RETINAL VEIN OCCLUSION
WHAT WORKS, WHATS NEW

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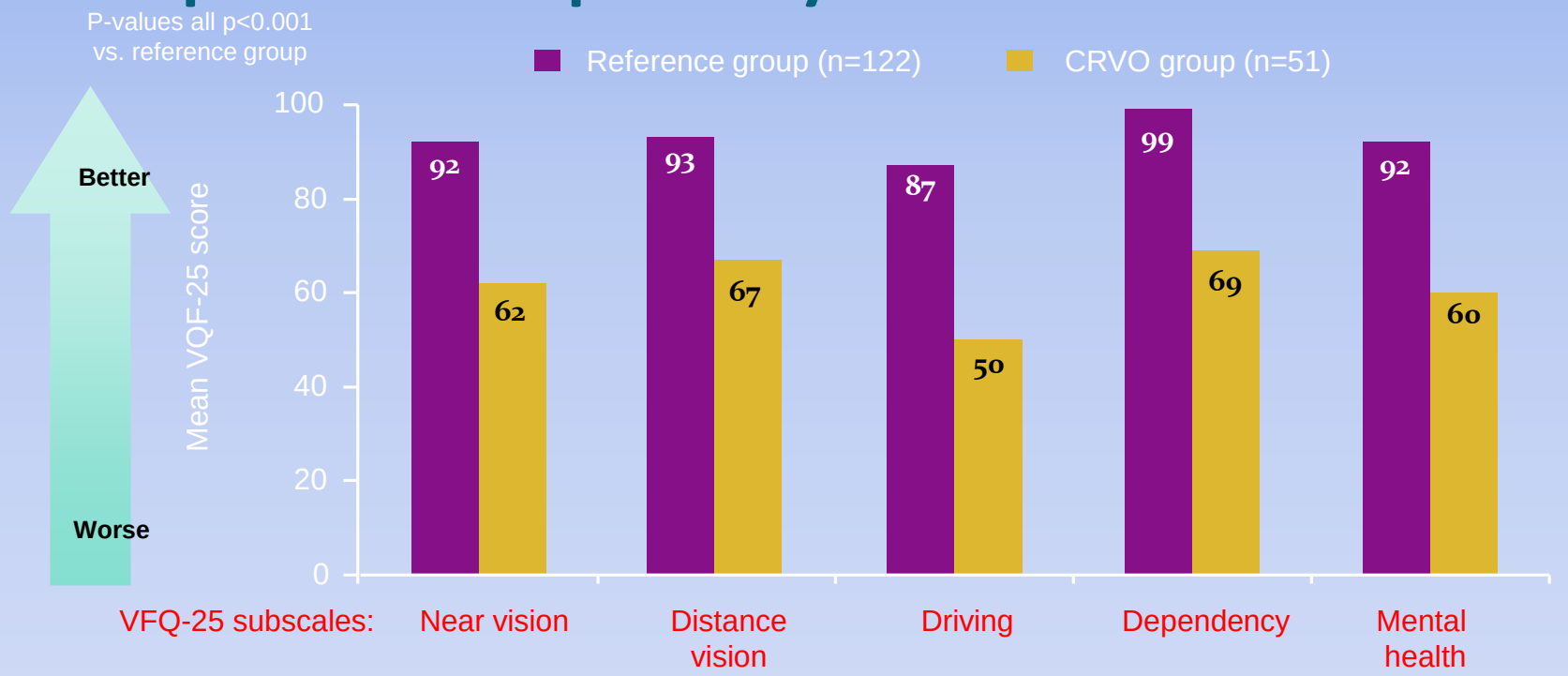
Declaration of interest

- I have sat on Advisory boards for Novartis and Bayer
- Involved in Novartis sponsored clinical trials
- I have been sponsored by Novartis and Bayer and Alimera at various clinical meetings

RVO is the second most common cause of reduced vision in retinal vascular disease

- Overall prevalence varies from 0.7% to 1.6%
- Prevalence of RVO varies with age rising to 5% in the over 80
- In the US there about 30,000 new case of central retinal vein occlusion (**CRVO**) and 150,000 new cases of branch retinal vein occlusion (**BRVO**) diagnosed per year

RVO severely impairs patient quality of life*



*Based on a US interviewer-administered study on vision-related quality of life for 51 participants with CRVO using the National Eye Institute Visual Function Questionnaire (VFQ-25)[1]

Reading newspapers

Watching movies

Night-time driving

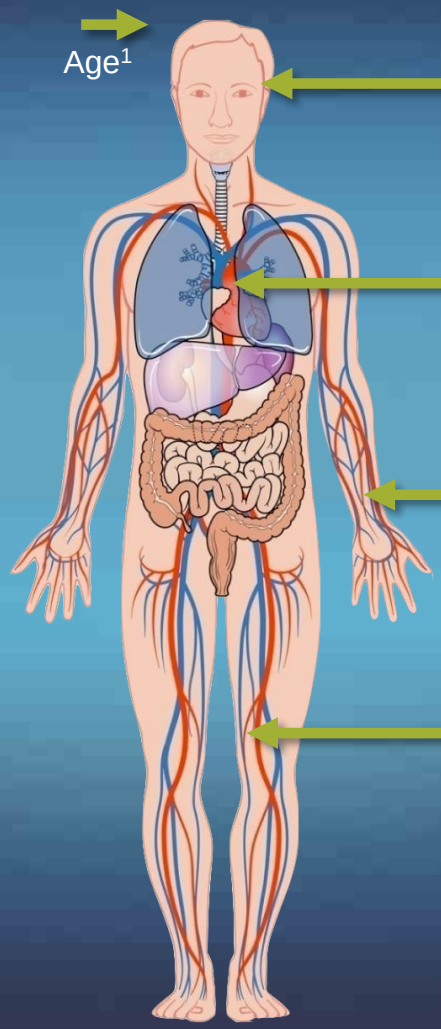
Mostly stay at home

Feel frustrated

1. Deramo VA *et al. Arch Ophthalmol* 2003;121:1297–302.
2. Mangione CM *et al. Arch Ophthalmol* 2001;119:1050–8.

Aetiology of RVO

- Ocular diseases[2]
- Systemic vascular diseases[2,3]
- Inflammatory/ autoimmune diseases[2,3]
- Hematological abnormalities[1–3]



Glaucoma[1–4]
Increased intraocular pressure (IOP)[4]

Diabetes[2,4,5]
Hypertension[1,2,4,5]
Atherosclerotic cardiovascular disease[3]

Systemic lupus erythematosus[2]
Inflamatory bowel disease

Hyperlipidemia[1,5]
Hyperviscosity syndromes[2,3]
Coagulation cascade abnormalities[2]

1. Mitchell P *et al*. *Arch Ophthalmol* 1996;114:1243–7.
2. Mruthyunjaya P *et al*. Chapter 70. In: *Retina*. Elsevier Mosby, 2006.
3. Morley MG *et al*. Chapter 6.17. In: *Ophthalmology*. Elsevier Mosby, 2009.
4. Klein R *et al*. *Arch Ophthalmol* 2008;126: 513–8.
5. Royal College of Ophthalmologists. *Retinal vein occlusion (RVO) interim guidelines.* 2010.

Predominant systemic associations for retinal vein occlusions

Patient group	Hypertension	Hyperlipidaemia	Diabetes Mellitus	No obvious cause
Young patients <50yrs old	25%	35%	3%	40%
Older patients >50 years	64%	34%	4% -15%	21%
Asian	64%	50%	29%	10.7%
West Indian	83%	33%	38%	8.3%
Recurrent cases	88%	47%	3%	6%

Ref RCOphth interim guidelines Dec. 2010

Risk factors

- **Hypertension**

  This is the predominant risk factor with up to 64% of patients having hypertension 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.

Thrombophilia screen

- Anti-thrombin III deficiency
- Prothrombin levels
- Factor IV Leiden
- In addition patients should be tested for:

- Protein C deficiency
- Protein S deficiency
- *Hyperhomocysteinemia*

- **address underlying medical conditions – to prevent recurrence**
- Consider HRT usage in the post menopausal woman
- Contraceptive pill
- Dehydration

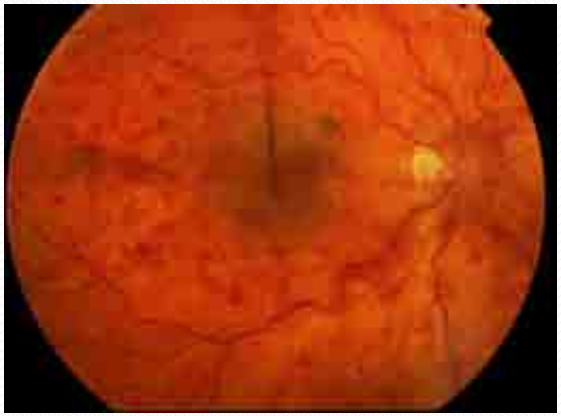
Tsaloumas MD, Kirwan J, Vinall H, O'Leary MB, Prior P, Kritzinger EE, Dodson
Nine year follow-up study of morbidity and mortality in retinal vein occlusion. *Eye. 2000.*
Kirwan JF, ***Tsaloumas MD****, Vinall H, Prior P, Kritzinger EE, Dodson PM.*
Sex hormone preparations and retinal vein occlusion. *Eye. 1997*

pathology

- **Non-ischaemic CRVO**
- site of occlusion is distal to the lamina cribrosa or the adjacent retrolaminar region
- sluggish retinal circulation due to fall in

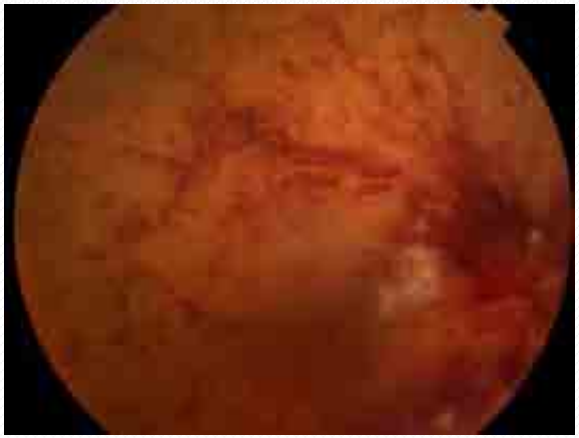
perfusion pressure resulting from a rise in

proximal venous pressure



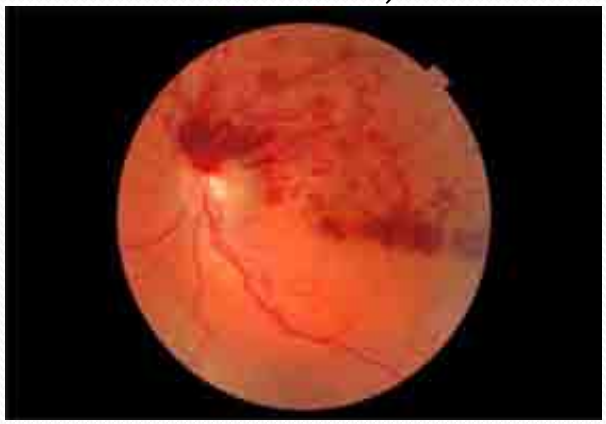
- **ischaemic CVRO**
- site of occlusion is in the region of the lamina cribrosa (or immediately posterior)
- marked rise in venous pressure
- retinal haemorrhage

due to rupture of ischaemic capillaries

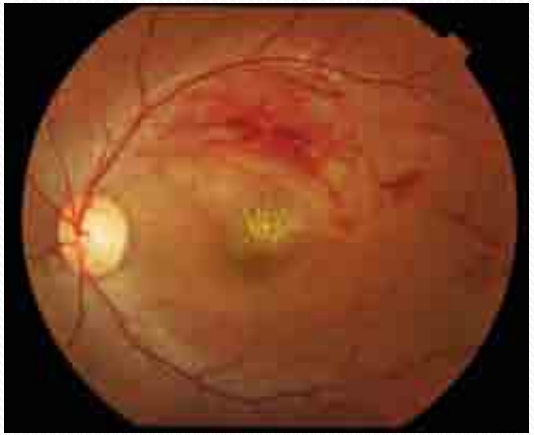


BRVO

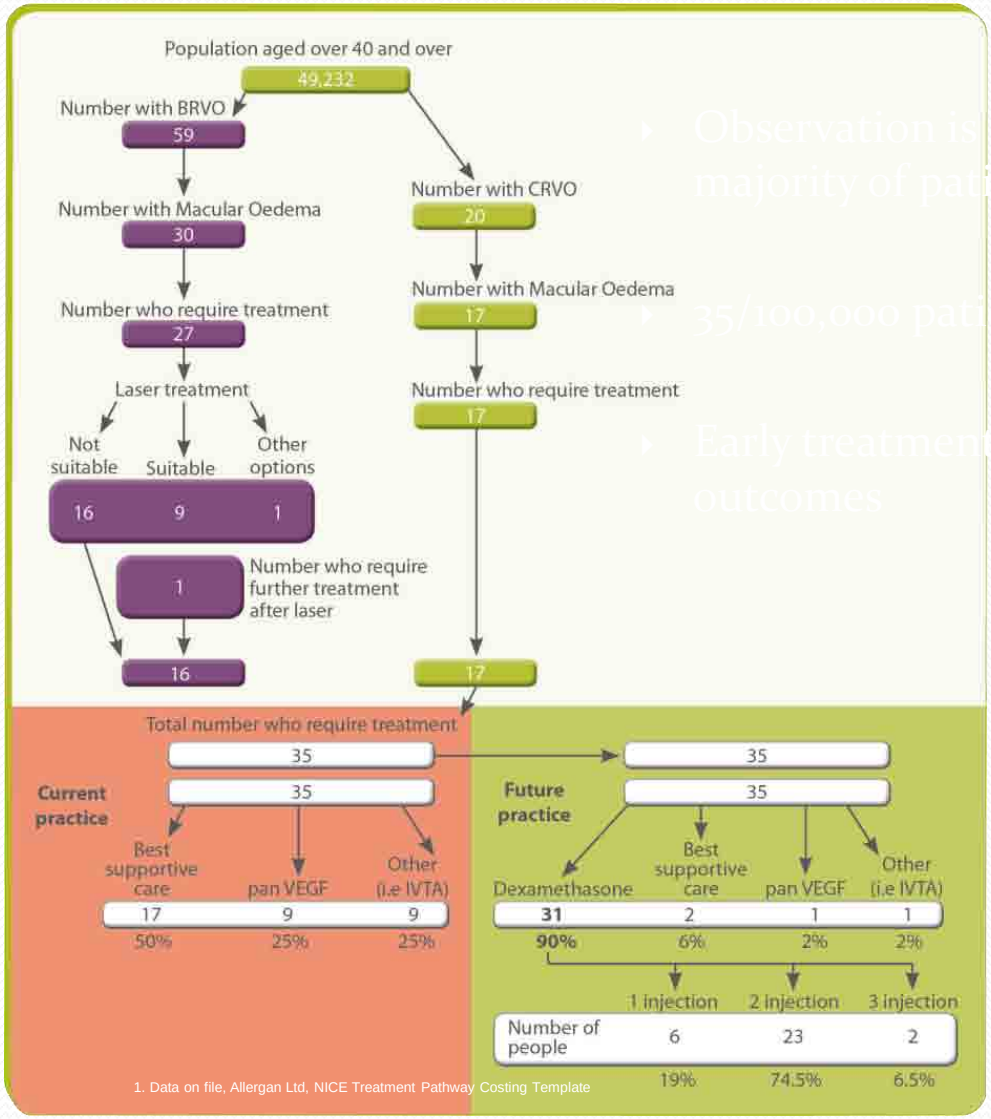
- **Defined by the site of occlusion**
- major BRVO (occlusion within one of the major branch retinal veins)
- macular BRVO (occlusion within one of the macular venules)



- Pathogenesis of BRVO may be due to a combination of three primary mechanisms
- compression of the vein at the A/V crossing
- degenerative changes of the vessel wall
- abnormal haematologic factors



NICE treatment pathway



What are we treating RVO with?

- What are we trying to achieve??
- improvement in vision that lasts
- decrease in central retinal thickness on the OCT scans
- Avoid sequlae

- Ozurdex – dexamethzone intravitreal implant - NICE ✓
- Lucentis injections - NICE ✓
- Avastin injections
- Eylea (CRV0 only) - NICE ✓
- **Retinal laser**

- Lets look at the studies (briefly!)

TA283 Ranibizumab for treating visual impairment caused by macular oedema secondary to retinal vein occlusion

View the summary and implementation tools

Next

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1 Guidance

1.1 Ranibizumab is recommended as an option for treating visual impairment caused by macular oedema:

- following central retinal vein occlusion **or**
- following branch retinal vein occlusion only if treatment with laser photocoagulation has not been beneficial, or when laser photocoagulation is not suitable because of the extent of macular haemorrhage **and**
- only if the manufacturer provides ranibizumab with the discount agreed in the patient access scheme revised in the context of NICE technology appraisal guidance 274.

1.2 People currently receiving ranibizumab whose disease does not meet the criteria in 1.1 should be able to continue treatment until they and their clinician consider it appropriate to stop.

- **Dexamethasone intravitreal implant for the treatment of macular oedema secondary to retinal vein occlusion**

- **NICE technology appraisals [TA229] Published date: July 2011**

- 1 Guidance
- 1.1 Dexamethasone intravitreal implant is recommended as an option for the treatment of macular oedema following central retinal vein occlusion.

- 1.2 Dexamethasone intravitreal implant is recommended as an option for the treatment of macular oedema following branch retinal vein occlusion when:

- treatment with laser photocoagulation has not been beneficial, **or**

- treatment with laser photocoagulation is not considered suitable because of the extent of macular haemorrhage.

- **Aflibercept for treating visual impairment caused by macular oedema secondary to central retinal vein occlusion**
- **NICE technology appraisals [TA305] Published date: February 2014**

- 1 Guidance

- 1.1 Aflibercept solution for injection is recommended as an option for treating visual impairment caused by macular oedema secondary to central retinal vein occlusion only if the manufacturer provides aflibercept solution for injection with the discount agreed in the patient access scheme.

OZURDEX – GENEVA STUDY

DEXAMETHASONE INTRAVITREAL IMPLANT

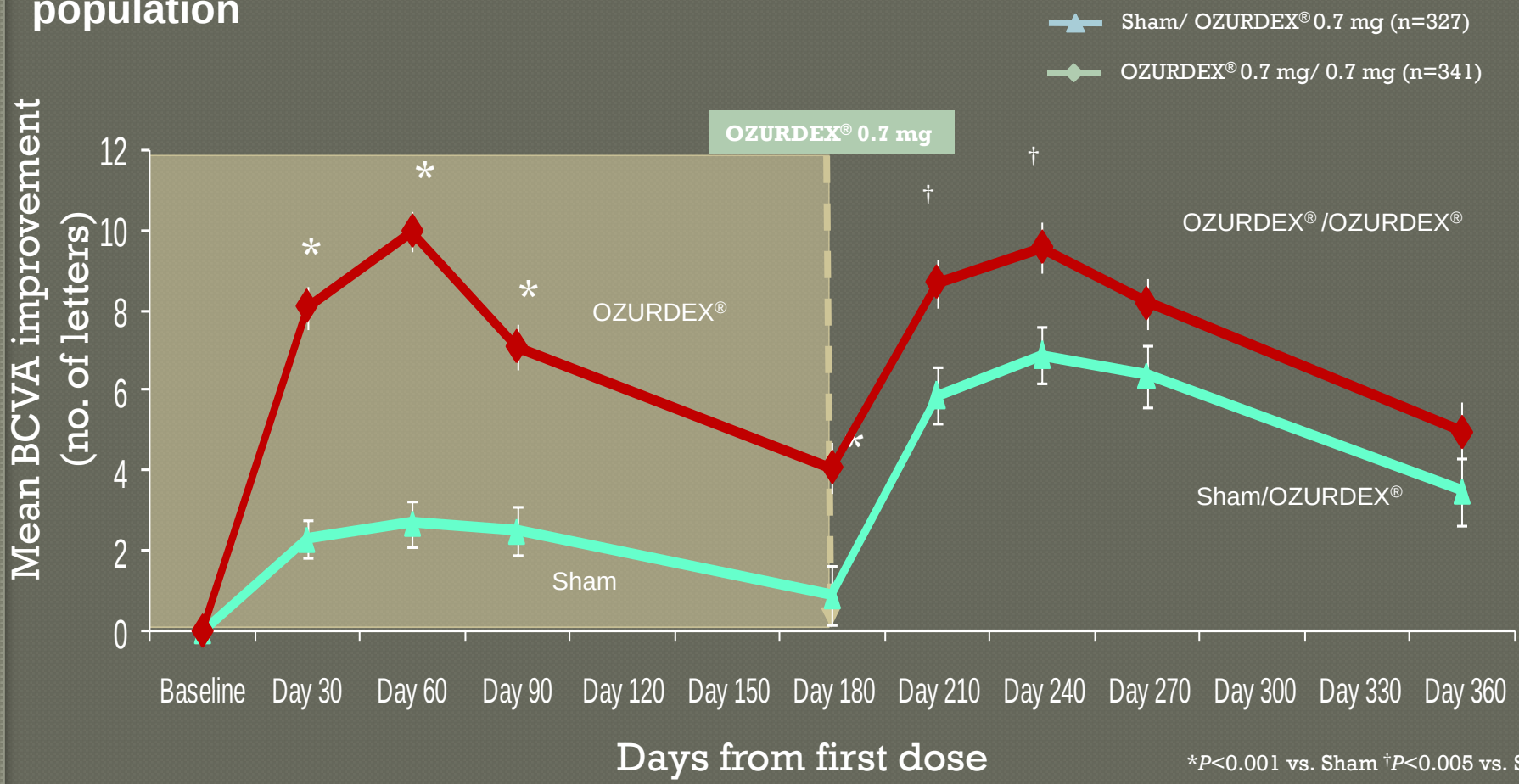
- Two identical, multicenter, prospective studies

PARTICIPANTS:

- 1256 patients with vision loss owing to **macular oedema** associated with BRVO or CRVO.
  - **Cumulative response rate for vision improvement was higher with OZURDEX® versus sham.**
  - **Single injection improved vision for up to 6 months**
  - **Effective in both BRVO and CRVO**
  - Efficacy outcomes favoured patients who received two injections of OZURDEX® compared to one
  - some cataract progression with the extension study (29.8% of phakic eyes) with second injection
  - Some IOP problems
  - **Approved by NICE**

Consistent BCVA improvements with retreatment: Earlier treatment with OZURDEX® improves outcomes

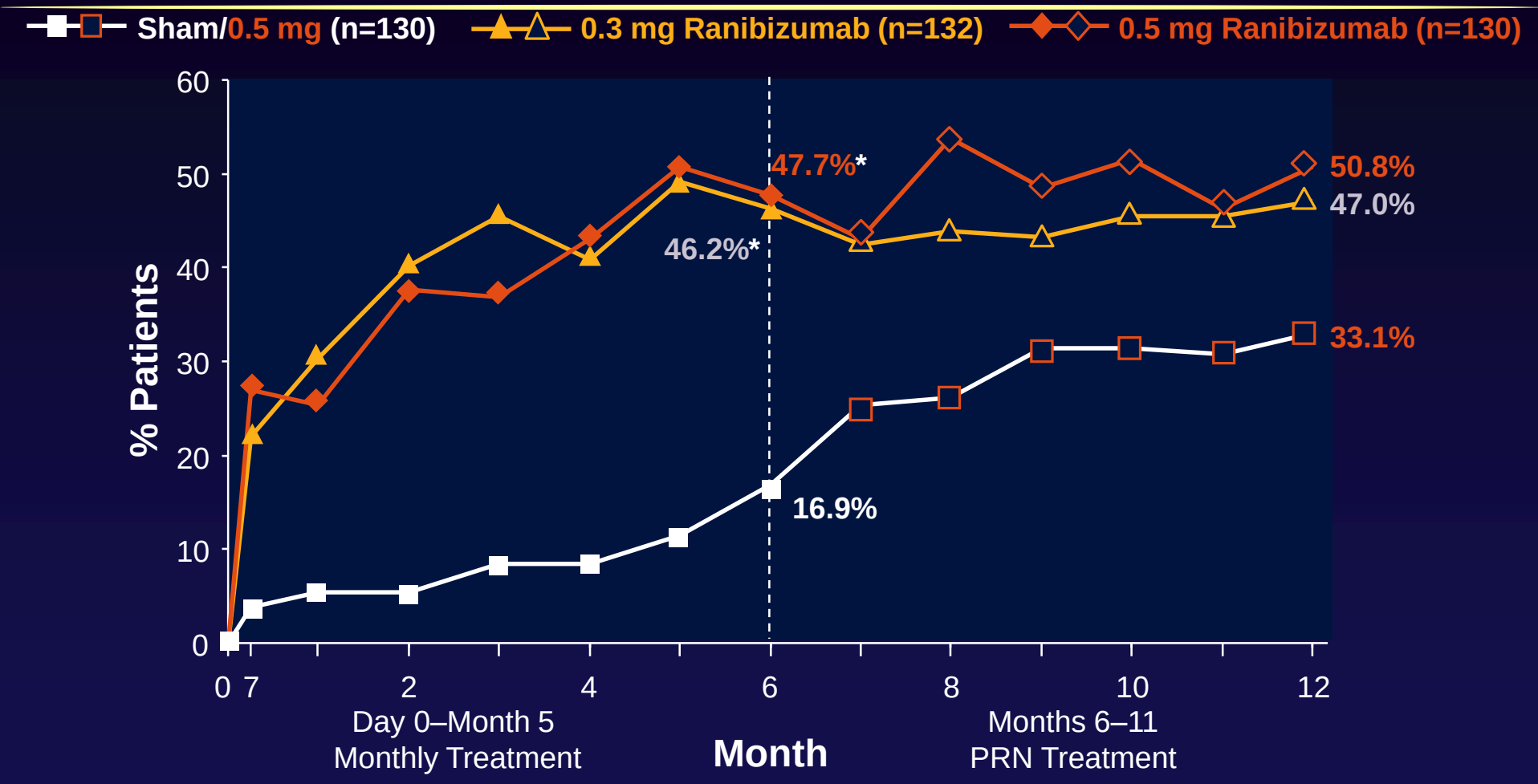
Mean change in BCVA from baseline - re-treated population



*P<0.001 vs. Sham †P<0.005 vs. Sham

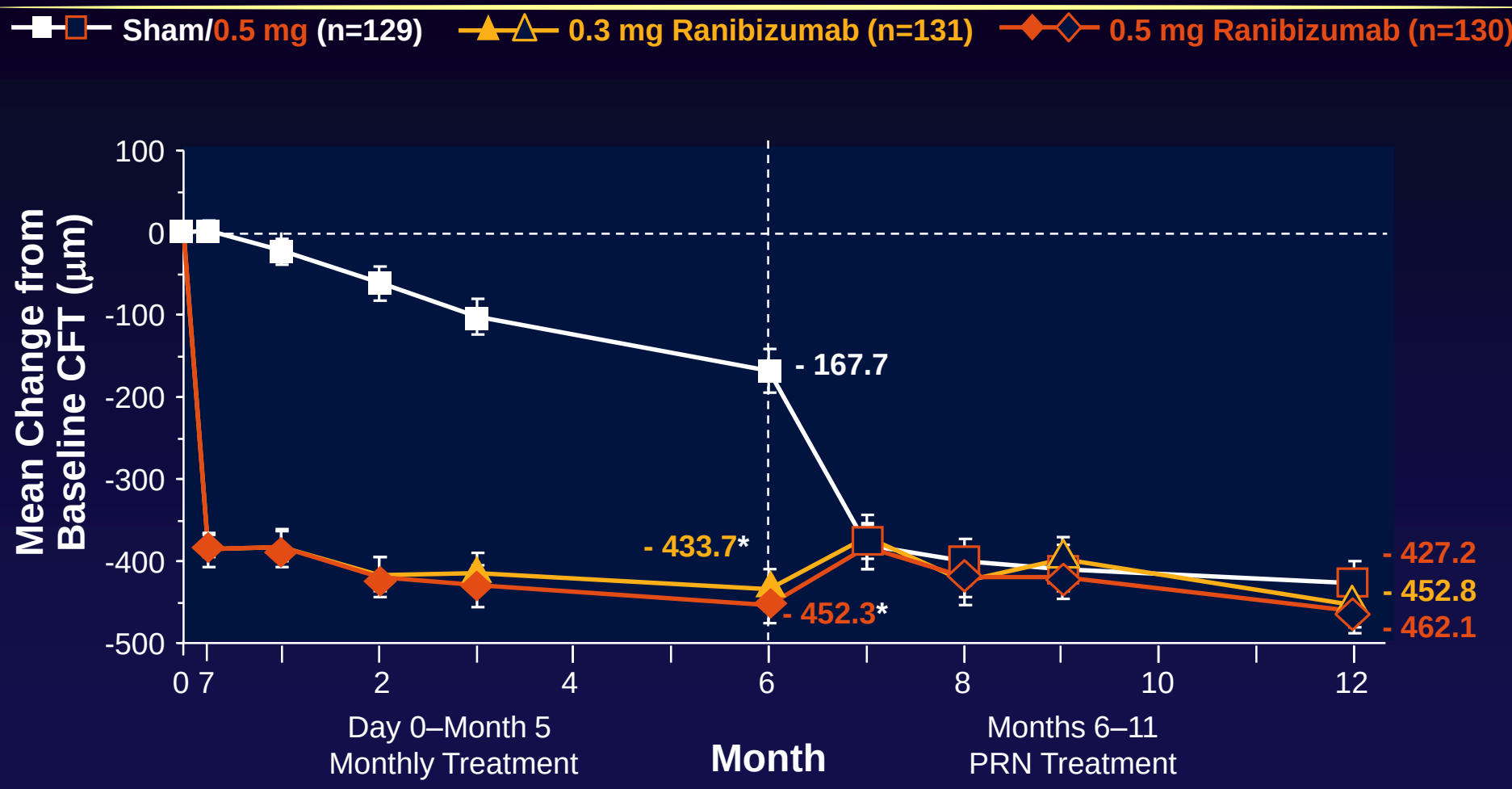
Allergan Data on File.

CRUISE Proportion of Patients who Gained ≥15 Letters from Baseline BCVA



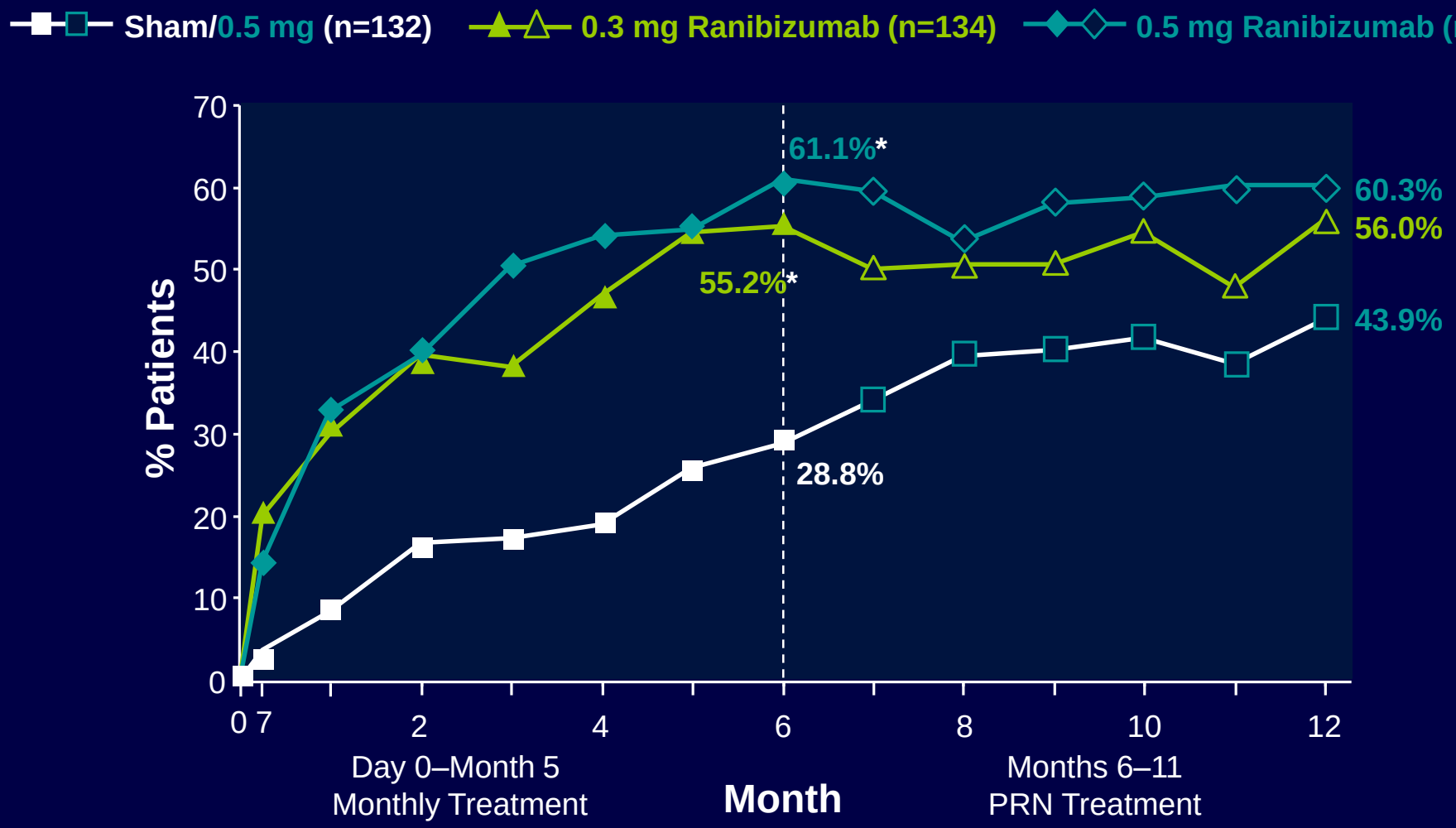
*P<0.0001 vs. sham (prespecified secondary endpoint). Ranibizumab vs. sham P<0.0001 at D7 and Months 1–5 (post hoc analyses). P values for 0.3 mg and 0.5 mg groups vs. sham/0.5 mg group at Month 12 were not calculated.
BCVA=best-corrected visual acuity, ETDRS=Early Treatment Diabetic Retinopathy Study.

CRUISE Mean Change from Baseline CFT over Time to Month 12



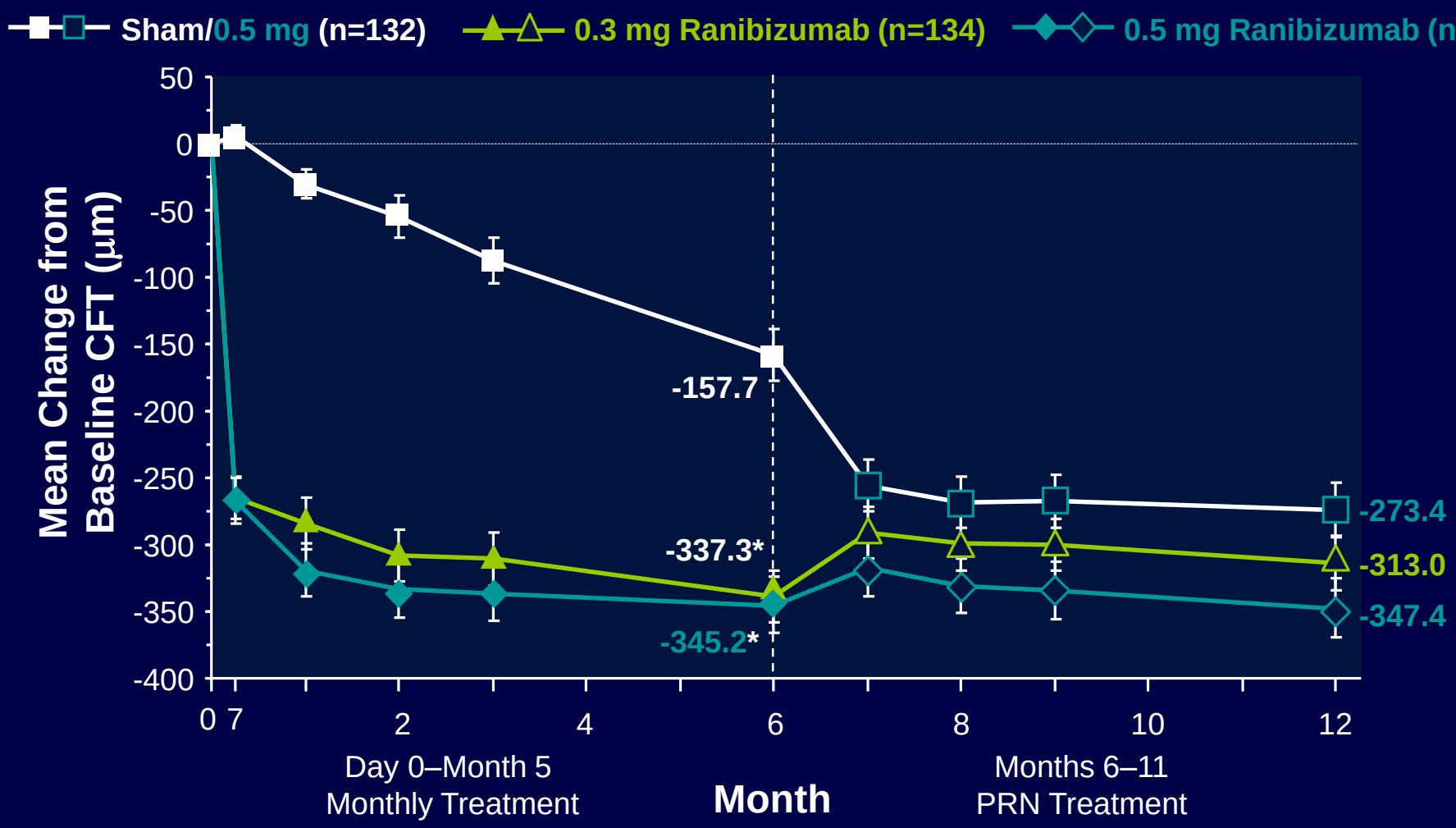
*P<0.0001 vs. sham. P values for 0.3 mg and 0.5 mg groups vs. sham/0.5 mg group at Month 12 were not calculated. Earliest statistically significant difference at Day 7. Vertical bars are ±1 standard error of the mean. CFT=central foveal thickness.

BRAVO Proportion of Patients who Gained ≥15 Letters from Baseline BCVA



*P<0.0001 vs. sham (prespecified secondary endpoint). Ranibizumab vs. sham P<0.005 at D7 and Months 1–5 (post hoc analyses). P values for 0.3 mg and 0.5 mg groups vs. sham/0.5 mg group at Month 12 were not calculated. BCVA=best-corrected visual acuity, ETDRS=Early Treatment Diabetic Retinopathy Study.

BRAVO Mean Change from Baseline CFT over Time to Month 12



*P<0.0001 vs. sham. P values for 0.3 mg and 0.5 mg groups vs. sham/0.5 mg group at Month 12 were not calculated. Earliest statistically significant difference at Day 7. Vertical bars are ±1 standard error of the mean. CFT=central foveal thickness.

What's the difference??

- **OZURDEX**, dexamethsone implant
- 23 g needle, local anaesthetic or topical,
- lasts for 6 months? Repeat x 2-3
- Increased incidence of cataract and glaucoma

- **Lucentis and Eylea:** 30g needle, topical, monthly injections for several months and then PRN or bimonthly regime to maintain vision
- Expensive and time consuming

- **Both can give a false sense of security especially with CRVO**

- **There is always a role for laser in retinal ischaemia**

Capillary Nonperfusion (CNP) in retinal vein occlusion

- **Amount at baseline variable**
  - Perfused RVO= little CNP
  - Nonperfused RVO= extensive CNP
- **CNP tends to increase over time**
  - Conversion of perfused to non perfused RVO
  - In clinical trials, measurements show increase over time of CNP
  - One third of non ischaemic CRVO will become ischaemic
- Experimental Question – How do anti VEGFs affect CNP?

Why does capillary non perfusion (CNP) increase over time?

- Old theory – Worsening of occlusion
- New finding – Blockade of VEGF suppresses the progression of retinal ischaemia (CNP)
- This indicates that VEGF plays a role in worsening of CNP
- Possible explanation: VEGF promotes leukostasis and capillary plugging

Conclusions ??

- Intravitreal injections of NICE approved anti VEGFs suppress progression of CNP in patients with RVO
- Aggressive treatment with anti VEGFs after RVO may blunt the overall severity of disease
  - Prevents “perfused to nonperfused conversion”
  - May act in concert with reduction in edema to improve visual outcomes
  - May reduce the duration of treatment required by interrupting a positive feedback loop
- Provides an explanation for the previous observation that the level of VEGF in aqueous at baseline has an inverse correlation with visual outcome

Many dosing regimens utilised in clinical practice

Fixed dosing -> potential to over or under-treat

- Monthly
  - most extensively studied regimen
- Bimonthly
  - limited real world data to date
- Quarterly
  - ? evidence indicates this is not an effective approach for all patients

Flexible dosing -> preferred approach, optimal treatment for each individual patient

- PRN
  - follows an initiation phase
  - definitions of when to retreat vary from study to study
  - can be ‘capped’, ensuring a minimum frequency of retreatment
- Observe and Plan
- Treat and extend
  - designed to mimic clinical practice
  - More RCT evidence needed

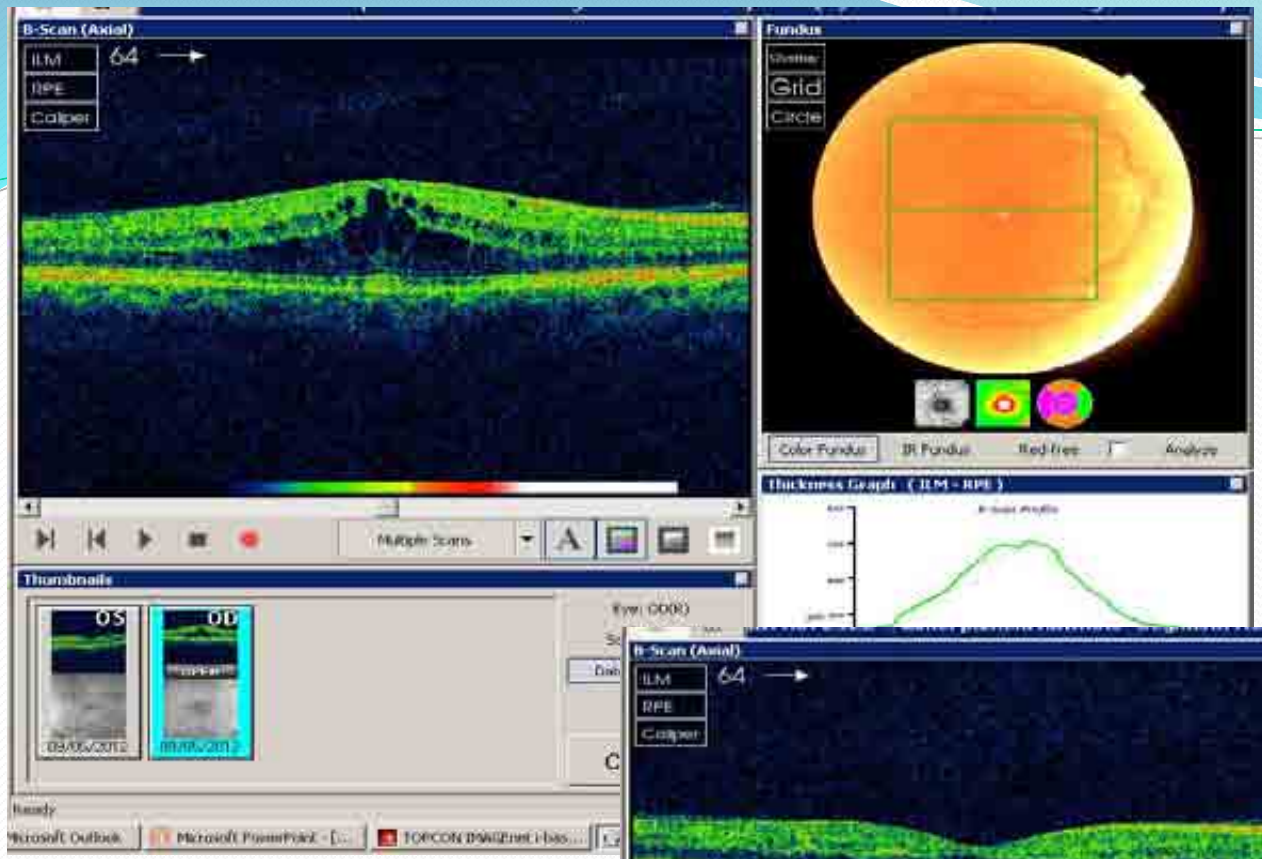
PRN, pro re nata

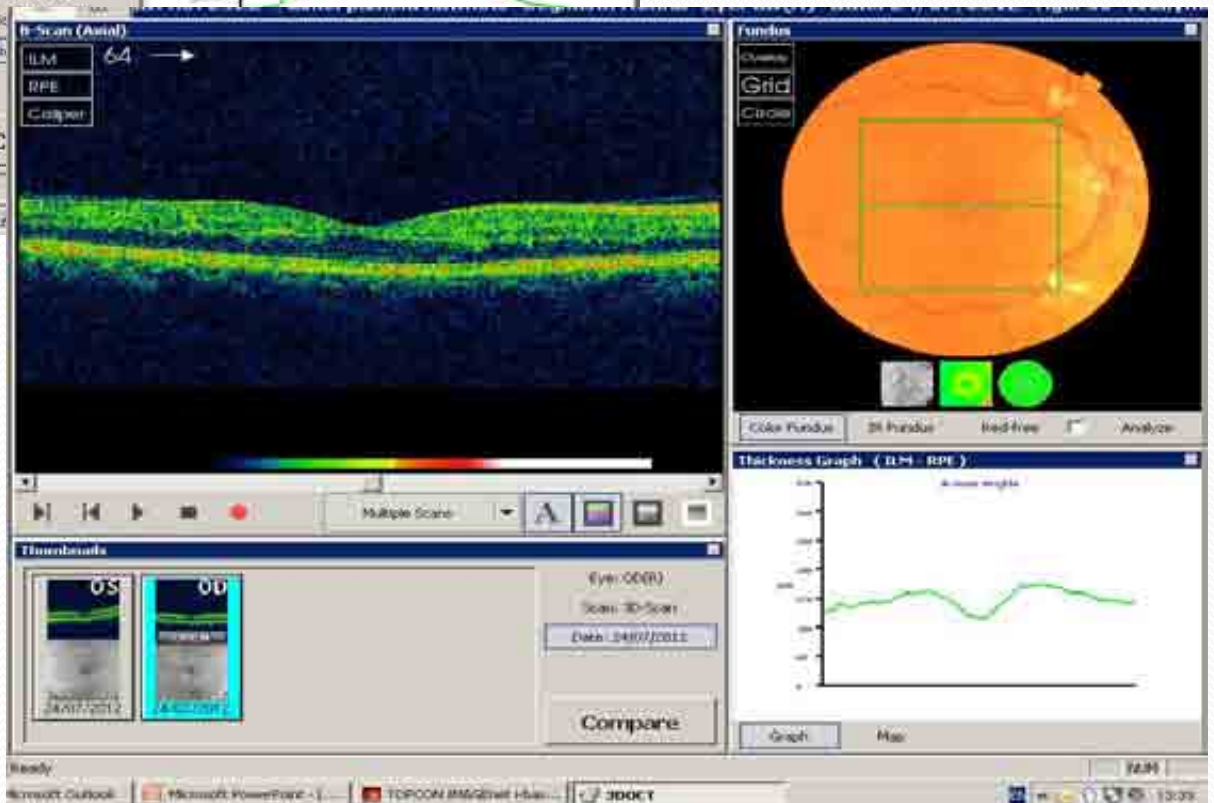
Safety?

- Anti-vegfs will overcome blood retinal barrier and enter systemic circulation
- safety data from trials-

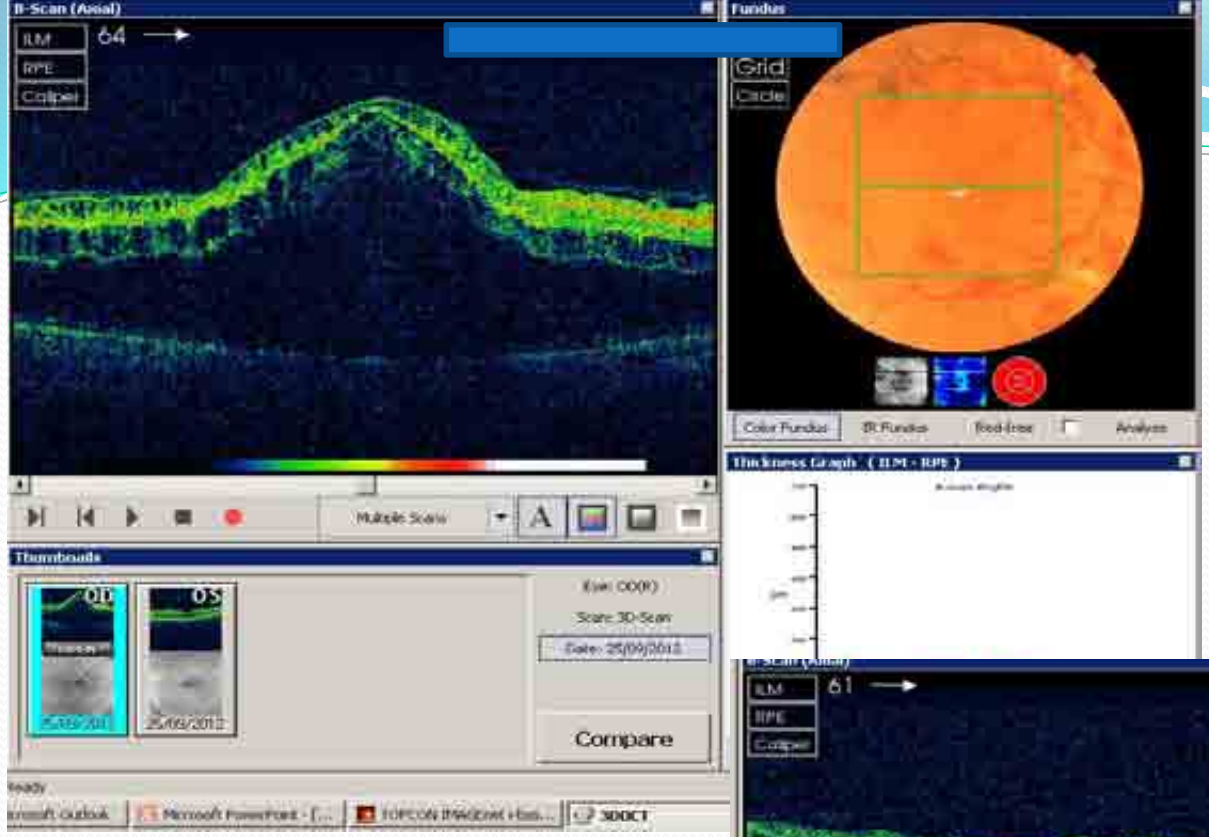
- **systemic adverse events**
- Both arterio thrombotic events and cerebrovascular events were recorded
- Rate of AE varied in the different clinical trials

- **however**
- the AE risk is sufficiently low when compared to natural incidence of arterial thrombotic and cerebrovascular events in the category of elderly patients

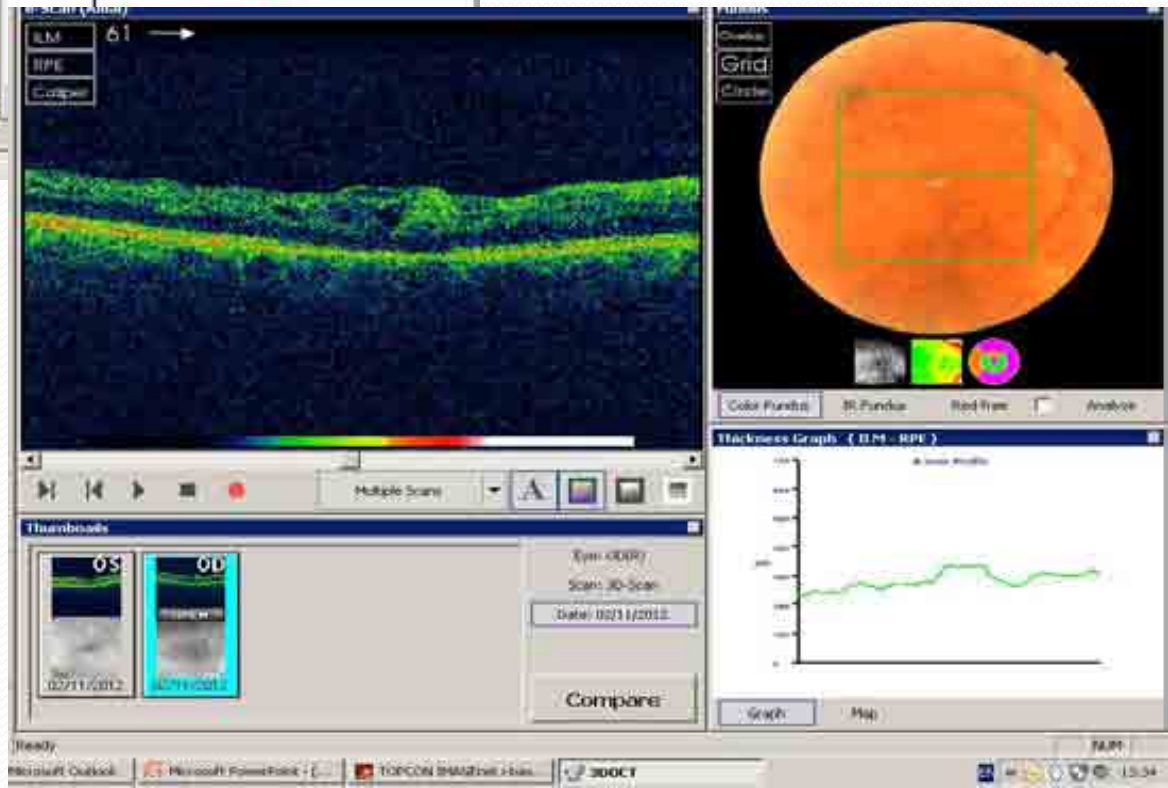


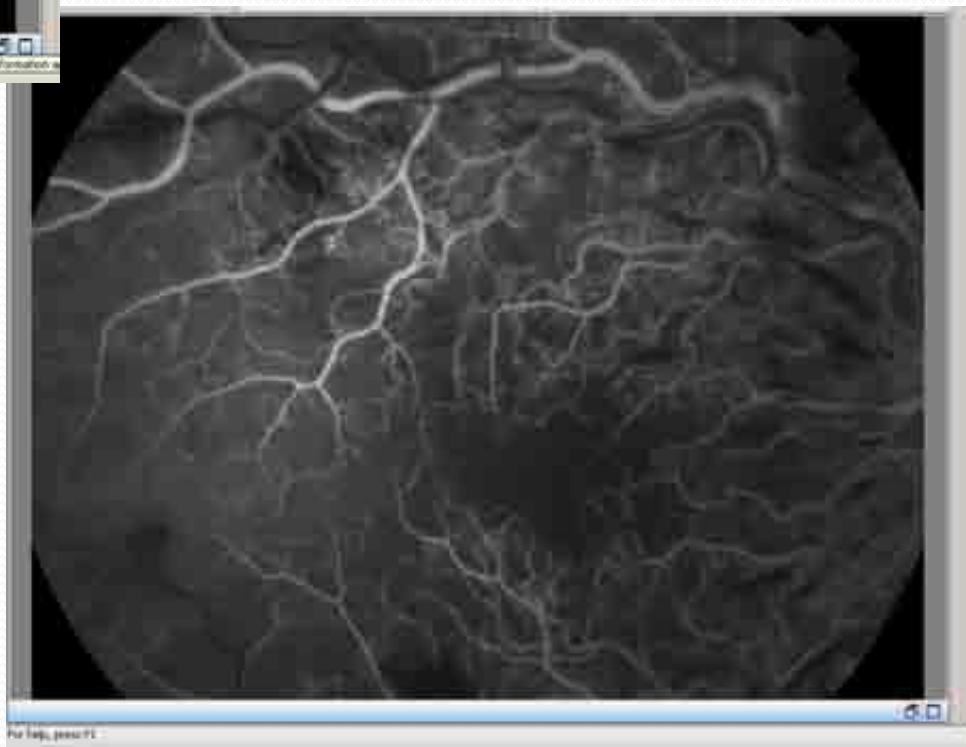


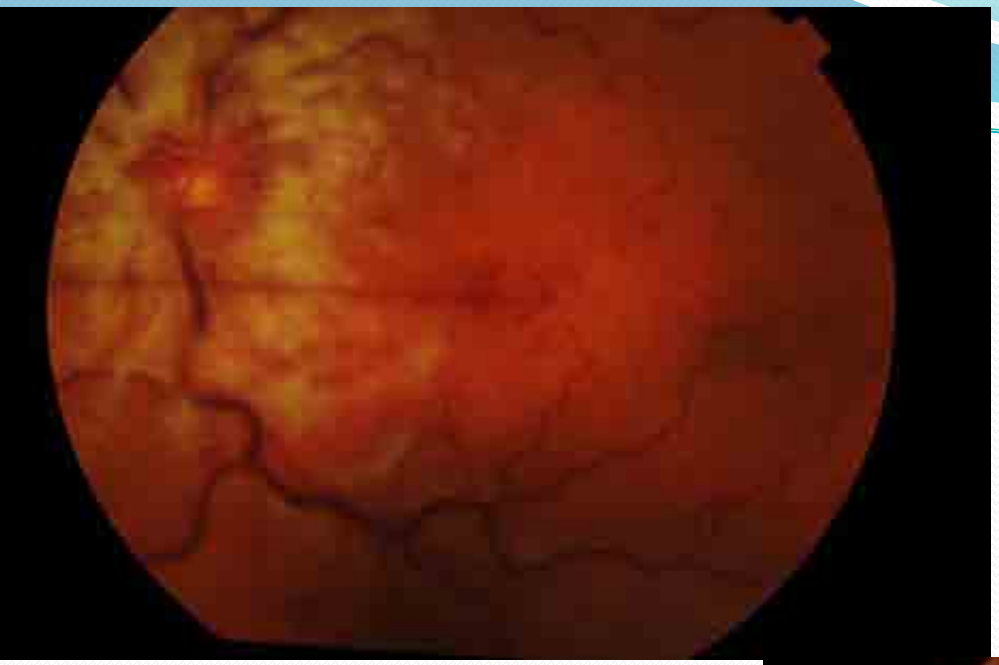
Treatment issues !!
Type 2 diabetic on tablets
66, hypertensive,
good BSL and BP.
Va 6/18



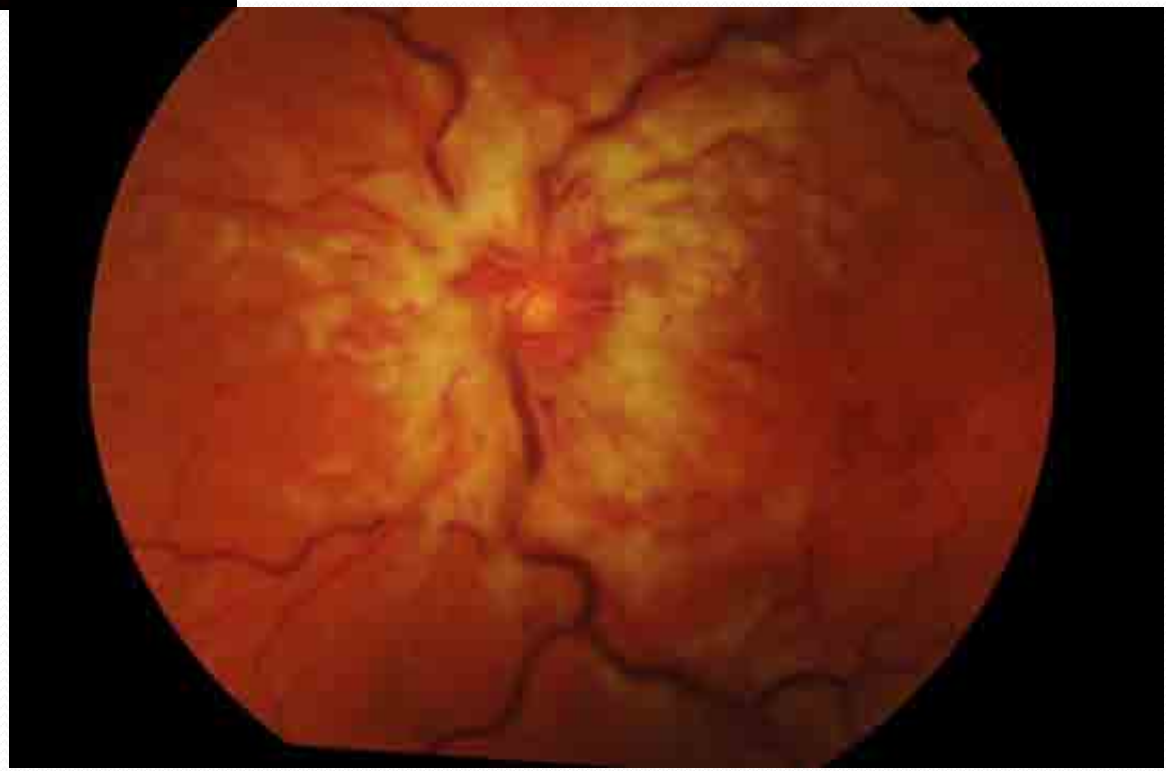
Massive return of macular oedema with retinal ischaemia and development of rubeosis. Va 3/60

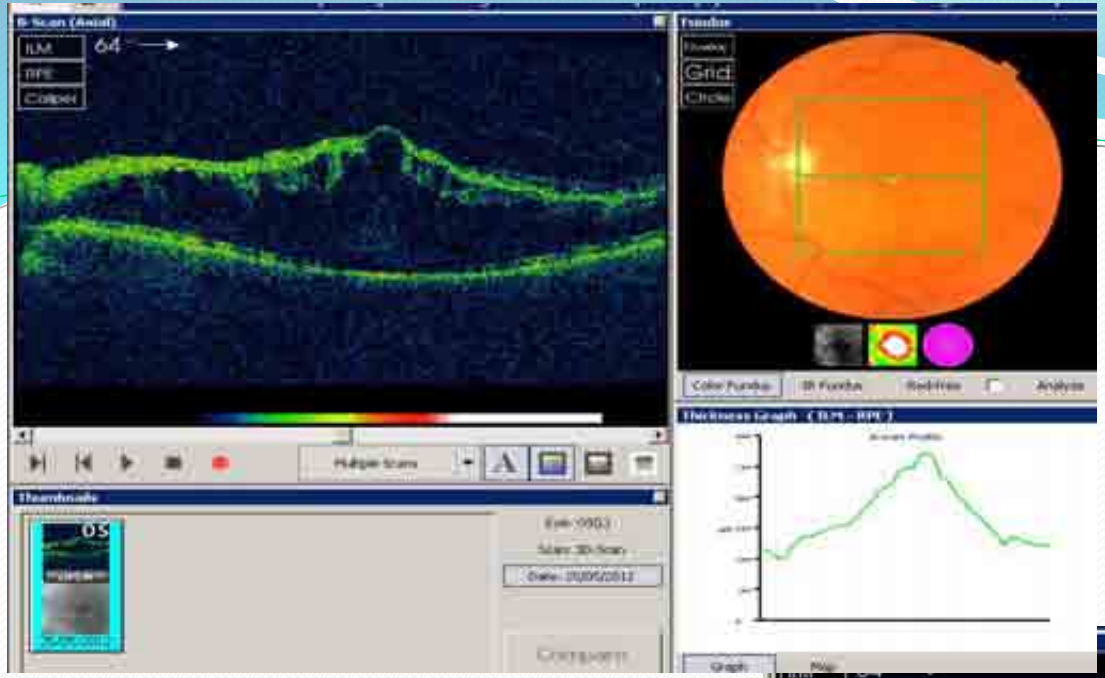






Male- -5o years. CRVO and papillophlebitis
phakic
hyperlipidaemia and
hyperhomocysteinaemia
ocular hypertension
3/60 at presentation Nov 2011
to 6/10 - 15 months
treated with systemic steroids and Avastin
18 months to stabilise




B-Scan (Axial)
ILM
RPE
Caliper
64
Fundus
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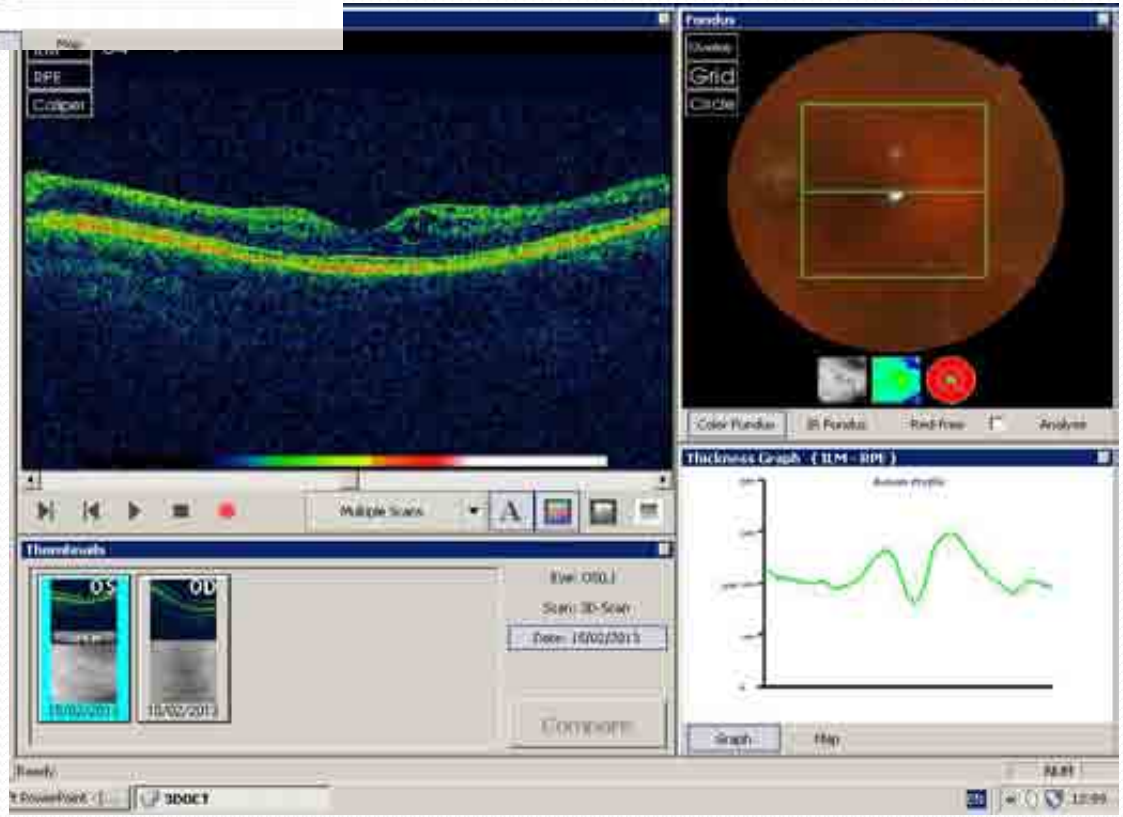
IR Fundus
Red-Free
Analyze
Thickness Graph (ILM - RPE)
Multiple Scans
Thumbnails
OS
Compare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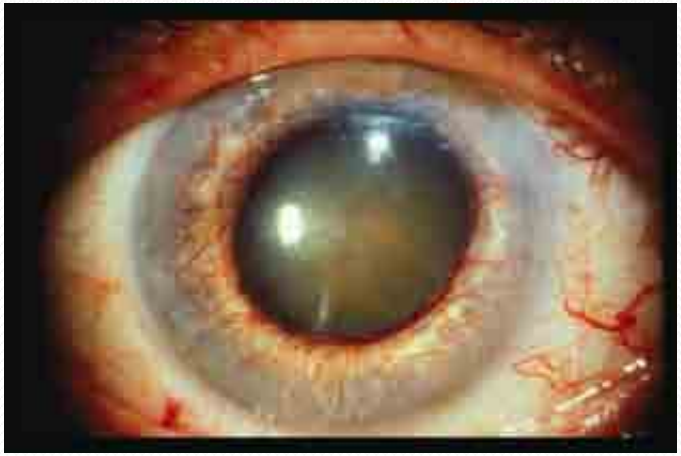
IR Fundus
Red-Free
Analyze
Thickness Graph (ILM - RPE)
Multiple Scans
Thumbnails
OS
OD
Compare
Graph
Map

RVO can be devious !!
48 years old medic, BRVO
hypertensive
6/5 at presentation. No oedema
dense vitreous haem despite adequate laser,
vitrectomy !! Lensectomy !!

AVASTIN - Bevacizumab

- no longer widely used now that we have NICE drugs
- to aid in the regression of Rubeosis (higher risk in the elderly patient with CRVO and significant capillary non perfusion)
- As an adjunct to diabetic vitrectomy
- non clearing vitreous haem.
- Persistent proliferative disease in the context of adequate laser



Summary of treatment of retinal vein occlusion disease

- The use of all anti-vegfs and intravitreal steroids
- Results in speedier resolution of retinovascular macular oedema than laser or observation
- With resulting increase in visual acuity
- rapid decrease in central retinal thickness which allows the retina to resume anatomical normality
- Especially if treatment is initiated early

However

- All modalities require repeat treatments over months or years
- they do not negate the need for retinal laser
- massive increase in procedure workload and monitoring of the patient
- **Systemic risk factors still need to be investigated and controlled**

- patient refractory to one mode of treatment may benefit from another