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EDITORIAL

Retinal vein occlusion (RVO) guideline: executive summary

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INTRODUCTION

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 [1, 2]. It is classically characterised by disc oedema, increased dilatation and tortuosity of all retinal veins, widespread deep and superficial retinal haemorrhages, cotton wool spots, retinal oedema and capillary non-perfusion in all four quadrants of the retina. 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 (MO) 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 [3, 4]. 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 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 MO and retinal ischaemia leading to iris and/or retinal neovascularisation.

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.

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.

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 defined ischaemic CRVO as fluorescein angiographic evidence of more than ten disc areas (DA) of capillary non-perfusion on seven-field fundus fluorescein angiography [5, 6]. 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 [7]. 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 [7, 8]. 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 visual acuity, relative afferent pupillary defect and electro-diagnostic test findings.

KEY RECOMMENDATIONS AND GOOD PRACTICE POINTS FOR IMPLEMENTATION

Central retinal vein occlusion

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 3 years. Prompt anti-VEGF therapy does not completely prevent worsening of retinal nonperfusion in eyes with CRVO [9]. 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

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 3 months of follow-up. However, presentation may be delayed in some patients and in others with significant visual impairment at presentation, only 18–41% 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 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.

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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 without hypoglycaemia is 48 mmol/mol (6.5%) (NICE NG28, 2015, updated 2021).

The testing for anti-phospholipid antibodies 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 [10]. 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) [11–14].
- Cardiovascular disease under age 70 was noted in one study [13] but not in another report [5].
- Peripheral venous disease is observed in (13/439) 3% pre diagnosis of CRVO [15].

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 RVO than would be recommended anyway.

RVO in younger patients (<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 [16]. The need for intravitreal anti-VEGF for MO is less in young patients with CRVO [17, 18]. However, at least 20% of patients develop poor visual outcome with severe neovascular complications [19].

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 oestrogen containing therapies in a woman with RVO should be made on a case-by-case basis.

Retinal imaging in RVO

- OCT is recommended in the diagnosis, monitoring and assessing treatment response of MO secondary to RVO
- FA/OCTA is recommended to assess retinal nonperfusion to aid the identification of eyes with ischaemic CRVO

Ophthalmological management of CRVO

- Intravitreal injections of licensed anti-VEGF or dexamethasone implant are the recommended treatment of MO secondary to CRVO, based on clinician and patient choice, taking into account treatment frequency, risk of IOP rise and cataract formation.
- Just over a third of patients will require only three anti-VEGF injections to reach maximum VA while another third will require six consecutive anti-VEGF injections. It is recommended to initiate treatment as the posology suggests which is monthly anti-VEGF treatment until maximum stable VA is achieved.
- In a PRN regimen, it is recommended that these patients are monitored at 4–8 weekly intervals and treated appropriately for optimal visual outcomes.
- A delay in initiating treatment up to 6 months resulted in lower 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 <6/96, careful consideration should be given to further therapy in such eyes that do not improve in terms of 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.
- For patients treated with intravitreal dexamethasone, monitoring and possible management of intraocular pressure and the risk of the development of cataract need to be considered
- There is also no evidence to suggest any benefit from a combination of macular grid laser or pan-retinal photocoagulation 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 intravitreal 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.
- In eyes receiving dexamethasone implant, identification of iris neovascularisation at the earliest opportunity is vital in its management.

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 [6] 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 [20].
- Commence anti-VEGF therapy at the earliest sign of iris or angle new vessels followed by sufficient pan-retinal 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 NVI and 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 6 months should be every 3 months for 1 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 3 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

- Licensed anti-VEGF or Dexamethasone implant, based on clinician choice considering treatment frequency, risk of IOP rise and cataract formation and subject to discussions with the patient are the recommended treatment of MO due to BRVO.
- If laser photocoagulation is contemplated, it should be performed in those eyes with MO secondary to BRVO of at least 3 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 3–4 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 500 µm 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
  Visual acuity assessments in ETDRS letters.
  Colour Fundus photographs and Fundus Fluorescein angiography (FFA)/OCT-A by trained technical staff
  Optical coherence tomography (OCT) with the SD-OCT by trained technical staff
  Treatment initiated within 1–2 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 perform 'screening' or first examination of patients suspected of having RVO.
  Fast track clinics acquiring imaging in the community or hospital can be set-up to triage those who are symptomatic with reduced vision and centre involving MO [21].

- Low Vision and Living with RVO:
  Patients with reduced BCVA secondary to RVO should be offered the access to low vision support and advice at an early stage.
  Do not 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.

The full Retinal Vein Occlusion Guideline is available at The Royal College of Ophthalmologists website: https://www.rcophth.ac.uk/resources-listing/retinal-vein-occlusion-rvo-guidelines/

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AUTHOR CONTRIBUTIONS

The Guideline Development Ground was chaired by SS. SS supervised the development of the guidelines and contributed to the final version of the guidelines. LN was responsible for reviewing the evidence and writing the guidelines. SJT authored the section on branch retinal vein occlusion and contributed to the final version of the guidelines. WA authored the section on service provision and contributed to the final version of the guidelines. KT provided expert input on haematology and authored the section on medical investigations in retinal vein occlusion.

COMPETING INTERESTS

Dr. LN has received speaker fees from Allergan and Bayer. Mr SJT 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. Mr WA has received research funding from Allergan, Bayer, Bausch and Lomb, Boehringer Ingelheim, CentreVue, Novartis, Optos plc, Topcon, and Pfizer, and served on ad hoc Advisory Boards for Alcon, Allergan, Novartis, Bayer, Alimera, Roche and Thrombogenics, and has received educational travel grants from Alimera, Allergan, 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; (v) Novartis REPAIR: Phase 2. Protocol CRFB002AGB10. PI; (vi) PI- Novartis. KESTREL Phase 3, Protocol CRTH258B2301, RTH in DMO; (vii) PI- Gyroscope CFI/SiGHt study: The Complement Factor I in AMD Study. Protocol GT005-01. He was also a member of the Macular Society Scientific Committee until 2015. Dr KT has received educational travel grants from CSL-Behring, Pfizer & Sobi. Prof SS 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: Novartis, Bayer, Allergan, Boehringer Ingleheim, Optos, Opthea.

ADDITIONAL INFORMATION

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