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1 Introduction

1.1 Background

Retinal vein occlusion (RVO) is a common cause of visual loss in the United Kingdom. It is an obstruction of the retinal venous system by thrombus formation and may involve the central, hemi-central or branch retinal vein. 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 typically occurs in middle aged and elderly patients (i.e over age of 50 years) with equal sex distribution in both branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO). CRVO 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 less severe forms the disc oedema may be absent. BRVO has similar features except that they are confined to a portion of the fundus. In view of the significant ophthalmological and medical consequences of retinal vein occlusion, these guidelines promote a good standard of practise and the achievement of best visual and medical outcome.

1.2 Remit of the guidelines

These guidelines provide recommendations for the diagnosis and ophthalmological management of central, branch, and hemispheric retinal vein occlusion. They also consider the risk factors for the disease and include recommendations for investigations and indications for medical management. They are intended for the use of ophthalmologists but may be useful for physicians and general practitioners.
2. Methods

2.1 The guideline development group

Members of the guideline development group represented ophthalmology, medicine and epidemiology.

2.2 Gathering the evidence

Literature searches were undertaken with the assistance of the Cochrane Eyes And Vision Group.

Databases searched were

- Cochrane Library
- Medline
- Embase

Keywords, literature search strategies and full reference list are available on request from the Scientific Department, Royal College of Ophthalmologists. Key references only are included in the guidelines.

2.3 Assessing the evidence and forming recommendations

Relevant literature was identified and the level of evidence graded. Evidence was then assessed for consistency, applicability, and clinical impact.

Recommendations for a good standard of practice were formed using the following categories (i.e. strength of the evidence) and included in the text of the guidelines:

- At least one meta-analysis, systematic review, or good quality randomised control trial (RCT) directly applicable to the target population; or a body of evidence consisting principally of RCTs, directly applicable to the target population, and demonstrating overall consistency of results.

- A body of evidence including high quality systematic reviews of case-control or cohort studies, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from RCTs.
A body of evidence including studies rated as well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as high quality systematic reviews of case-control or cohort studies.

Evidence from non-analytic studies, e.g. case reports, case series or expert opinion

2.4 Consultation process

The guideline development group invited comments on this guideline from all UK consultant ophthalmologists and Royal College of Ophthalmologists Patient Advisory Committee prior to publication.
3. **Aetiology and risk factors**

Retinal vein occlusion is due to thrombosis of retinal veins (central, hemi or branch). Established cardiovascular risk factors are the predominant medical associations for both central and branch vein occlusions and are summarised below and include differentiation by age and ethnic groups. (See table 1)

**Strength of evidence**

- **Hypertension**
  This is the predominant risk factor with up to 64% of patients having hypertension (Table 1) in the older age group (more than 50 years). This is more prevalent in BRVO than CRVO. A new diagnosis or uncontrolled hypertension is a common finding. Inadequately controlled hypertension is associated with recurrence of RVO in the same eye or fellow eye involvement.

- **Hyperlipidaemia**
  Hyperlipidaemia (cholesterol ≥ 6.5 mmol/l) is the predominant association in the younger age group (<50 years) of patients with retinal vein occlusion and is associated in up to 50% of older patients.

- **Diabetes mellitus**
  Diabetes mellitus (Table 1) is associated with retinal vein occlusion. This may be due to an increase of other cardiovascular risk factors (e.g. 70% of type II diabetics are hypertensive).

- **Glaucoma**
  Current evidence suggests an association between central retinal vein occlusion and glaucoma. One study suggests that BRVO is associated with glaucoma.

- **Thrombophilia**
  Factor V Leiden and other such abnormalities have been implicated in RVO but their aetiology is unclear. Deficiency or abnormal activity of various factors have been identified in patients with RVO including protein S, C, anti-thrombin 3, activated protein C resistance, hyperhomocysteinaemia and the presence of lupus anticoagulant or anti-cardiolipin antibody deficiency. Thrombophilia and the other rarer associations e.g. oral contraceptive pill, and optic disc vasculitis assume more importance in the younger patients (<50 years).

**Other Important Observations**

Myeloproliferative disorders occur in 1% of patients presenting with retinal vein occlusion.
Other rare associations with retinal vein occlusion include Inflammatory disease that cause or are associated with retinal vasculitis – Behçets disease, polyarteritis nodosa, sarcoidoisis, Wegener’s Granulomatosis, Goodpasture’s Syndrome.

Chronic renal failure and other secondary causes of hypertension and diabetes e.g. acromegaly, Cushing’s syndrome.

Secondary causes of hypercholesterolaemia eg hypothyroidism.

4. 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.

Although the systemic investigation and treatment in all types of vein occlusion is similar, the ophthalmological management of branch and central retinal vein occlusion differs. These will therefore be considered separately.
OPHTHALMOLOGICAL MANAGEMENT

4.1 Central retinal vein occlusion

There is no proven early treatment that will alter the visual prognosis in established central retinal vein occlusion. 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 for which laser photocoagulation may be 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). 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 [CVOS])

2. Relative afferent pupillary defect

3. Presence of multiple dark deep intra-retinal haemorrhages

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

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.
4.1.1 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 when iris new vessels (INV) or angle new vessels (ANV) are visible. Monthly follow up is advised for six months in all untreated patients with features of retinal ischaemia and must include undilated pupil examination and detailed examination of the iris with gonioscopy. (However, this monthly follow up may be impracticable in some UK eye clinics). PRP should be applied at the earliest sign of INV and or ANV.

In circumstances when regular follow-up is impractical, prophylactic treatment may be appropriate.

4.1.2 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. It has been reported that this complication does not usually require active therapy.

4.1.3 Pan-retinal Photocoagulation Technique

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 seconds 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.

There is an alternate view to the management of iris neovascularisation. There is a suggestion that rubeosis does not inevitably lead to glaucoma and therefore laser photocoagulation should be withheld because this treatment leads to further contraction of the visual field. However, it is our opinion that the weight of evidence supports the recommendations stated above.

4.1.4 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 or cyclo-ablative procedures. Drainage procedures are of limited value.
4.1.5 Macular oedema

Macular oedema following central retinal vein occlusion results from leakage of perifoveal capillaries. It results in visual loss but there is no proven treatment for this condition. Randomised controlled trials have failed to indicate benefit from grid treatment, 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.

4.2 Recommendations for Further Follow-up

Follow-up after 6 months for ischaemia (> 10DD non-perfusion) should be every 3 months for 1 year. Non ischaemic eyes should have initial follow up every 3 months for 6 months. Subsequent follow-up for all patients will depend upon laser treatment and complications but will not normally be required after 2 years in uncomplicated cases. The development of disc collaterals +/- resolution of the CRVO should lead to discharge from clinical supervision.

Experimental treatments

Chorio-retinal anastomosis is an experimental treatment and the results of randomised trials of this therapy are awaited. However, there are significant complications associated with laser-assisted chorioretinal venous anastomosis eg choroidal neovascularisation, retinal and subretinal fibrosis or traction, and vitreous haemorrhage.

Trials of other treatments such as radial optic neurotomy with pars plana vitrectomy, and thrombolytic therapies are under way. These, however, are only experimental at present and are, therefore, not recommended except as part of clinical trials.
5. 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. 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.

5.1 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. 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.

5.1.1 Technique

Photocoagulation for neovascularisation is applied to the sector of retinal capillary closure. 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.

5.2 Treatment of macular oedema

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 haemorrhage. 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 photocoagulation. It will also help to avoid laser to collaterals.
It is the consensus view of the group that 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 photocoagulation.

5.2.1 Technique

Laser photocoagulation for macular oedema requires gentle burns of 100-200 microns. 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.

5.2.2 Follow-up

Initial follow-up in all patients 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.

5.3 New treatments

Vitrectomy and sheathotomy as treatment for BRVO are currently under evaluation. No recommendations on these new treatments are possible at present.

5.4 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 laser treatment being those described above for retinal branch vein occlusion.
MEDICAL MANAGEMENT

6. Referral for medical investigation and treatment

IT IS THE RESPONSIBILITY OF THE OPHTHALMOLOGICAL TEAM TO ENSURE MEDICAL INVESTIGATION AND TREATMENT IS INITIATED ON DIAGNOSIS OF RETINAL VEIN OCCLUSION.

Recommended investigations for patients with retinal vein occlusion are listed in Table 2. It is the responsibility of the diagnosing physician or ophthalmologist to:

- Investigate and interpret results.
- Refer the patient for appropriate medical advice with urgency according to the severity of underlying risk factor(s).
- Ensure that specialists in the relevant field should manage the rarer causes of retinal vein occlusion.
- Ensure that initiation of medical management occurs within 2 months of diagnosis.

The importance of detecting and treating underlying medical conditions lies in the need to prevent further non-ocular target organ damage, as well as to prevent recurrence of venous occlusion particularly in the fellow eye.\textsuperscript{40} Two long-term follow-up studies of patients with retinal vascular disease (retinal vein occlusion and retinal arterial occlusion) demonstrate excess cardiovascular morbidity, mortality from stroke, and myocardial infarction over a ten-year period\textsuperscript{41,42}

Therefore, medical management should be targeted at three areas:

6.1 Reverse retinal vein occlusion

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)\textsuperscript{43} 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. Anti-platelet agents may be of benefit. In exceptional circumstances other measures may be considered, but there is only anecdotal evidence of their benefit, and they may be potentially harmful.
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.

Haemodilution

The effects of haemodilution have been inconsistent in completed control trials in RVO although results from further trials are awaited.

7. **Ameliorate cardiovascular morbidity and mortality associated with retinal vein occlusion**

Retinal vein occlusions are associated with an increase in vascular causes of death (both cerebral and cardiac) in large prospective follow up studies. It is now proven that drug treatment of hypertension reduces the severity of its complications, and additional therapy of aspirin in well controlled hypertensive subjects given as a primary prevention reduces cardiovascular event rate. Recent trials of cholesterol lowering using statins have confirmed the beneficial effect of this therapy with reduction of cardiovascular morbidity and mortality. Patients with rarer underlying conditions such as myeloma and inflammatory disorders should be referred and managed by appropriate specialists.

Cardiovascular risk factors identified in patients with retinal vein occlusion should be managed according to the joint guidelines of the British Hypertension Society, British Hyperlipidaemia Association and British Diabetic Association. This approach should ameliorate adverse cardiovascular outcomes for patients with retinal vein occlusion. Target levels for medical management recommended by the joint societies and the recent British Hypertension Society guidelines are shown in Table 3 and, unless a specific contra-indication, aspirin, 75-150 mg daily is appropriate.
7.1 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 with the addition of aspirin/persantin.

7.2 The use of hormone replacement therapy following retinal vein occlusion

Although estrogen-containing HRT should not be commenced in those women with retinal vein occlusion, continued use does not appear to be associated with a higher rate of recurrence. Historically, HRT was contraindicated and discontinued following central vein thrombosis. Following the work of the Eye Disease Case-Control Study Group and Kirwan and associates, medical practice showed a trend to continue HRT following retinal vein occlusion due to the epidemiological evidence supporting HRT in the prevention of cardiovascular disease. This policy has not lead to the potentially disastrous visual outcome of recurrence of retinal vein occlusion in the fellow eye. Currently, the decision about whether to continue HRT in a woman with retinal vein occlusion should be made on a case by case basis. The decision should be based on the woman’s individual case history, including the indication for HRT use. The degree of residual visual impairment may influence the decision as a recurrence in the fellow eye may have a potentially devastating visual outcome. Further guidance may be obtained from the results of thrombophilia screening, as this may provide an indicator of future risk. The current uncertainty about the effects of HRT on cardiovascular risk and recent guidelines for the use of HRT should also be considered.

8. Management of younger patients (less than 50 years of age)

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 in Table 2. In females the contraceptive pill is the most common underlying association, and is contraindicated 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.
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.47

Some authorities advocate the use of steroid therapy but this has not been tested in controlled trials.


9. Tables

9.1 Table 1: Predominant associations for vein occlusions

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Hypertension</th>
<th>Hyperlipidaemia</th>
<th>Diabetes Mellitus</th>
<th>No obvious cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young patients less than 50 years old</td>
<td>25%</td>
<td>35%</td>
<td>3%</td>
<td>40%</td>
</tr>
<tr>
<td>Older patients over 50 years</td>
<td>64%</td>
<td>34%</td>
<td>4-15%</td>
<td>21%</td>
</tr>
<tr>
<td>Asian</td>
<td>64%</td>
<td>50%</td>
<td>29%</td>
<td>10.7%</td>
</tr>
<tr>
<td>West Indian</td>
<td>83%</td>
<td>33%</td>
<td>38%</td>
<td>8.3%</td>
</tr>
<tr>
<td>Recurrent cases</td>
<td>88%</td>
<td>47%</td>
<td>3%</td>
<td>6%</td>
</tr>
<tr>
<td>Odd ratio</td>
<td>1.8 - 2.5</td>
<td>--------</td>
<td>1.6 - 2.1</td>
<td>--------</td>
</tr>
</tbody>
</table>
### Table 2: Initial Medical Investigations for Patients Presenting with Retinal Vein Occlusion

<table>
<thead>
<tr>
<th>ALL PATIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full blood count and ESR or plasma viscosity</td>
</tr>
<tr>
<td>Urea, electrolytes, creatinine</td>
</tr>
<tr>
<td>Random blood glucose</td>
</tr>
<tr>
<td>Random cholesterol and HDL cholesterol +</td>
</tr>
<tr>
<td>Plasma protein electrophoresis</td>
</tr>
<tr>
<td>ECG +</td>
</tr>
<tr>
<td>Thyroid function</td>
</tr>
<tr>
<td>+ It is essential to record these investigations for the Framingham equation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MORE SPECIALISED TESTS ACCORDING TO CLINICAL INDICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombophilia screen</td>
</tr>
<tr>
<td>Anti-cardiolipin antibody, lupus anticoagulant</td>
</tr>
<tr>
<td>C-reactive protein</td>
</tr>
<tr>
<td>Serum ACE</td>
</tr>
<tr>
<td>Auto-antibodies - rheumatoid factor / anti-nuclear / anti DNA / ANCA</td>
</tr>
<tr>
<td>Chest X-ray</td>
</tr>
<tr>
<td>Fasting homocystine level</td>
</tr>
</tbody>
</table>
### 9.3 Table 3: Guide to diagnosis and targets for cardiovascular risk factors.

| Blood pressure (mmHg) | Diagnosis of hypertension ≥ 140/ and, or ≥ 90 sustained  
|                       | Optimal blood pressure is < 140/85  
|                       | Audit standard is < 150/90  
| Cholesterol (mmol/l)  | Primary prevention - (CHD risk ≥ 15% or total CVD risk ≥ 20%  
|                       | 10 year risk)* +, statin usually required  
|                       | Secondary prevention target is <4.8 mmol/l, use of statin required  
| Diabetes mellitus     | Diagnosis = fasting glucose > 7.0 mmol/l (multiple sampling)  
|                       | Glycosylated haemoglobin target is < 7%  
|                       | Optimal blood pressure is <130/80  
|                       | Audit standard is <140/<80  
| Aspirin               | Indicated if CHD risk ≥ 15% 10 year* and (or CVD risk ≥ 20%) +, in hypertensive patients, providing satisfactory blood pressure control and no contra-indication (peptic ulcer, allergy, history of haemorrhage e.g. recent haemorrhagic stroke, or in the initial stages of a severe haemorrhagic retinal vein occlusion)  

* Coronary Heart Disease (CHD) and Total Cardiovascular Disease (CVD) risk calculated using the Framingham Equation, either using chart, discs or computerised programs (See Joint British Guidelines and British Hypertension Society guidelines).  

Variables required for the calculation include random cholesterol, HDL cholesterol, systolic blood pressure levels, and age, sex, the presence of diabetes mellitus, smoking, and the presence of left ventricular hypertrophy on ECG.  

+ British Hypertension Society guidelines 2004
10. Cited References


11. **Working group membership**

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