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Managing retinal vein occlusion

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Retinal vein occlusion—obstruction of the retinal venous system by thrombus formation, external compression, or disease of the vein wall¹—is the second most common retinal vascular disease after diabetic retinopathy.² Pooled data from population studies in the United States, Europe, Asia, and Australia suggest that about 16 million adults are affected by this condition.³ Not all cases need treatment. In the past, the visual prognosis for most patients was poor because treatment comprised lowering the pressure in the eye, if raised, and laser treatment to try to control associated complications. However, two new treatments have recently been licensed in the US and the European Union, one of which has been approved by the National Institute for Health and Clinical Excellence (NICE) for use in England and Wales. Consequently, the outlook for patients with retinal vein occlusion is likely to improve. We review the diagnosis and management of retinal vein occlusion and examine the evidence for the effectiveness of the newly licensed drugs.

How and where does retinal vein occlusion occur?

Compression of the retinal vein by a thickened adjacent retinal artery (typically thickened by atherosclerosis or arteriosclerosis) is thought to be the most common cause of retinal vein occlusion. Retinal vein occlusion may occur in the central retinal vein, where the central retinal vein exits the eye or proximal to the lamina cribrosa of the optic nerve, or in a branch retinal vein at an arteriovenous crossing (fig 1).² Branch retinal vein occlusion may represent the end stage of arteriovenous nipping, in which the vein is compressed by the crossing artery without being completely occluded. If the superior or inferior branch of the central retinal vein becomes obstructed, a hemicentral retinal vein occlusion occurs and the corresponding half of the retina is affected.

Who gets retinal vein occlusion?

Retinal vein occlusion typically occurs in people aged over 50 years, with an equal sex distribution.¹ Table 1 summarises the main risk factors, which include several well established cardiovascular risk factors. People over the age of 50 with high blood pressure, and those under 50 with hypercholesterolaemia, are particularly at risk.

Population based studies report a prevalence rate of 0.5–2.0% for branch retinal vein occlusion and 0.1–0.2% for

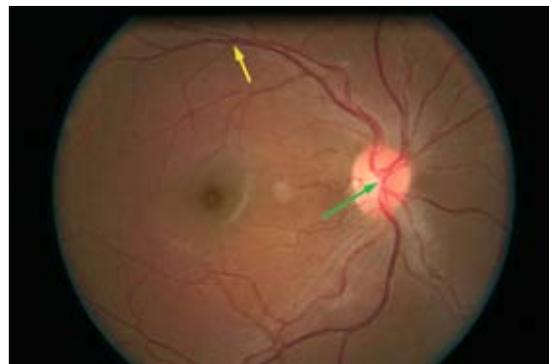


Fig 1 | Common sites of retinal vein occlusion in a normal right eye. The green arrow indicates the point at which the central retinal vein exits the eye—the typical site of a central retinal vein occlusion. The yellow arrow points to an arteriovenous crossing where a branch retinal vein occlusion could occur

central retinal vein occlusion.^{w13} The 15 year incidence rate is estimated to be 1.8% for branch retinal vein occlusion and 0.5% for central retinal vein occlusion.^{w14}

How do patients present?

Patients with retinal vein occlusion typically present with sudden painless loss or distortion of vision, although occlusion of a branch retinal vein may be asymptomatic. If the sight threatening complication of neovascular glaucoma develops, the patient may present with pain in the eye as well as loss of vision.

How is the condition assessed and diagnosed?

Clinical examination

The basic clinical assessment of a patient with suspected retinal vein occlusion includes a test of visual acuity using a Snellen or LogMAR chart, confrontational visual fields, pupillary reactions to light, and funduscopy. Visual acuity may be unilaterally reduced, depending on the extent of retinal involvement and whether the macula is affected. Testing of confrontational visual fields may show a peripheral visual field defect that corresponds with an area of retinal non-perfusion in a branch retinal vein occlusion. The affected side may have a relative afferent pupillary defect. This is identified by constriction of both pupils

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► Diagnosis and management of thalassaemia (*BMJ* 2012;344:e228)

► Diagnosis and management of ANCA associated vasculitis (*BMJ* 2012;344:e26)

SUMMARY POINTS

Retinal vein occlusion is the second most common retinal vascular disease after diabetic retinopathy

Occlusion can occur in the central retinal vein or, more commonly, in a branch retinal vein

The main risk factors for retinal vein occlusion are age over 50 and hypertension

Signs of retinal ischaemia include poor visual acuity, relative afferent pupillary defect, multiple intraretinal haemorrhages, multiple cotton wool spots, and dilated and tortuous retinal veins

Management of underlying medical conditions and cardiovascular risk factors is important
Ophthalmic treatments now include intraocular dexamethasone implants and, potentially, vascular endothelial growth factor inhibitors

SOURCES AND SELECTION CRITERIA

We searched PubMed for articles on retinal vein occlusion that had been published in 2010 and 2011 and looked for published evidence that had been presented in major ophthalmology meetings up to 1 October 2011, focusing mainly on well designed randomised controlled clinical trials. We also used the latest guidance from the UK Royal College of Ophthalmologists on the management of retinal vein occlusion and National Institute for Health and Clinical Excellence guidance on dexamethasone intravitreal implants for the treatment of macular oedema secondary to retinal vein occlusion.

Table 1 | Risk factors for developing retinal vein occlusion

Risk factor	Comments
Rare	
Common	
Hypertension	The main risk factor in those aged >50 years ^{w1} ; it is more common in branch retinal vein occlusion than in central retinal vein occlusion ¹
Hyperlipidaemia	Cholesterol >6.5 mmol/L is the main risk factor in patients aged <50 years; it is associated with retinal vein occlusion in about 50% of older patients ^{w2}
Diabetes	The association may result from cardiovascular risk factors, such as hypertension, being more common in type 2 diabetes ^{w1 w3 w4}
Renal disease	A population based cross sectional study of 6147 patients in the United States showed that renal dysfunction was an independent risk factor for retinal vein occlusion ^{w5}
Glaucoma	A large and well designed study found an association between central retinal vein occlusion and glaucoma ^{w6} ; evidence also suggests that glaucoma is a risk factor for branch retinal vein occlusion ^{w3}
Thrombophilia	Antiphospholipid antibody syndrome and hyperhomocysteinaemia have been associated with central retinal vein occlusion, although this has not been proved; associations with a deficiency of factor V Leiden, protein S, protein C, and antithrombin 3 have also been reported ¹
Oral contraceptive use	The most common association in young women ^{w7}
Optic disc vasculitis	Consider carefully in patients aged <50 years ^{w8}
Multiple myeloma and myeloproliferative disorders	There are multiple case reports on retinal vein occlusion as a result of multiple myeloma ^{w9 w10} and essential thrombocythaemia ^{w11 w12}
Systemic inflammatory diseases	Consider Behçet's syndrome, polyarteritis nodosa, sarcoidosis, Wegener's granulomatosis, and Goodpasture's syndrome ¹

when a bright light is shone into the normal eye, but initial dilation of both pupils when the light is then immediately shone into the affected eye because the stimulus passing through the affected optic nerve is weaker.

Funduscopy

Funduscopy can be performed by a non-specialist using a handheld direct ophthalmoscope. The diagnosis is mainly based on typical abnormal findings on a fundal examination. The key sign of central retinal vein occlusion is widespread retinal haemorrhage in all quadrants of the retina. This may be accompanied by dilated and tortuous retinal veins, cotton wool spots, macular oedema, and a swollen optic disc (fig 2). In branch retinal vein occlusion only a sector of the retina is covered in haemorrhages. Macular oedema may also be seen (fig 3).

Central retinal vein occlusion may be ischaemic or non-

ischaemic (depending on whether the retina is ischaemic), and it is important to recognise signs of ischaemia because this has implications for prognosis. Box 1 lists the main clinical signs of an ischaemic central retinal vein occlusion.

Fluorescein angiography

A specialist will perform fundus fluorescein angiography, which can help to distinguish between ischaemic and non-ischaemic retinopathy. If ischaemia has occurred, angiography typically shows extensive areas of capillary non-perfusion. Fluorescein angiography will also identify areas of capillary leakage (fig 4). Optical coherence tomography is used to measure the amount of oedema at the macula (fig 5).

What are the differential diagnoses?

Other conditions that can mimic retinal vein occlusion include papillophlebitis and diabetic papillitis, in both of which the swollen optic disc is the main feature, with localised retinal haemorrhages around the optic disc.

What is the outcome if untreated or treated conservatively?

Subsequent visual acuity seems to depend on visual acuity at presentation.³⁻⁵ Eyes with an initial visual acuity of at least 6/12 are more likely to retain good vision. Patients who present with poorer vision continue to have poor vision.⁶ Patients who present with central retinal vein occlusion at less than 45 years are likely to have a more benign outcome than those who present at an older age.^{w15}

Observational studies have reported that 0-34% of patients with non-ischaemic central retinal vein occlusion develop ischaemia.^{4 6 w16-w18} Patients with ischaemic central retinal vein occlusion can develop neovascularisation, which may lead to painful neovascular glaucoma that can be difficult to treat.⁶ New vessels can develop on the retina, or on the iris and in the angle between the cornea and the iris, through which aqueous fluid normally leaves the eye. In non-ischaemic central retinal vein occlusion, macular oedema has been shown to resolve in about 30% of eyes over time, and subsequent neovascular glaucoma in this context is

Box 1 | Clinical signs of an ischaemic central retinal vein occlusion²

- Poor visual acuity (often <6/60)
- Relative afferent pupillary defect
- Presence of multiple dark, deep intraretinal haemorrhages
- Presence of multiple (>10) cotton wool spots
- Markedly dilated and tortuous retinal veins



Fig 2 | Central retinal vein occlusion (ischaemic) in the right eye. Note the widespread retinal haemorrhages in all four quadrants, the cotton wool spot (yellow arrow), venous tortuosity (black arrow), and blurred optic disc margins (white arrow) suggestive of optic disc oedema

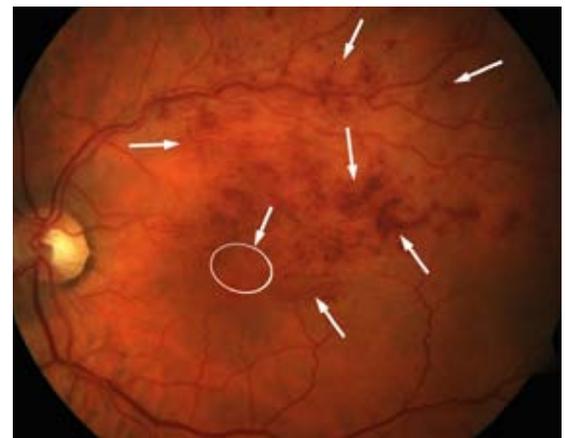
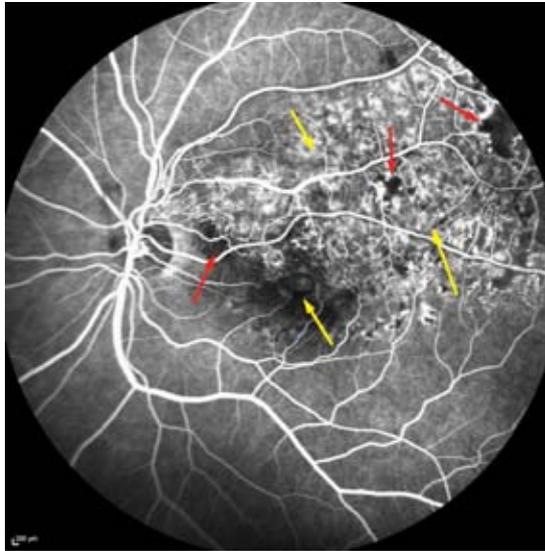


Fig 3 | Left superotemporal branch retinal vein occlusion. Note the retinal haemorrhages in the superotemporal quadrant and in the macular area (white arrows). The blurred appearance at the macula (circle) is suggestive of macular oedema

Fig 4 | Fundus fluorescein angiogram of a left eye with a superotemporal branch retinal artery occlusion. Note the white areas where dye has leaked (yellow arrows), including at the macula, and the areas where dye has been blocked (red arrows). Leakage of dye indicates capillary leakage and therefore retinal oedema. Blockage of dye may be caused by capillary non-perfusion or retinal haemorrhage. The position of the haemorrhages can help distinguish between the two options



rare.⁶ A multicentre randomised clinical trial reported the cumulative 36 month incidence of new vessels on the iris or neovascular glaucoma in untreated or conservatively managed participants with central retinal vein occlusion as 4.2%, and that of retinal neovascularisation (including vitreous haemorrhage) as 7.5%.^{w19}

A recent systematic review of observational studies that examined the natural course of branch retinal vein occlusion found that in some cases visual acuity spontaneously improves but, on average, this did not result in visual acuity better than 6/12.⁷ As many as 41% (95% confidence interval 22% to 64% of eyes with macular oedema at presentation showed some resolution by 12 months, but in about a fifth of untreated eyes visual acuity deteriorated over time, with more than 15 letter loss. Branch retinal vein occlusion in a fellow eye occurred in about 10% of cases over time.⁷ Ischaemia with subsequent neovascularisation is not uncommon in branch retinal vein occlusion, but neovascular glaucoma is rare. The cumulative 36 month incidence of new vessels on the iris or neovascular glaucoma in untreated or conserva-

tively managed participants in a multicentre randomised clinical trial was reported to be 0.8%, compared with an incidence of retinal neovascularisation of 10.2%.^{w19}

What are the general principles of management?

The optimal management of retinal vein occlusion has important general, as well as ophthalmological, components. The Royal College of Ophthalmologists in the United Kingdom recommends that initial evaluation and treatment by the retinal specialist should be no more than two to four weeks after presentation.¹ This guidance has been issued in light of new ophthalmological treatments for patients with haemorrhagic retinopathies, which might result in better visual outcomes if patients are treated early.

What medical management is important?

General practitioners play an important role in the medical management of retinal vein occlusion through the identification and management of modifiable risk factors. The retinal specialist works with the generalist to treat risk factors. The detection and treatment of underlying medical conditions, such as hypertension and diabetes, are aimed at preventing further non-ocular target organ damage and recurrence of venous occlusion, particularly in the fellow eye.^{1 w20}

Reports on the association of retinal vein occlusion with cardiovascular morbidity and mortality are conflicting.^{8 9} The Royal College of Ophthalmologists recommends that cardiovascular risk factors in patients with retinal vein occlusion 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.^{w21-w23} Boxes 2 and 3 summarise the management of risk factors for retinal vein occlusion. Perform electrocardiography on all patients and also check their full blood count, erythrocyte sedimentation rate or plasma viscosity, urea, electrolytes, creatinine, random blood glucose, random cholesterol, high density lipoprotein cholesterol, plasma protein electrophoresis, thyroid function, and blood pressure. More

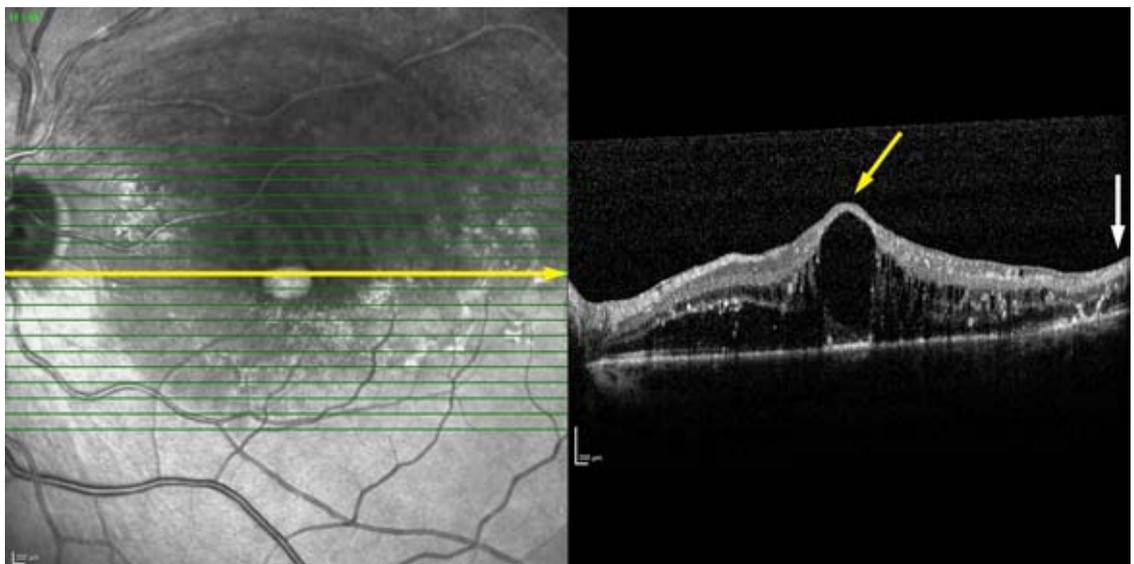


Fig 5 | Optical coherence tomogram of the left retina of the same patient as in fig 3. (A) The arrow highlights the section of the retina that was scanned—in a nasal to temporal direction. (B) The scan shows macular oedema with a large cyst at the centre of the macula (yellow arrow); the white arrow highlights an area of normal retinal thickness

specialised tests can be done according to clinical indication. Target blood pressure is less than 140/85 mm Hg for patients without diabetes and less than 130/80 mm Hg for those with diabetes. Statins may be needed to keep cholesterol below 4.8 mmol/L.

Aspirin is not recommended for primary prevention of cardiovascular events in patients with retinal vein occlusion. Its role remains equivocal partly because of the variable evidence that retinal vein occlusion is a risk factor for stroke or mortality from vascular disease. Pooled data from two large population based cohorts showed that retinal vein occlusion was not associated with mortality from cardiovascular or cerebrovascular disease in participants of all ages, but that in those under 70 years, baseline retinal vein occlusion was associated with higher mortality from cardiovascular disease. A potential doubling of cardiovascular risk was seen in this subgroup.^{w24} Because compression of the retinal vein by a thickened atherosclerotic adjacent retinal artery is thought to be the most common cause of retinal vein occlusion, it is

not clear how antiplatelet or anticoagulant drugs could be of benefit.^{w25} A recent observational study found that patients who are taking antiplatelet aggregating agents or anticoagulants when they develop a central retinal vein occlusion tend to have more severe haemorrhages and a worse visual outcome than those who are not taking these drugs.^{w25} Although this study does not specifically look at the value of starting such treatment after retinal vein occlusion has taken place, the Royal College of Ophthalmologists (box 3) does not recommend treatment with aspirin unless there is another reason for doing so.

Oestrogen containing hormone replacement therapy is relatively contraindicated in women with retinal vein occlusion. However, continued use does not seem to be associated with a higher rate of recurrence. The oral contraceptive pill is the most common underlying association in young women, and it should be prescribed with caution in patients with retinal vein occlusion.¹

Patients with rare underlying conditions that predispose them to thrombosis, such as multiple myeloma and inflammatory disorders, are best referred to and managed by appropriate specialists.

What ophthalmological treatments are used?

Ophthalmological treatments focus on the prevention and management of the main sight threatening complications—ocular neovascularisation and macular oedema.

Management of ocular neovascularisation

Evidence from randomised controlled trials performed in the early 1990s supported the use of laser panretinal photocoagulation in central retinal vein occlusion when new iris vessels or new angle vessels are visible.⁵ The Branch Vein Occlusion Study Group recommended peripheral scatter laser photocoagulation of ischaemic retina in the presence of retinal and disc neovascularisation.^{w26} The precise mechanism of action of laser photocoagulation remains unknown. It may reduce the hypoxic state of the retina by destroying oxygen consuming photoreceptor cells and retinal pigment epithelium.^{w27} The potential adverse effects of photocoagulation include reductions in visual acuity, visual field, colour vision, night vision, and contrast sensitivity. Pain, choroidal neovascularisation, haemorrhage, epiretinal fibrosis, and serous detachment of the peripheral retina are also possible.^{w27} More recent evidence from observational studies and early randomised trials, however, indicates that intravitreal injection of anti-vascular endothelial growth factor (VEGF) agents, in combination with panretinal photocoagulation, results in dramatic regression of neovascularisation.^{10 w28-w30} These treatments can be repeated if new vessels recur.

If neovascular glaucoma is already established and the eye is blind, the aim is to keep the eye pain free, usually with topical steroids and atropine. However, if the eye has any visual potential, it is important to try to control the intraocular pressure with topical pressure lowering agents or surgery to preserve vision. Intracameral and intravitreal bevacizumab cause regression of new iris vessels and reduce obstruction of the angle.^{11 w31}

Box 2 | Initial investigations for patients presenting with retinal vein occlusion²

All patients

Full blood count and erythrocyte sedimentation rate or plasma viscosity
Urea, electrolytes, creatinine
Random blood glucose
Random cholesterol and high density lipoprotein cholesterol*
Plasma protein electrophoresis
Electrocardiography*
Thyroid function

More specialised tests according to clinical indication

Thrombophilia screen
Anticardiolipin antibody, lupus anticoagulant
C reactive protein
Serum angiotensin converting enzyme
Autoantibodies: rheumatoid factor, antinuclear antibodies, anti-DNA antibodies, antineutrophil cytoplasmic antibodies
Chest radiography
Fasting homocysteine concentration
*It is essential to record these investigations for the Framingham equation.

Box 3 | Medical management of risk factors for retinal vein occlusion²

Blood pressure

Diagnosis of hypertension: >140 mm Hg systolic or >90 mm Hg diastolic (or both), sustained
Optimal blood pressure: <140/85 mm Hg

Cholesterol

Primary prevention (10 year risk of coronary heart disease >15% or 10 year risk of total cardiovascular disease >20%)*†: statin usually required
Secondary prevention target is <4.8 mmol/L, use of statin required

Diabetes

Diagnose using World Health Organization blood glucose criteria or glycated haemoglobin criteria (where appropriate)
Glycated haemoglobin target: <7%
Optimal blood pressure: <130/80 mm Hg

Aspirin

Aspirin is indicated in patients with hypertension if the 10 year risk of coronary heart disease is >15% or the 10 year risk of total cardiovascular disease is >20% (or both), providing blood pressure control is satisfactory and there is no contraindication (peptic ulcer, allergy, history of haemorrhage (such as recent haemorrhagic stroke), or patient in the initial stages of a severe haemorrhagic retinal vein occlusion)*†
*Risk of coronary heart disease and of total cardiovascular disease are calculated using charts, discs, or computer programs and the Framingham equation.^{w21} Variables needed for the calculation include random cholesterol concentration, high density lipoprotein cholesterol concentration, systolic blood pressure level, age, sex, presence of diabetes, smoking status, and the presence of left ventricular hypertrophy on electrocardiography. †British Hypertension Society guidelines 2004.^{w42}

Table 2 | Summary of results of the major clinical trials of treatments for macular oedema as a result of central retinal vein occlusion (6 month data)

Details	Study							
	CRUISE ¹²			COPERNICUS ¹³		GENEVA ¹⁴		
Drug	Ranibizumab			VEGF Trap-Eye		Dexamethasone implant		
No of participants	392			189		437		
Arms	0.3 mg	0.5 mg	Sham injection	2 mg	Sham injection	0.7 mg	0.35 mg	Sham injection
Mean change in VA	12.7	14.9	0.8	17.3	-4	0	2	-2
% seeing ≥15 more letters	46.2	47.7	16.9	56.1	12.3	18	17	12

VA=visual acuity.

Table 3 | Summary of results of the major clinical trials of treatments for macular oedema as a result of central retinal vein occlusion (12 month data)

Details	Study							
	CRUISE ^{w34}			SCORE ¹⁵			GENEVA ^{w33}	
Drug	Ranibizumab			Triamcinolone			Dexamethasone implant	
No of participants	392			271			231	
Arms	0.3 mg	0.5 mg	Sham injection	1 mg	4 mg	Sham injection	0.7 mg	Sham injection
Mean change in VA	13.9	13.9	7.3	-1.2	-1.2	-12.1	2.3	-1
% seeing ≥15 more letters	46.2	47.7	16.9	26.5	25.6	6.8	0	0

VA=visual acuity.

Table 4 | Summary of results of the major clinical trials of treatments for macular oedema as a result of branch retinal vein occlusion (6 month data)

Details	Study					
	BRAVO ¹⁶			GENEVA ¹⁴		
Drug	Ranibizumab			Dexamethasone implant		
No of participants	397			830		
Arms	0.3 mg	0.5 mg	Sham injection	0.7 mg	0.35 mg	Sham injection
Mean change in VA	16.6	18.3	7.3	7.5	7.5	5
% seeing ≥15 more letters	55.2	61.1	28.8	23	21	20

VA=visual acuity.

Table 5 | Summary of results of the major clinical trials of treatments for macular oedema as a result of branch retinal vein occlusion (12 month data)

Details	Study							
	BRAVO ^{w35}			SCORE ^{w32}			GENEVA ^{w33}	
Drug	Ranibizumab			Triamcinolone			Dexamethasone implant	
No of participants	397			411			437	
Arms	0.3mg	0.5 mg	Sham injection	1 mg	4 mg	Laser	0.7mg	Sham injection
Mean change in VA	16.4	18.3	12.1	5.7	4	4.2	6	6
% seeing ≥15 more letters	56	60.3	43.9	26	27	29	0	0

VA=visual acuity.

Management of macular oedema secondary to retinal vein occlusion

Macular oedema, thought to be caused by leakage of fluid from capillaries in the central macular area, is the most common cause of visual loss in patients with retinal vein occlusion, and a wide range of treatments has been explored. Laser photocoagulation has traditionally been used to treat macular oedema secondary to branch retinal vein occlusion. More recently, injections and implants of steroids, as well as intravitreal injections of anti-VEGF, have been evaluated. Tables 2-5 summarise the results of the major clinical trials of treatments for macular oedema.¹²⁻¹⁶

Laser photocoagulation

Randomised controlled trials of central retinal vein occlusion have shown no benefit on visual acuity from treating

macular oedema with macular grid laser photocoagulation.¹⁷ However, in branch retinal vein occlusion, grid laser photocoagulation in the area of leaking capillaries is beneficial, but it is recommended only three to six months after the initial event and after absorption of most of the haemorrhage.^{18 19} In one study, significantly more patients treated with laser than controls gained at least two lines of visual acuity from baseline and maintained this for two consecutive visits (P=0.00049).¹⁸ Patients with severe visual loss (<6/60 vision) and those who have had symptoms for more than a year are unlikely to benefit from laser treatment.¹⁹

Triamcinolone acetonide

Corticosteroids reduce retinal capillary permeability and inhibit the expression and metabolic pathway of VEGF, a driver of macular oedema. In the SCORE study, a multicentre randomised clinical trial of 271 patients with central retinal vein occlusion, two different doses of Trivaris, a preservative-free form of intravitreal triamcinolone, produced anatomical and functional improvement of macular oedema, compared with observation.¹⁵ More than 25% of patients with central retinal vein occlusion treated with Trivaris (at either dose) could read 15 or more extra letters on the visual acuity chart after treatment compared with just 6.8% of patients receiving sham injections. Trivaris failed to show superiority over laser treatment in branch retinal vein occlusion.^{w32}

Trivaris is not available for use in clinical practice and there are several differences between Trivaris and other currently available triamcinolone preparations. There is no high quality evidence to suggest that the outcomes seen with Trivaris would be replicated with available triamcinolone preparations.²⁰

Dexamethasone biodegradable implant

Dexamethasone is a more potent corticosteroid than triamcinolone. In the randomised sham controlled GENEVA study,¹⁴ six monthly 0.7 mg and 0.35 mg dexamethasone implants (Ozurdex) were compared with a sham injection in patients with central retinal vein occlusion and branch retinal vein occlusion in two parallel multicentre studies.

Six month data showed that 18% of patients with central retinal vein occlusion and 23% of those with branch retinal vein occlusion receiving 0.7 mg implants were seeing 15 or more letters than at baseline, compared to just 12% and 20% of these two groups of patients receiving sham treatment. The maximal visual benefit of treatment was seen at 60-90 days, leading some to question the logic behind using it every six months.

More recent data have shown that single and repeated dexamethasone implants have a good safety profile over 12 months.^{w33} At 12 months the mean change in visual acuity of patients receiving this treatment for central retinal vein occlusions was a gain of 2.3 letters, compared with a loss of one letter without treatment. For branch retinal vein occlusions at 12 months the mean gain in visual acuity was six letters for those treated with dexamethasone and the same for those treated with sham injection.

Ozurdex is now licensed for use in retinal vein occlusion in the US and Europe. It has recently been approved by NICE as a cost effective treatment.

ADDITIONAL EDUCATIONAL RESOURCES

Resources for healthcare professionals

For more information on the management of retinal vein occlusion see:
 Royal College of Ophthalmologists. [www.rcophth.ac.uk/page.asp?section=451§ionTitle=Clinical±Guidelines](http://www.rcophth.ac.uk/page.asp?section=451§ionTitle=Clinical%20Guidelines)
 National Institute for Health and Clinical Excellence. Macular oedema (retinal vein occlusion)—dexamethasone. TA229. 2011. www.nice.org.uk/TA229
 For the Joint British recommendations on prevention of coronary heart disease and the recent updates on the management of hypertension and the use of statins see:
 Joint British Societies guidelines on prevention of cardiovascular disease. *Heart* 2005;91(suppl V):v1-52. www.bcs.com/download/651/JBS2final.pdf
 National Institute for Health and Clinical Excellence. Lipid modification for prevention of cardiovascular disease. CG67. 2010. www.nice.org.uk/nicemedia/pdf/CG67NICEguideline.pdf
 Martin SC, Butcher A, Martin N, Farmer J, Bartlett WA, Jones AF, et al. Cardiovascular risk assessment in patients with retinal vein occlusion. *Br J Ophthalmol* 2002;86:774-6.
 For guidance on how to diagnose diabetes according to World Health Organization criteria see:
 WHO. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia. 2006. www.who.int/diabetes/publications/diagnosis_diabetes2006/en/index.html
 WHO. Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus. 2011. www.who.int/diabetes/publications/diagnosis_diabetes2011/en/index.html

Resources for patients

Patient.co.uk (www.patient.co.uk/doctor/Central-Retinal-Vein-Occlusion.htm)—Information for patients on retinal vein occlusion

Ranibizumab

Ranibizumab blocks all isoforms of VEGF. It was given at doses of 0.3 mg or 0.5 mg every month for six months and compared with sham injection in the CRUISE and BRAVO randomised controlled trials for central retinal vein occlusion and branch retinal vein occlusion, respectively.¹²⁻¹⁶ There were 392 patients in the CRUISE study and 397 in the BRAVO study.

Just under 48% of patients receiving monthly ranibizumab 0.5 mg (Lucentis) for central retinal vein occlusion

TIPS FOR NON-SPECIALISTS

Manage underlying risk factors 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^{w17-w19}
 Refer any patient with haemorrhagic retinopathy to an ophthalmologist early because earlier review results in better outcomes

QUESTIONS FOR FUTURE RESEARCH

Although earlier treatment can improve outcomes, some patients improve spontaneously. Should we therefore wait before starting steroid treatment?
 Which ophthalmological treatment is the most effective? COMO (NCT01427751), COMRADE-B (NCT01396057), and COMRADE-C (NCT01396083) are head to head studies that aim to answer this question
 Antivascular endothelial growth factor drugs increase the risk of stroke and cardiovascular events when used to treat age related macular degeneration; is this also the case for retinal vein occlusion?
 How cost effective are the different treatment options?
 Do anticoagulants have a role in the treatment of retinal vein occlusion?
 Are there any effective surgical treatment options? Several techniques, such as radial optic neurotomy and optic nerve decompression, have been tried but conclusive evidence of benefit is lacking

and 61.1% of patients receiving it for branch retinal vein occlusion could read 15 or more letters after six months of treatment compared with 16.9% and 28.8% receiving sham injections, respectively. Ranibizumab therefore showed significant visual benefit in both conditions, and the visual gains were maintained over 12 months with additional injections.^{w34 w35}

Because ranibizumab is given monthly, the large number of injections needed is a potential limiting factor of this treatment. It is licensed in the US and the EU for retinal vein occlusion. Currently, NICE has not recommended it for use in the NHS.

VEGF Trap-Eye

VEGF Trap-Eye is a fusion molecule that has anti-VEGF effects. In phase III clinical trials on 189 patients with central retinal vein occlusion (COPERNICUS study),¹³ the monthly 2 mg dose showed significant visual benefit in central retinal vein occlusion at six months, with 56.1% of patients seeing 15 or more letters than at baseline, compared with 12.3% of patients receiving sham injections. Those receiving treatment had a mean visual acuity gain of 17.3 letters, compared with a loss of four letters in those without treatment. Currently, there are no published data for the 12 month time point, but it is thought that the visual gain will be maintained. The number of injections needed is a drawback.

Bevacizumab

The pan-VEGF blocker bevacizumab is unlicensed for intraocular use. Several case series (without controls) indicate that around 50% of patients with non-ischæmic central retinal vein occlusion and branch retinal vein occlusion have a visual acuity gain of two or more lines with intravitreal bevacizumab. Vision stabilised by 12 months in 90% of eyes.^{21-24 w36}

Pegaptanib

A phase II trial and prospective case series indicate that intravitreal 0.3 mg pegaptanib sodium, when given every six weeks for six months to treat macular oedema secondary to central retinal vein occlusion, improved visual acuity by about seven letters at six months.²⁵ The reported follow-up periods are short, so the optimal treatment regimen and the response to treatment in the long term are unclear.

Combination treatments

A small prospective study of 18 eyes with macular oedema as a result of branch retinal vein occlusion, in which eyes were randomised to receive treatment with either intravitreal bevacizumab injections alone or in combination with laser treatment, found that combined treatment reduced the lower number of reinjections.^{w37}

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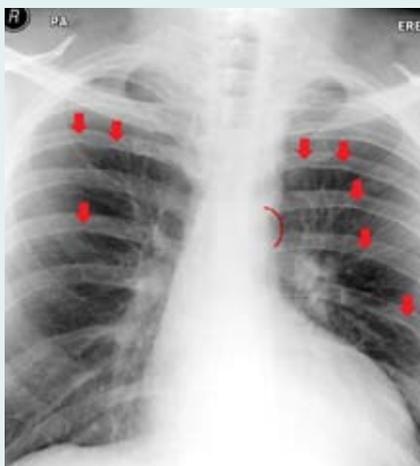
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PICTURE QUIZ

A man with hypertension and two murmurs



Posteroanterior chest radiograph showing characteristic inferior rib notching (Roesler's sign, red arrows) owing to expansion of collateral vasculature in response to coarctation. Loss of the aortic knuckle (usual location indicated by red broken arc) and cardiomegaly are also seen

- Rib notching (figure), cardiomegaly, loss of aortic knuckle, systolic hypertension, and systolic murmur are consistent with coarctation of the aorta; the widened pulse pressure, loud early diastolic murmur, and prominent carotid pulse suggest aortic valve regurgitation. The aortic valve is bicuspid, thus prone to regurgitation, in 20-85% of patients with coarctation.
- Transthoracic echocardiography would enable diagnosis of aortic coarctation and aortic valve regurgitation. Computed tomography and cardiac magnetic resonance imaging are the investigations of choice for assessing coarctation; evaluation of the aortic valve and cardiac function may require transoesophageal echocardiography, especially if surgical intervention is planned.
- Aggressive medical management of hypertension is usually started before definitive treatment of aortic coarctation (usually endovascular stenting); even with definitive treatment, most patients remain hypertensive for life. Coexistence of aortic valve regurgitation and aortic coarctation usually warrants surgical replacement or repair of the aortic valve.

CASE REPORT

A man with a blistering eruption and tuberculosis

- Differential diagnoses include drug eruption, bullous pemphigoid, pemphigus foliaceus, and porphyria cutanea tarda.
- Further investigations include spot urine for porphyrins and tests for faecal porphyrins with fractionation.
- The patient has hepatitis C infection, which is closely associated with porphyria cutanea tarda. Moreover, the patient was given rifampicin.
- Identification and avoidance of precipitating factors, abstinence from alcohol, and iron reduction treatment with phlebotomy.

STATISTICAL QUESTION

Cohen's coefficient k

Statement *b* is true, while *a* and *c* are false.