of 50 to 100um. The power depends on the individual patient. 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 (i.e. the burns must not approach the foveal centre by less than 1/2 DD). Collaterals should be avoided. 5,70 Initial follow-up in all patients treated with laser photocoagulation should be at three months following the occlusion. Subsequent follow-up at three to six monthly intervals will depend on complications and laser treatment, and will not normally be required after two years in uncomplicated cases.

Other treatment options for macular edema
Triamcinolone acetonide: Evidence for the use of a specific preparation of triamcinolone in BRVO is from the SCORE-BRVO Study (SCORE Study Report 6).71,72 In this study, a preservative-free form of triamcinolone (TRIVARIS, Allergan) given at different doses, 1mg and 4mg, at four monthly intervals and with pre-defined re-treatment criteria, was compared to laser photocoagulation. Results showed that both doses of IVTA produced both anatomical and functional improvement of macular oedema due to BRVO, but this was similar in magnitude to laser. In addition, at month 12, both the 1mg and 4mg doses had an inferior safety profile compared to laser in terms of a higher incidence of raised intraocular pressure >35mmHg (IOP) (2% and 14%, vs. 1%), incidence of cataract formation or progression (25% and 35%, vs. 13%) and need for cataract surgery (0% and4%, vs. 3%). As such, laser is considered to have a more favourable benefit: risk profile to IVTA in BRVO. Similar to the case in CRVO, there is no Grade A evidence to suggest that the visual and anatomical responses seen with TRIVARIS in SCORE-BRVO would be replicated with off-label IVTA preparations such as KENALOG73,74,75

Dexamethasone Biodegradable Implant
Based on the GENEVA study programme which has been discussed earlier, OZURDEX has received also approval for the 0.7 mg preparation for the treatment of patients with macular oedema following BRVO.
**Ranibizumab:** The pan-VEGF blocker, ranibizumab (LUCENTIS, Novartis) given in 2 doses (0.3mg and 0.5mg) every month for 6 months, was compared with sham, in the BRAVO study. At 6 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 vs 29% in the sham treated group. However from months 3-5, a single application of rescue laser photocoagulation was also allowed in all study arms if hemorrhages had cleared sufficiently to allow safe application of laser, based on predetermined criteria. Approximately 20% of patients in both ranibizumab arms received adjunctive laser, versus 55% in the sham injection arm. Following the first 6 months, all patients were enrolled into an open-label extension for an additional 6 months and the overall 12 months results suggest that the visual gain established in the first 6 months can be retained with a slightly less intensive pro re nata (PRN) therapy with ranibizumab (an average of 5.7 injections in 1st 6 months, vs. 2.7 injections in 2nd PRN 6 month phase). However, as seen with the results of GENEVA & CRUISE studies, the visual acuity outcome never caught up in this delayed treated group compared to eyes treated earlier.

**Bevacizumab:** Currently, increasing short-term data support the fact that multiple intravitreal bevacizumab injections reduce macular oedema secondary to branch retinal vein occlusion including those that had failed previous laser treatment. The most common treatment regimen is two to three injections over the first 5-6 months. However, further randomized, controlled trials are required to assess longterm safety and efficacy of intravitreal bevacizumab.

**Periocular triamcinolone:** Periocular (orbital floor or retrobulbar) triamcinolone has been administered as treatment of macular oedema in BRVO. Although both routes of administration demonstrated efficacy, the results are short-lived.

### Intravitreal Drug trials in BRVO

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Regimen</th>
<th>Indication</th>
<th>Outcome</th>
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</thead>
<tbody>
<tr>
<td>BRAVO 6 mths</td>
<td>Lucentis 0.5 mg</td>
<td>Monthly injection for 6 months</td>
<td>Atleast 3 month old BRVO with no RAPD 20/40-20/400 vision CFT &gt; 250 mic No ERM/ VMT</td>
<td>61% improved by 3 lines or more Vision gain of 18 letters</td>
</tr>
<tr>
<td>GENEVA 6 mths</td>
<td>Oxurdex 0.7 mg</td>
<td>Single injection</td>
<td>At least 6 wk old BRVO 20/50-20/200 vision CFT &gt; 300 mic Nn ERM/VMT</td>
<td>Atleast 27% improved by 15 letters Effect best upto 90 days</td>
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### Other Treatments

The evidence on the efficacy of surgical interventions in BRVO are limited to case reports and case series. Metaanalysis studies has reviewed the evidence of arteriovenous sheathotomy for this condition and recommended that this procedure be done only as part of a research study.

### Management of younger patients (less than 50 years of age)

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. However, at least 20% of patients develop poor visual outcome with severe neovascular complications. Some authorities advocate the use of steroid therapy but this has not been tested in controlled trials. Patients in this age group with BRVO usually have underlying systemic conditions such as hypertension or hyperlipidaemia which should be managed appropriately. Those with CRVO present a particular problem in investigation and management. Many of these patients will have no identifiable underlying cause despite extensive investigation including the specialised investigations listed before. In females the contraceptive pill is the most common underlying association, and caution is advised in patients with retinal vein occlusion. There is debate as to the exact prevalence of thrombophilic disorders in this patient group as well as appropriate therapy. Identified inflammatory disease should be treated as appropriate to the condition and referred for specialist medical advice.

### 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. The risk of disc neovascularisation appears greater for hemispheric vein occlusion than either ischaemic CRVO or BRVO. The management of hemispheric vein occlusion is similar to that described for branch retinal vein occlusion, the guidelines for treatment options being those described above for retinal branch vein occlusion.
Fig 12; patient with BRVO with macular edema treated with intravitreal avastin
A; baseline OCT with severe CME and Submacular detachment, B; dry fovea at 6 months follow up after 3 injections

Fig; 13 Hemi CRVO A; fundus photo with ischaemic looking macula and cystoid macular edema
B,C; FFA showing macular ischaemia and extensive capillary nonperfusion in the inferior hemisphere of the retina

REFERENCES


32. Lipid modification for prevention of cardiovascular disease - NICE Clinical Guideline 67.2010


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