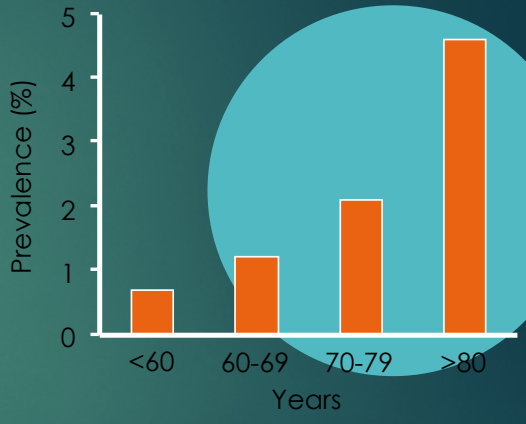
Retinal vein occlusion (RVO)

- Second most common retinal vascular disorder[1]
- Estimated worldwide projection: 16 million people affected in at least one eye[3]
- ~520 new cases annually per million population[3]
- 10-year incidence of 1.6% in people aged ≥49 years[4]

Prevalence of RVO varies with age (n=3654)[2]



Vision loss substantially affects quality of life

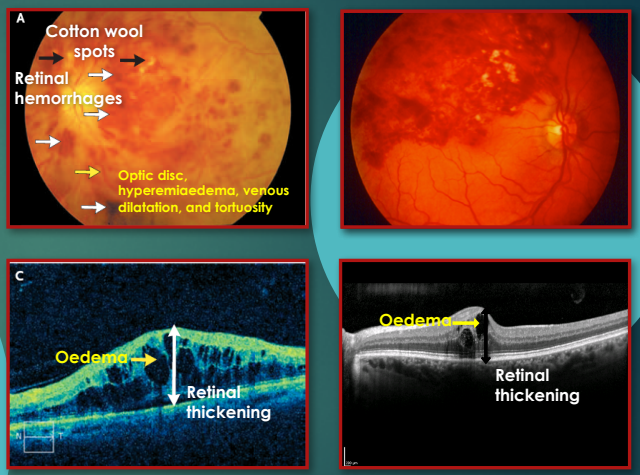
- Of 325 people with visual loss of 20/40 or worse in >1 eye, the average person with 20/40 vision in the better eye was willing to trade 2 of 10 years of life in return for perfect vision[5]

1. Shahid *et al. Br J Ophthalmol* 2006; 90: 627-639; 2. Mitchell *et al. Arch Ophthalmol* 1996; 114: 1243-1247 (figure Copyright © 1996 American Medical Association. All rights reserved); 3. Rogers *et al. Ophthalmology* 2010; 117: 313-319; 4. Cugati *et al. Arch Ophthalmol* 2006; 124: 726-732; 5. Brown. *Trans Am Ophthalmol Soc* 1999; 97: 473-511.

Branch and central retinal vein occlusion

70% of RVO are branch retinal vein occlusions (BRVO); the remainder are central retinal vein occlusions (CRVO)[1]

CRVO **BRVO**



1. Mitchell *et al. Arch Ophthalmol* 1996; 114: 1243-1247; 2. Rogers *et al. Ophthalmology* 2010; 117: 313-319; 3 Wong *et al. N Engl J Med*. 2010; 363: 2135-2144. CRVO fundus photograph from Wong *et al.* Clinical practice: retinal-vein occlusion. Copyright © 2010 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. BRVO fundus photograph reproduced with permission from Dr Tim Hillson.

Pathogenesis of RVO

BRVO

- Occlusion occurs at the arteriovenous intersection
  - major branch retinal vein, or
  - macular venule

CRVO

- Non-ischaemic (perfused)
  - occlusion is distal to the lamina cribrosa or the adjacent retrolaminar region
- Ischaemic (non-perfused)
  - occlusion is in the region of the lamina cribrosa (or immediately posterior)
  - defined by >10 disc areas of capillary non-perfusion (fluorescein angiography)[1]

1. Central Vein Occlusion Study Group. *Arch Ophthalmol* 1993; 111: 1087-1095. BRVO fundus photograph (top) reproduced with permission from Dr Tim Hillson; CRVO fundus photographs (middle and bottom) reproduced from Morley and Heier. Chapter 6.17. In Yanoff and Duker: Ophthalmology. 3rd ed, Copyright Elsevier 2008

Clinical features of RVO

- Sudden, painless, unilateral loss of vision
- Not always perceived by patient
- Degree of vision loss dependent on retinal involvement and retinal perfusion status

Simulated BRVO vision

Simulated CRVO vision

BRVO

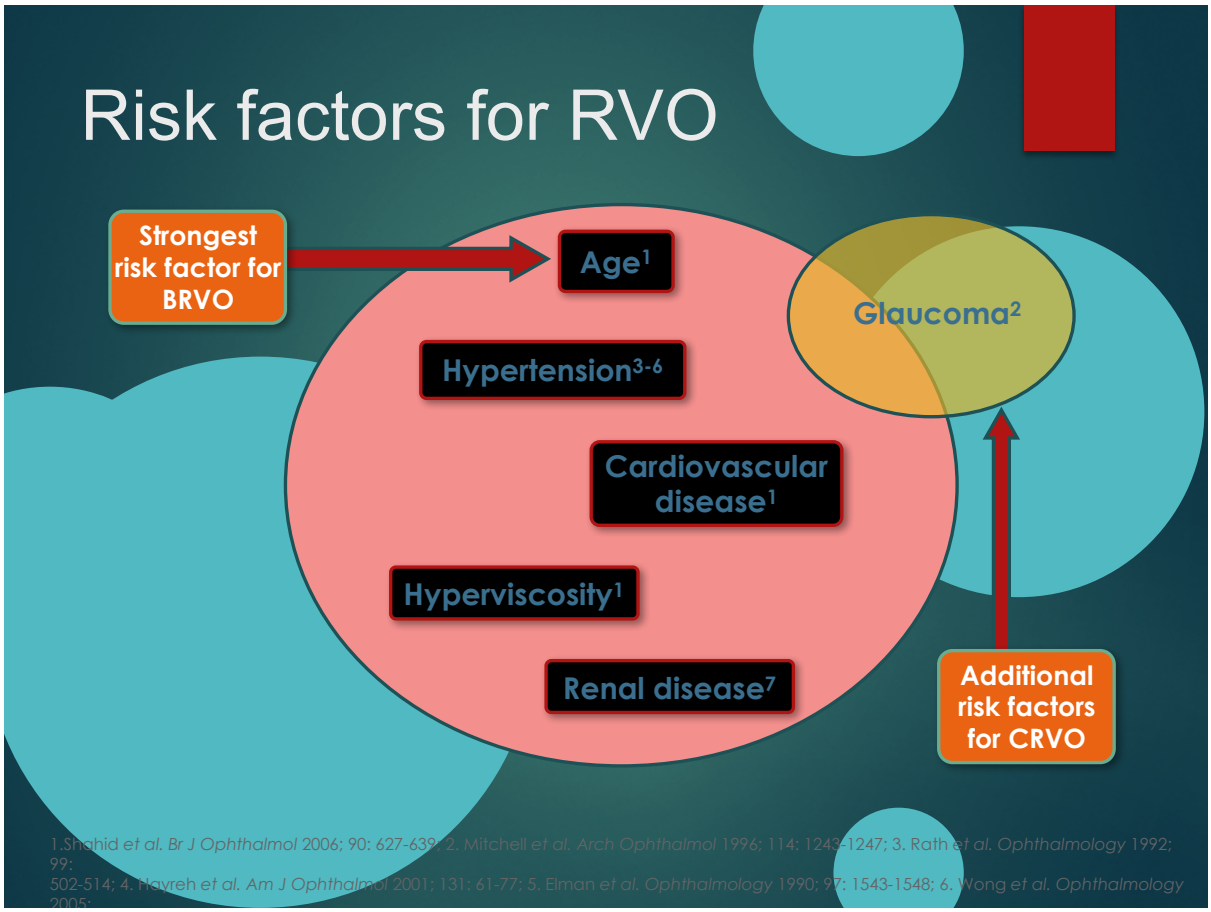
- Inferotemporal or nasal BRVO often asymptomatic[1]

CRVO

- VA at time of presentation is a strong predictor of prognosis for vision[2]
- Vision prognosis worse in CRVO than BRVO, particularly when non-perfused[3]

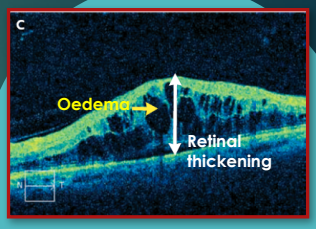
VA, visual acuity

1. Shirodkhar *et al. Br J Hosp Med* 2012; 73: 20-23; 2. Central Vein Occlusion Study Group. *Arch Ophthalmol* 1993; 111: 1087-1095;

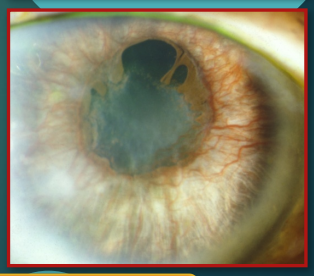

Risk factors for RVO
Strongest risk factor for BRVO
Age[1]
Hypertension[3-6]
Cardiovascular disease[1]
Hyperviscosity[1]
Renal disease[7]
Glaucoma[2]
Additional risk factors for CRVO
1.Shahid et al. Br J Ophthalmol 2006; 90: 627-639; 2. Mitchell et al. Arch Ophthalmol 1996; 114: 1243-1247; 3. Rath et al. Ophthalmology 1992; 99:
502-514; 4. Hayreh et al. Am J Ophthalmol 2001; 131: 61-77; 5. Elman et al. Ophthalmology 1990; 97: 1543-1548; 6. Wong et al. Ophthalmology 2005;

What happens if we don't treat?

- Retinal ischaemia upregulates VEGF production[1]
- High VEGF levels stimulate[2]
  - capillary leakage leading to macular oedema
  - lamellar hole formation
  - epiretinal membrane formation and retinal atrophy
  - neovascularisation[3]
    - neovascular glaucoma



Neovascular glaucoma

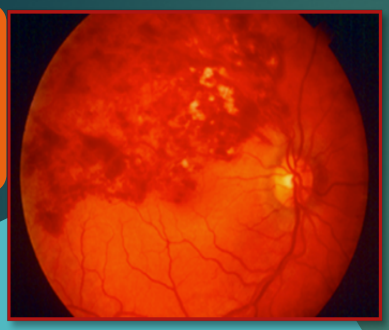


Macular oedema, with or without macular non-perfusion, is the most frequent cause of visual impairment in patients with RVO[1]

1.
3.
oc
al practice: retinal
cal Society.

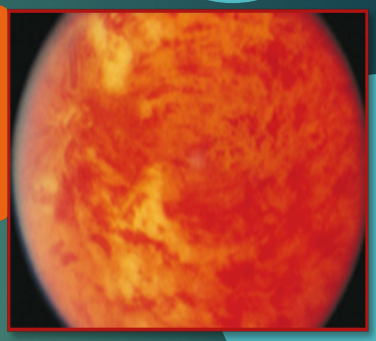
At initial presentation…

BRVO



- Review VA
- RAPD
- Baseline IOPs : ?disc morphology
- Co-existing pathology : CATARACT , diabetes, hypertension, glaucoma suspect

CRVO



- Ishaemic?
- Poor VA
- RAPD
- Retina

- Prognosis?
- Ischemic
- Other pathology
- Glaucoma

Further evaluation

- Fundus fluoroscein angiography

-ischemia?

-role for laser?

- OCT imaging

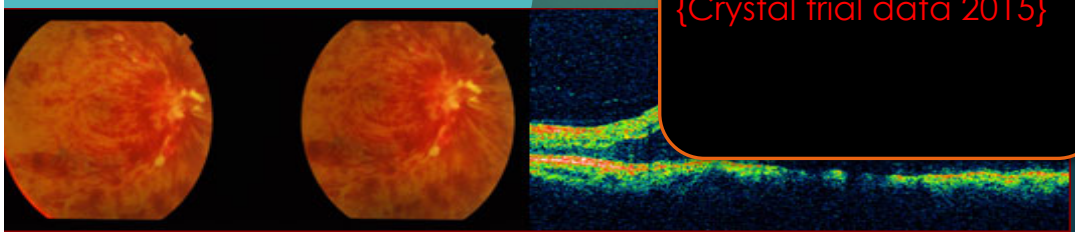
-patient education

- follow-up

Even patients with macular ischemia improved with

anti-VEGF injections

{Crystal trial data 2015}



Cataract surgery and RVO

- Patient education as to cause of visual loss
- Treat retinal pathology first
- Careful mangement of IOP

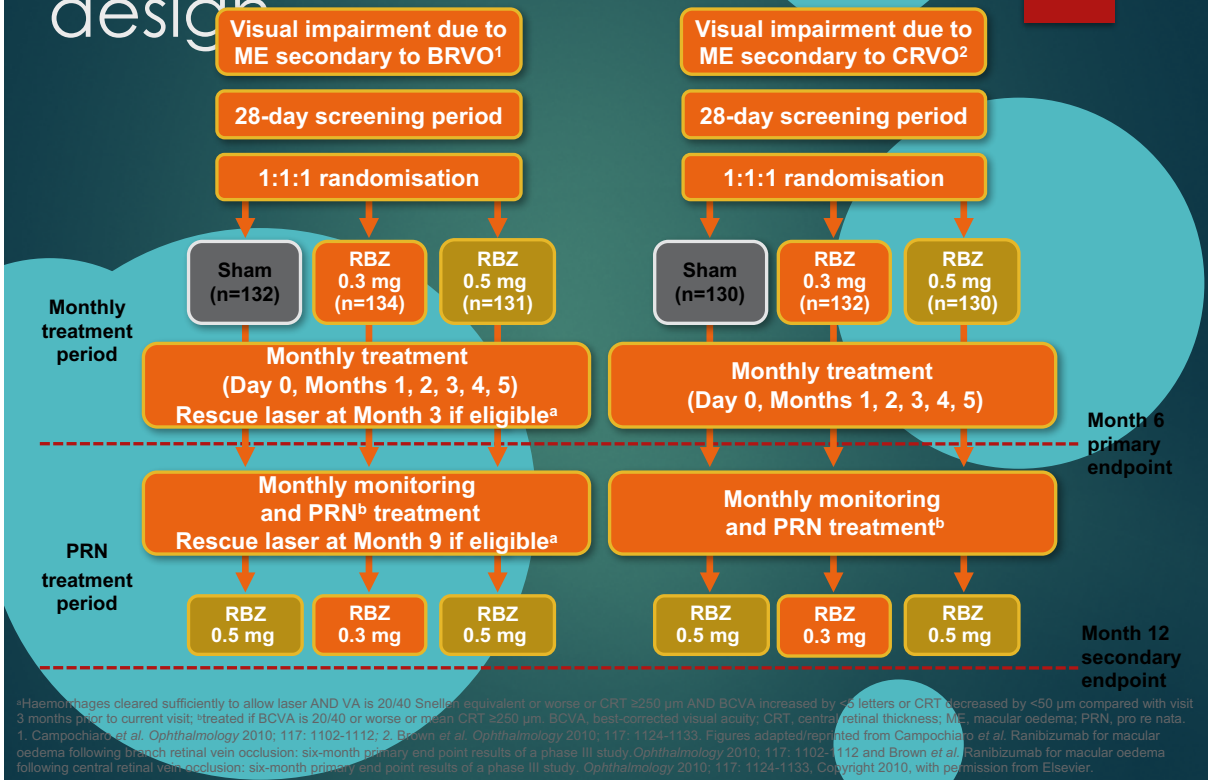
- Consider changes to pre-op and post-op drop regimen
- Consider intravitreal therapy at time of surgery
- Changes to follow up regimen

Tailoring treatment in RVO

- **The advent of anti-VEGF therapy represents a significant advancement**

Based on the CRUISE and BRAVO studies, ranibizumab received marketing authorisation in many countries for treatment of visual impairment due to macular oedema secondary to RVO (BRVO or CRVO)

BRAVO and CRUISE: study design

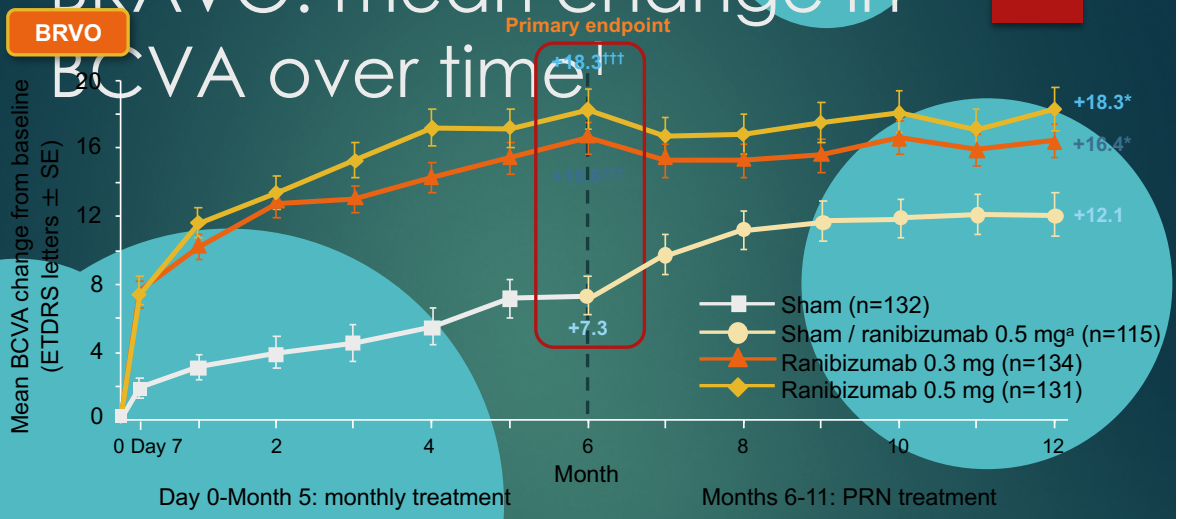


[a]Haemorrhages cleared sufficiently to allow laser AND VA is 20/40 Snellen equivalent or worse or CRT ≥250 µm AND BCVA increased by <5 letters or CRT decreased by <50 µm compared with visit 3 months prior to current visit; [b]treated if BCVA is 20/40 or worse or mean CRT ≥250 µm. BCVA, best-corrected visual acuity; CRT, central retinal thickness; ME, macular oedema; PRN, pro re nata.

1. Campochiaro *et al. Ophthalmology* 2010; 117: 1102-1112; 2. Brown *et al. Ophthalmology* 2010; 117: 1124-1133. Figures adapted/reprinted from Campochiaro *et al.* Ranibizumab for macular oedema following branch retinal vein occlusion: six-month primary end point results of a phase III study. *Ophthalmology* 2010; 117: 1102-1112 and Brown *et al.* Ranibizumab for macular oedema following central retinal vein occlusion: six-month primary end point results of a phase III study. *Ophthalmology* 2010; 117: 1124-1133, Copyright 2010, with permission from Elsevier.

BRAVO: mean change in BCVA over time[1]

BRVO



Day 0-Month 5: monthly treatment

	Mean (SD) no. of injections
Sham	5.5 (1.1)
Ranibizumab 0.3 mg	5.7 (0.9)
Ranibizumab 0.5 mg	5.7 (0.9)

Months 6-11: PRN treatment

	Mean (SD) no. of injections
Sham / ranibizumab 0.5 mg[a]	3.6 (2.1)
Ranibizumab 0.3 mg	2.8 (2.1)
Ranibizumab 0.5 mg	2.7 (2.2)

[a]Sham patients received 0.5 mg ranibizumab, PRN treatment from Month 6 to 11. *p<0.01 vs sham / ranibizumab 0.5 mg; †††p<0.0001 vs sham (pairwise ANOVA). Randomised patients, LOCF (last observation carried forward). ANOVA, analysis of variance; BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; PRN, pro re nata; SD, standard deviation; SE, standard error. 1. Brown *et al. Ophthalmology* 2011; 118: 1594-1602. Figure reprinted from Brown *et al.* Sustained benefits from ranibizumab for macular oedema following branch retinal vein occlusion: 12-month outcomes of a phase III study. *Ophthalmology* 2011; 118: 1594-1602, Copyright 2011, with permission from Elsevier.

Tailoring treatment in RVO

Reducing treatment burden: how many injections is enough to maintain stable visual vision ?

What is the most appropriate therapy combination for my patient ?
(retinal laser, anti-VEGF, steroid)

How do we improve outcomes in ischaemic occlusions?

HORIZON cohort 2[5]
(Phase III; completed)

- Macular oedema secondary to BRVO and CRVO
- 2-year extension study: ranibizumab , multicenter
- PRN dosing resulted in sustained BCVA & OCT improvement in first 12 months
- Quarterly monitoring visits or more frequently
- patients received fewer injections during first year

BRIGHTER[6]

- Macular oedema secondary to BRVO
- 24-month study: PRN ranibizumab alone or with adjunctive laser
- ranibizumab with adjunctive laser is non-inferior to ranibizumab monotherapy wrt to mean average BCVA change from baseline
- ranibizumab with adjunctive laser reduces the number of ranibizumab retreatments

CRYSTAL[7]

- Macular oedema secondary to CRVO
- 24-month study: 3 x monthly injections then PRN ranibizumab
- Maintenance of BCVA
- Some cases of improvement despite macular ischemia at baseline

BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; PRN, pro re nata; RVO, retinal vein occlusion.

1. Brown *et al. Ophthalmology* 2011; 117: 1124-1133; 2. Campochiaro *et al. Ophthalmology* 2010; 117: 1102-1112; 3. Brown *et al. Ophthalmology* 2010; 117: 1124-1133; 4. Campochiaro *et al. Ophthalmology* 2011; 118: 2041-2049; 5. http://www.clinicaltrials.gov/ct2/show/NCT01442064; 6. http://www.clinicaltrials.gov/ct2/show/NCT01599650; 7. http://www.clinicaltrials.gov/ct2/show/NCT01535261.