# Lucentis and Avastin in Diabetic Retinopathy

Professor Jonathan Gibson

Aston University and Birmingham Heartlands Hospital

# Declarations

- I have received research funding and consultancy fees from Novartis UK, Bayer UK, Allergan, Pfizer and Alimera.

- I have sat on the NICE appraisal panels representing RCOphth and RNIB.

# Lucentis and Avastin – what you need to know

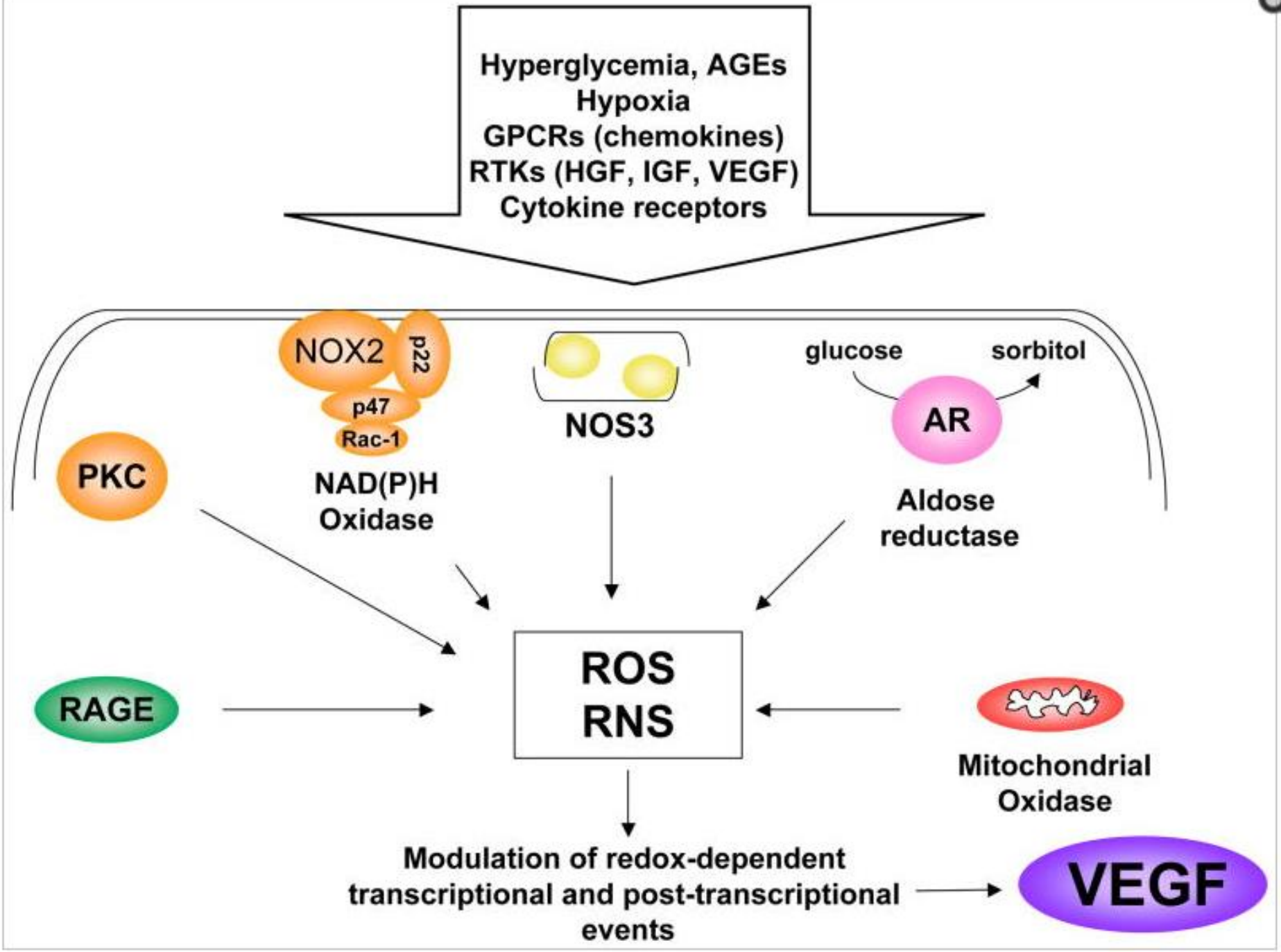
- What are they?
- Similarities but important differences
- How are they given?
- Indications for use  DR?
- What is the evidence?
- A case example
- Future developments.

# What are they?

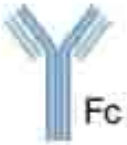
- Lucentis = ranibizumab
- Avastin = bevacizumab
- Both are humanised monoclonal antibodies against vascular endothelial growth factor (Anti-VEGF)
- *-mab = monoclonal antibody*
- *-zu = humanised*

# VEGF (VASCULAR ENDOTHELIAL GROWTH FACTOR)

- VEGF protein important in repair of tissues
- VEGF in vivo promotes angiogenesis and increased permeability of retinal blood vessels
- Deregulated, abnormal VEGF expression is found in tumours, retinal disorders etc
- VEGF A is important isoform


Hyperglycemia, AGEs
Hypoxia
GPCRs (chemokines)
RTKs (HGF, IGF, VEGF)
Cytokine receptors
NOX2
p22
p47
Rac-1
NAD(P)H
Oxidase
NOS3
glucose
sorbitol
AR
Aldose
reductase
PKC
RAGE
ROS
RNS
Mitochondrial
Oxidase
Modulation of redox-dependent
transcriptional and post-transcriptional
events
VEGF

# Lucentis and Avastin – similar but important differences.

| | Ranibizumab | Aflibercept | Bevacizumab |
|---|---|---|---|
| Size | 48 kDa[25] | 97-115 kDa[27] | 149 kDa[30] |
| Structure | Antibody fragment  | Recombinant fusion protein  Fc domain | Full-length antibody  Fc domain |
| Target | All VEGF-A isoforms[26] | All VEGF-A isoforms, VEGF-B and placental growth factor[27] | All VEGF-A isoforms[30] |
| Half-life in humans | | | |
| Ocular | 9 days[25] | Unknown | 6.7 days[31] |
| Systemic | ~2 hours[25] | 4-5 days[28,29] | 20 days[30] |

Safety of antivegf therapy. Ophthalmology Times Europe, Supplement, July-Aug, 2013

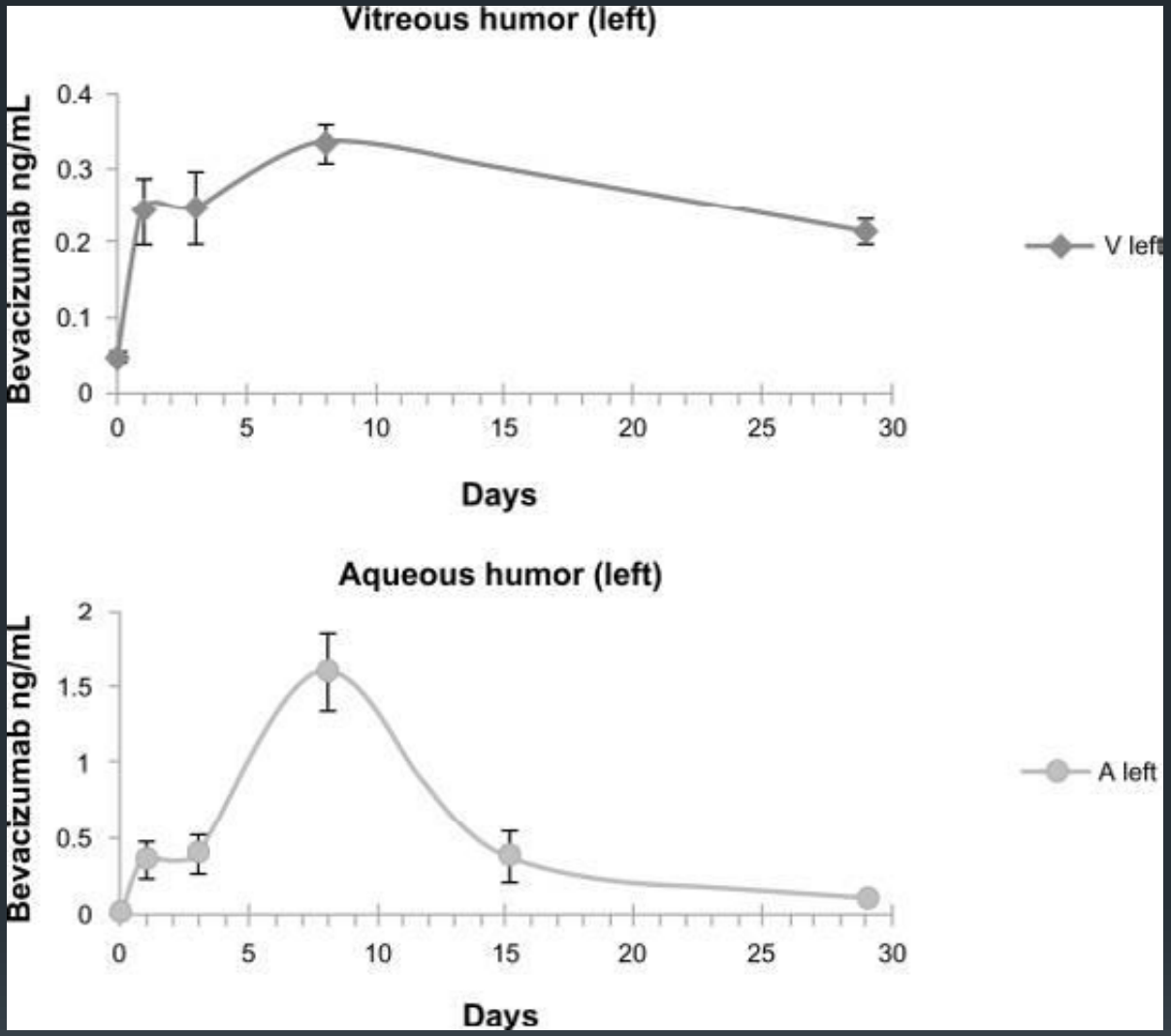
## Ranibizumab

- *LUCENTIS*
- Developed for ocular use only
- Given by intravitreal injection
- Licensed for eye use
- NICE approved
- Expensive drug c.£420
- Extensive evidence
- Safety data and post marketing surveillance programme.
- No safety concerns

## Bevacizumab

- *AVASTIN*
- Developed for bowel cancer
- Given by intravitreal injection
- Unlicensed for eye use

- Not appraised by NICE
- Cost variable £5-100
- Extensive use but limited evidence
- Limited safety data; no post marketing surveillance
- Probably equally effective as ranibizumab
- Some safety concerns



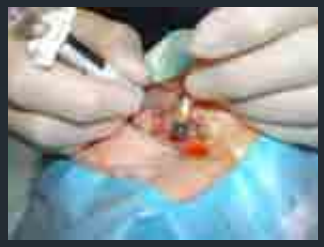

Avastin is systemically absorbed and appears in circulation after intravitreal injection

Bevacizumab concentration in the vitreous and the aqueous humor of the noninjected left eye after intravitreal injection of 1.25 mg/0.05 mL bevacizumab into the fellow eye. Values at day 0 indicate background levels of bevacizumab detection in control animals.

**Pharmacokinetics of intravitreal bevacizumab (Avastin®) in rabbits**

Christos I Sinapis,[1*] John G Routsias,[2*] Angelos I Sinapis,[1*] Dimitrios I Sinapis,[1*] George D Agrogiannis,[3] Alkistis Pantopoulou,[1] Stamatis E Theocharis,[4] Stefanos Baltatzis,[5] Efstratios Patsouris,[3] and Despoina Perrea

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3104800/ *J Ocul Pharmacol Ther 2011*



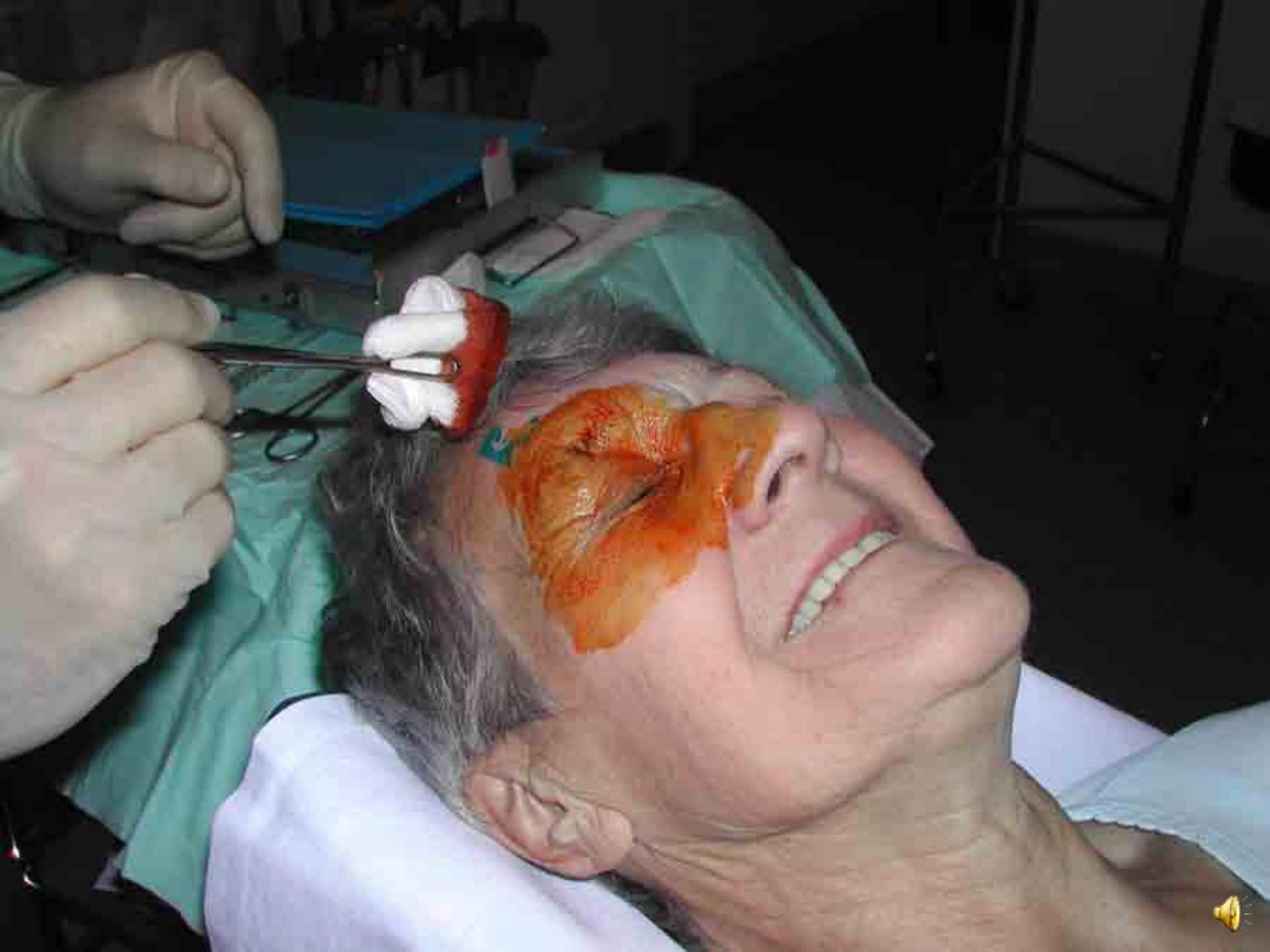
# Potential systemic worries with anti-VEGF's

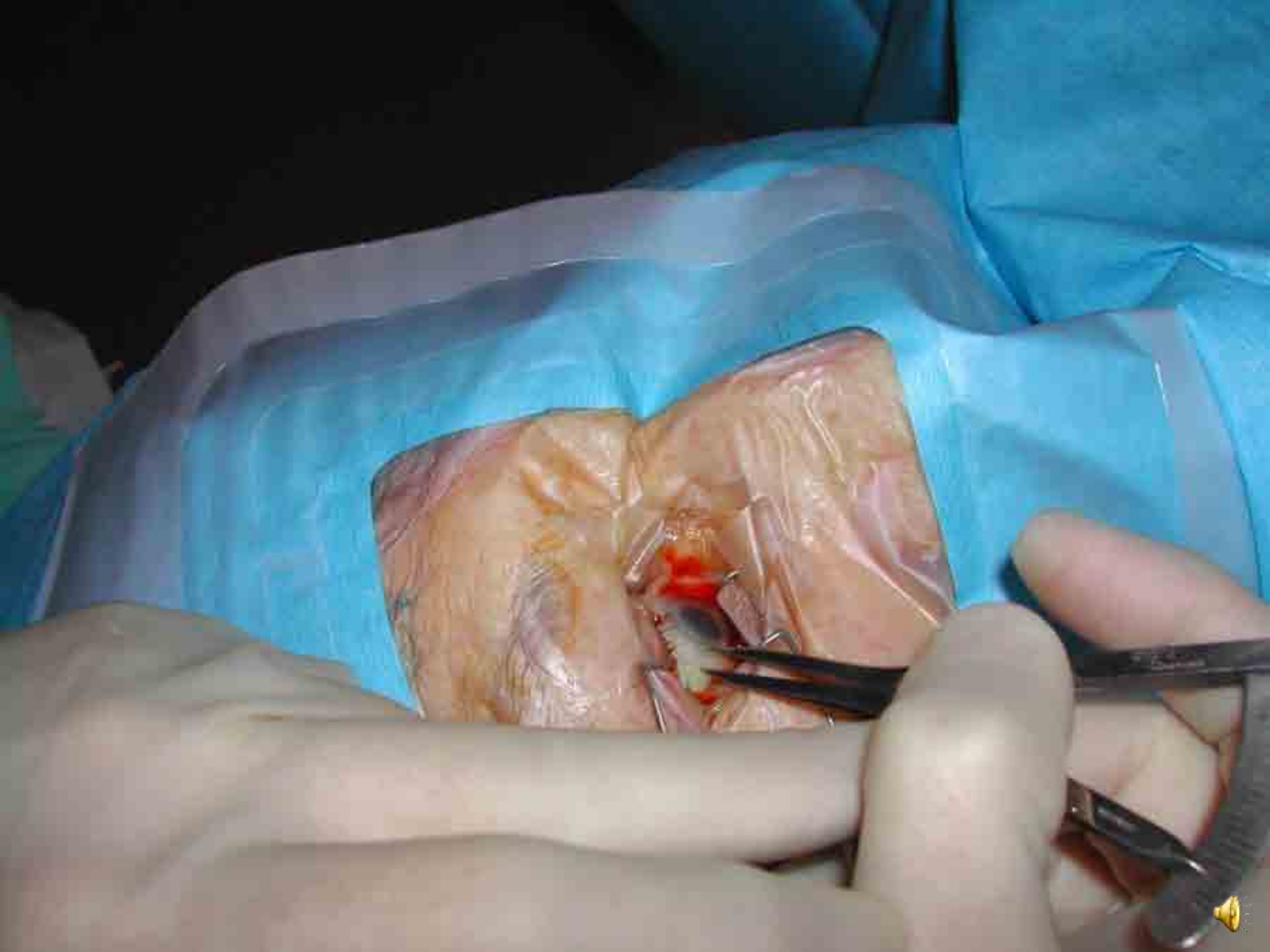
- We know from AMD….Both drugs are safe but…
- Increase risk of CVA, Myocardial Infarction and Arterio-Thrombotic effects
- In view of systemic absorption of more concern in Avastin
- Increased risks of untoward gastro-intestinal events with Avastin.
- What about in diabetic patients?
- Long term safety issues in diabetic patients-cardiovascular/cerebrovascular events. No significant adverse safety signals to date

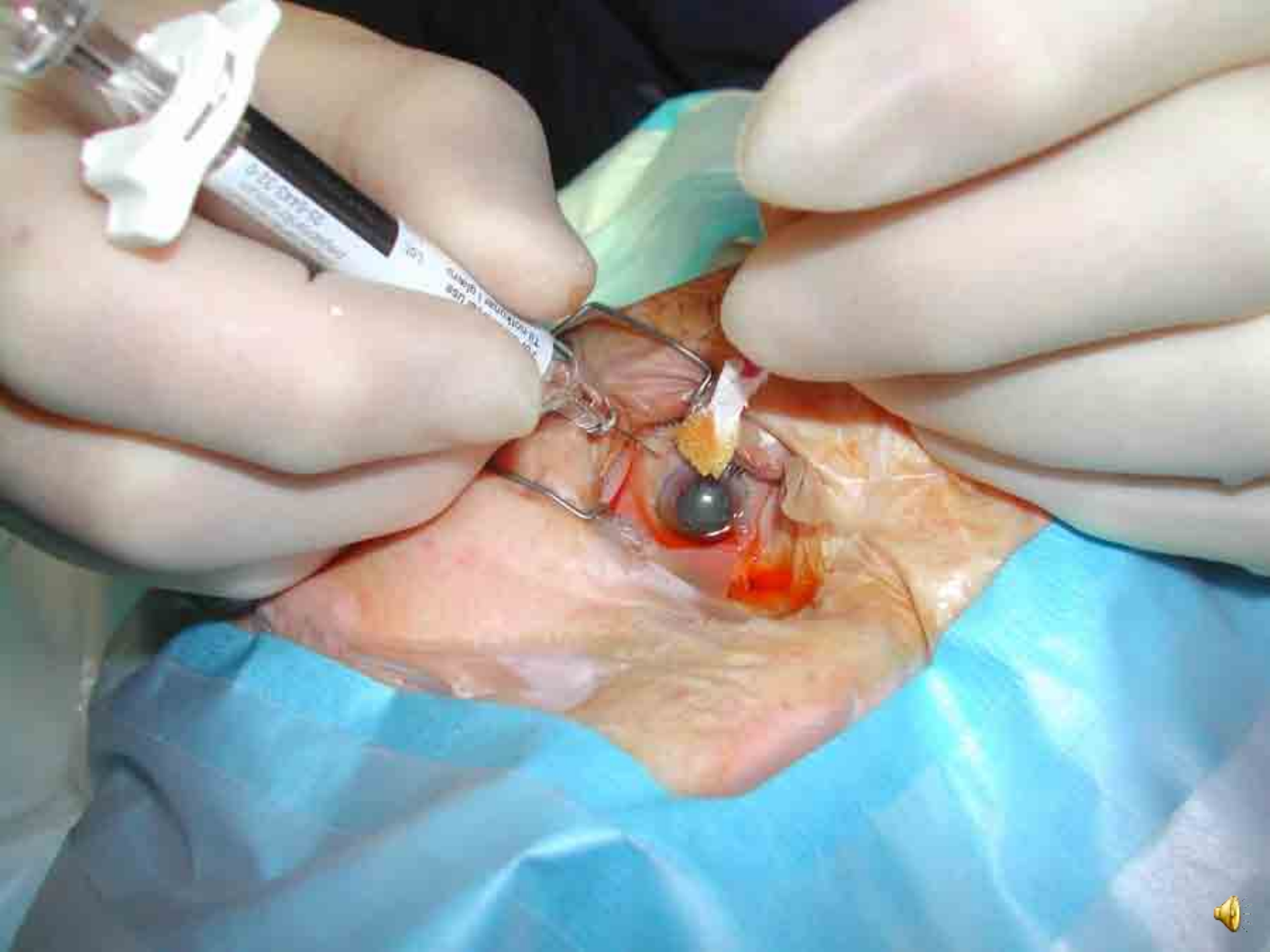
# How are anti-VEGF's given?

- Intravitreal injection of drug is most effective way of delivering drug to retina.
- Given in a clean room with local anaesthesia drops
- Safe and effective

- Potential risks:
- Endophthalmitis 1 in 1000
- Haemorrhage intraocularly – rare
- Cataract from lens trauma – rare
- Systemic side effects – probably rare







# How effective are they?

- Clinical trials
- A case report

# The Diabetic Retinopathy Clinical Research Network

Randomized Trial Evaluating Ranibizumab Plus Prompt or Deferred Laser or Triamcinolone Plus Prompt Laser for Diabetic Macular Edema

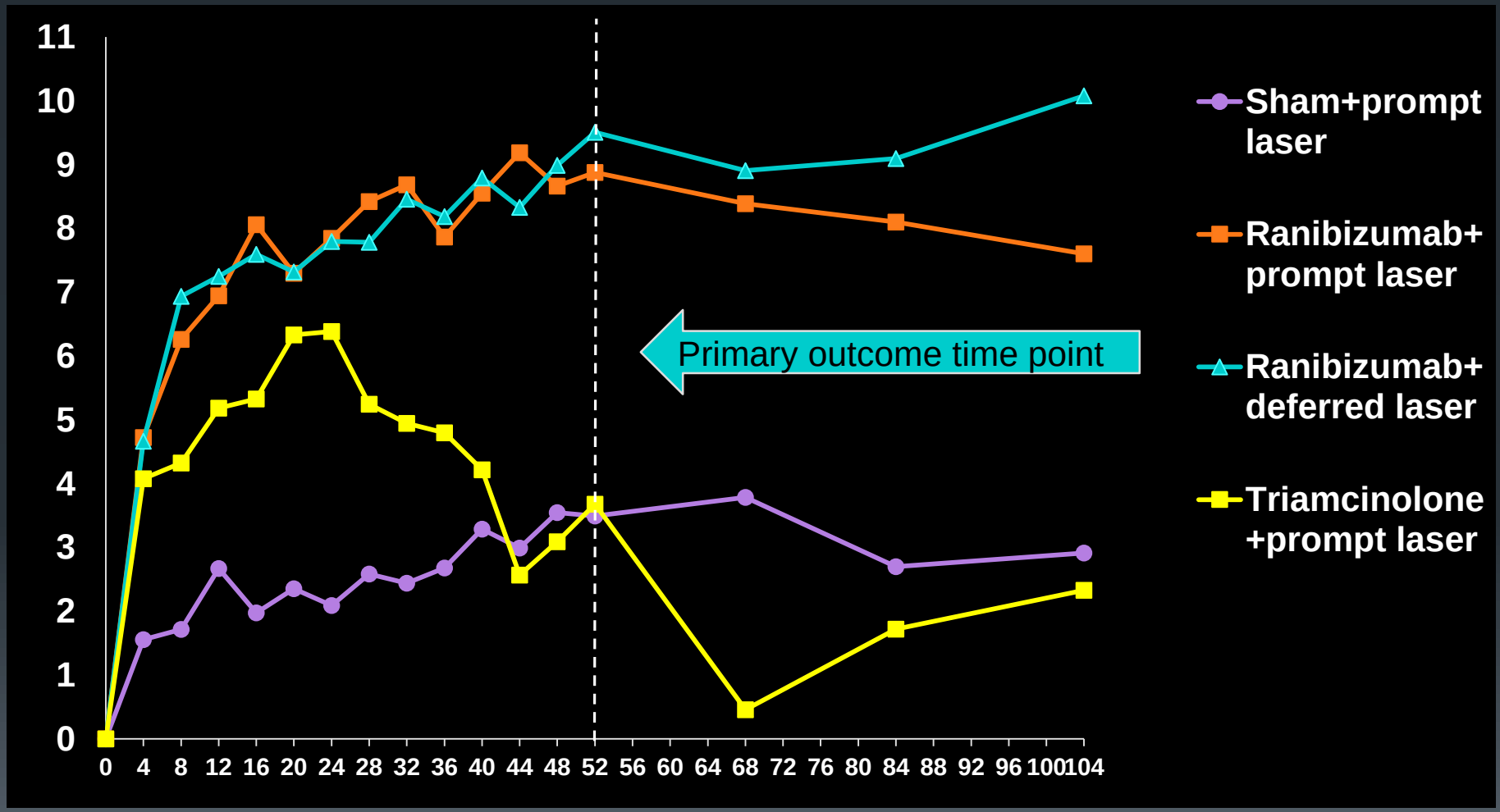

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Eye Institute


Supported through a cooperative agreement from the National Eye Institute and the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services EY14231, EY14229, EY018817



# Study Rationale

- To determine if anti-VEGF therapy alone or in combination with laser, or if triamcinolone in combination with laser, might result in improved outcomes compared with laser alone for treatment of DME, the DRCR.net designed a clinical trial to evaluate 3 treatment modalities for DME in comparison with focal/ grid laser:
  - Intravitreal ranibizumab+prompt (within 1 week) focal/grid laser
  - Intravitreal ranibizumab + focal/grid laser deferred for at least 24 weeks
  - Intravitreal triamcinolone+prompt (within 1 week) focal/grid laser




* Values that were ±30 letters were assigned a value of 30

*P*-values for difference in mean change in visual acuity from sham+prompt laser at the 52-week visit: ranibizumab+prompt laser <0.001; ranibizumab+deferred laser <0.001; and triamcinolone+prompt laser=0.31.

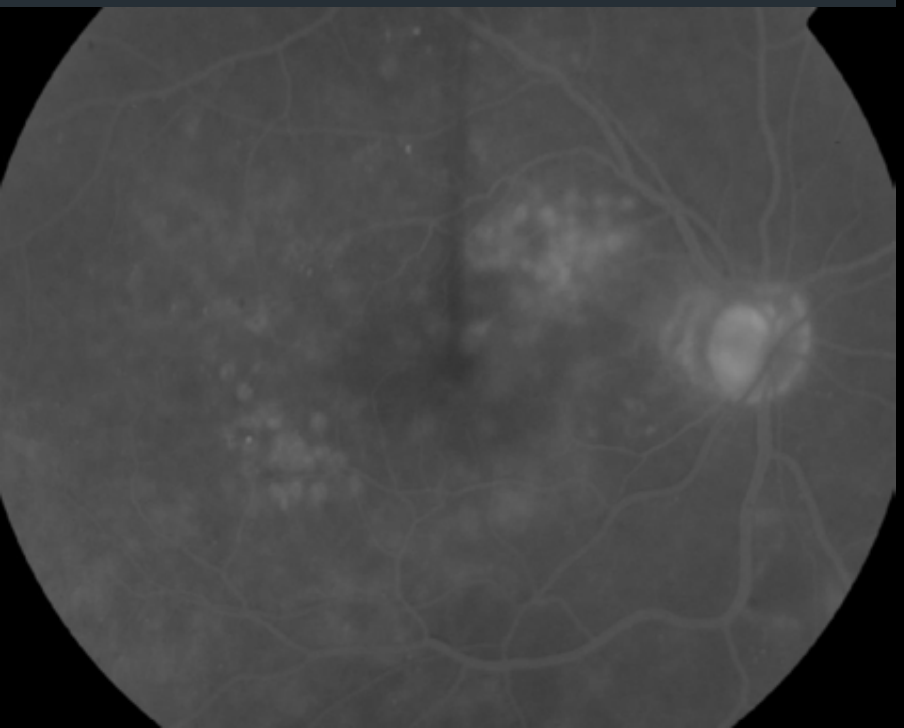
# PT – "the case of the diabetic groundsman"

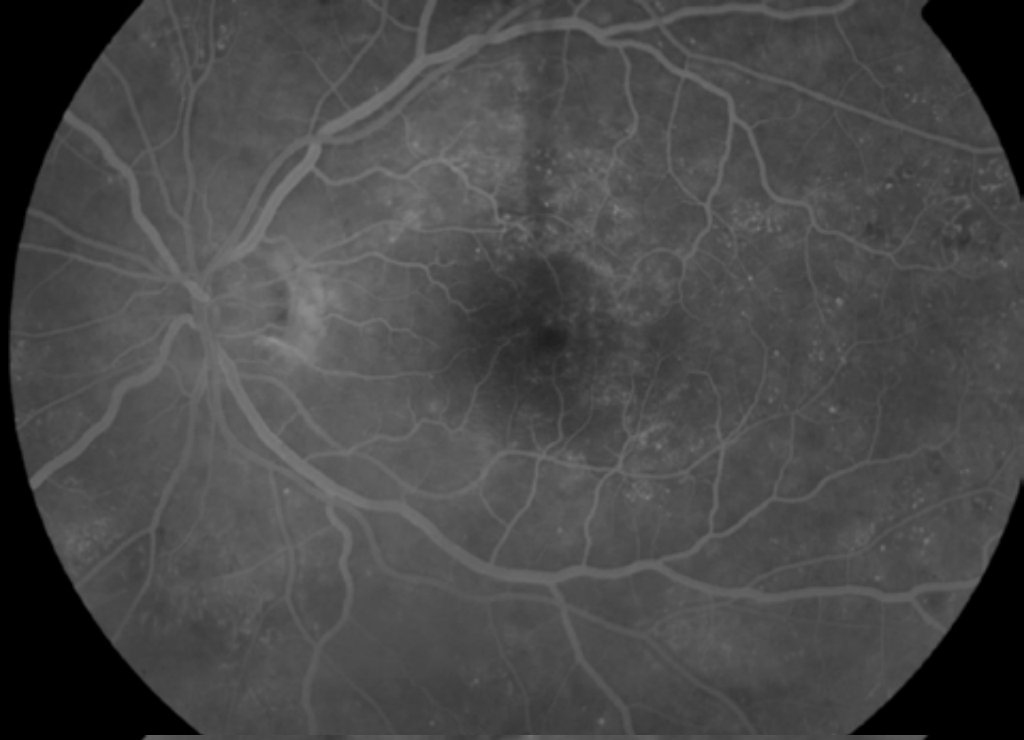
- 63 year old , male caucasian ,head groundsman at a local prep. school
- Type 2 diabetes for 15 years
- Reasonably well controlled with Gliclazide, Metformin.
- HbA1C 7.5-8.2

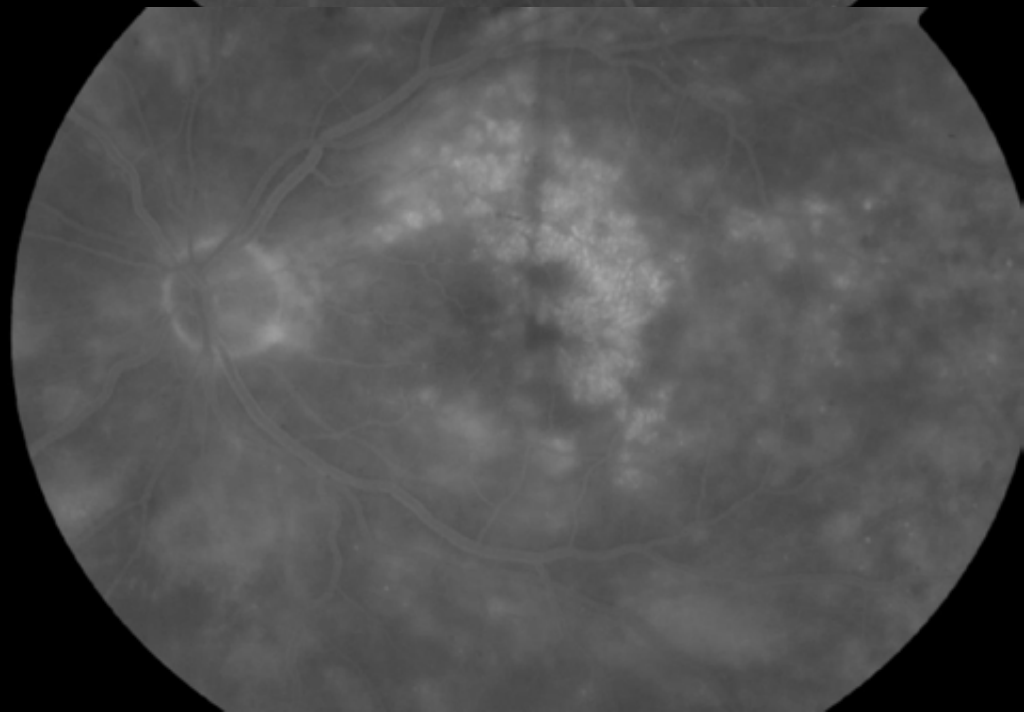
# History

- 2007 noted that he could not judge distances  well and crashed mower into cricket pavilion
- Headmaster slightly concerned – parents had reported seeing mower being driven erratically –Head suggested a visit to optometrist.
- Vision was 6/36 right, 6/7.5 LE
- Had diffuse DMO RE>LE
- Referred to HES

Previous laser to both maculae– difficult to get good response – gradual deterioration



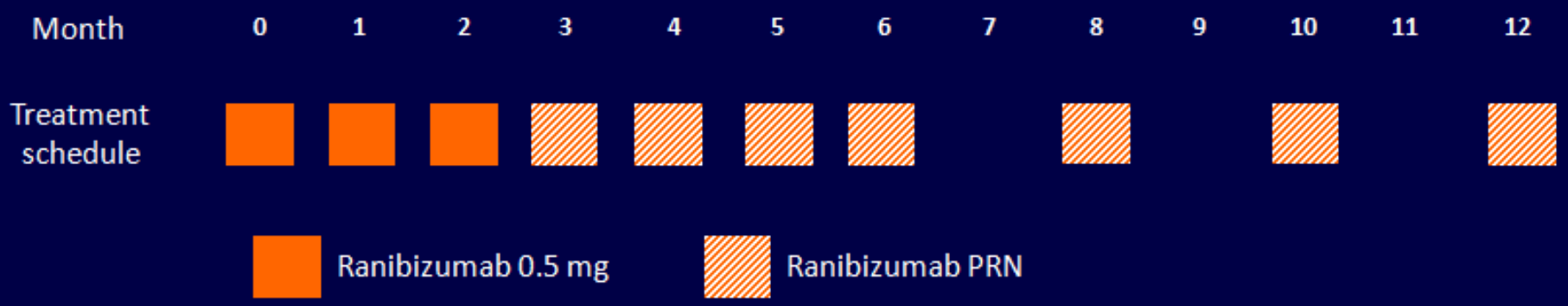




| Date | Right eye | Left Eye |
|---|---|---|
| 2007 | 6/36 Diffuse DMO - laser grids x2 | 6/9 some DMO – laser x1 |
| Nov 2007 | DMO – refractory to laser – vision problems RE IVTA (1) | Stable |
| Mar 2008 | RE IVTA (2) Some improvement in OCT after first IVTA but not much change after second. Vision 6/24 | Stable |
| Sep 2008 | Raised IOP RE - | Glaucoma diagnosed and drops |
| April 2009 | IOP uncontrolled and field loss worse – RE trab. | LE diffuse DMO worse – laser 6/12 |
| August 2009 | RE stable – cupped pale disc, glaucoma stable but cataract noted. Still DMO | LE vision 6/18 DMO worse |
| Sep-Nov 2009 | | LE treated with Avastin a 3 injections – vision improves to 6/12 DMO better |
| Jan –Dec 2010 | RE stable – listed for cataract op | LE deteriorating vision 6/12 part at best |
| Jan 2011 | RE phaco. Vision 6/36 post op BCVA | LE monitored “Observation” |
| May 2011 | RE 6/60, CRT 635um | LE 6/24 CRT 655um. Enrolled in RELIGHT Study – Left= Study Eye |
| May -2011 – Jan 2013 | RE 6/60 | LE 6/9, CRT = 320um |

SS12

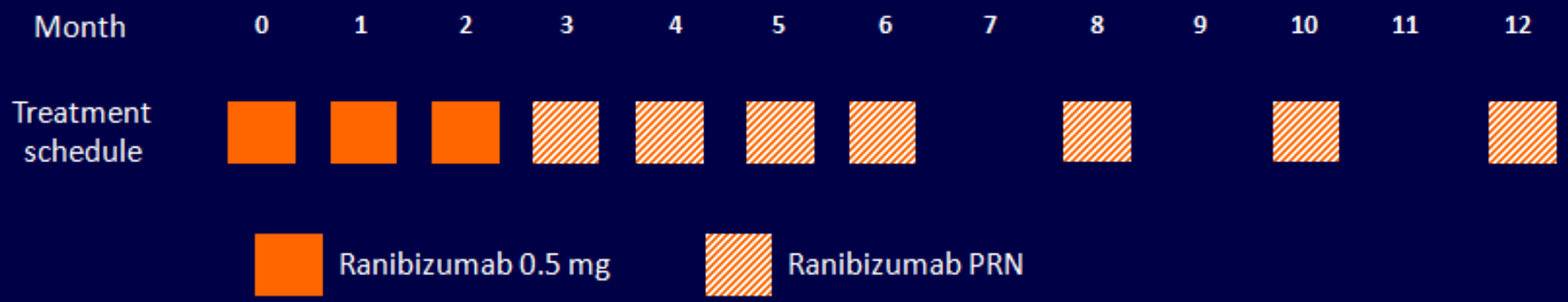
# RELIGHT study design




- Prospective, open-label, multicentre, single-arm, 18-month study to evaluate the efficacy and safety of ranibizumab 0.5 mg for the treatment of visual impairment due to DMO (N = 110)
- Retreatment criteria:
  - Residual central subfield retinal oedema (an OCT reading of ≥225 micrometers)
  - Increase in central subfield retinal oedema by >10% or 25 micrometers from the lowest in-study reading
  - No residual central subfield retinal oedema, but a total drop of 5 or more ETDRS letters from the in-study BCVA

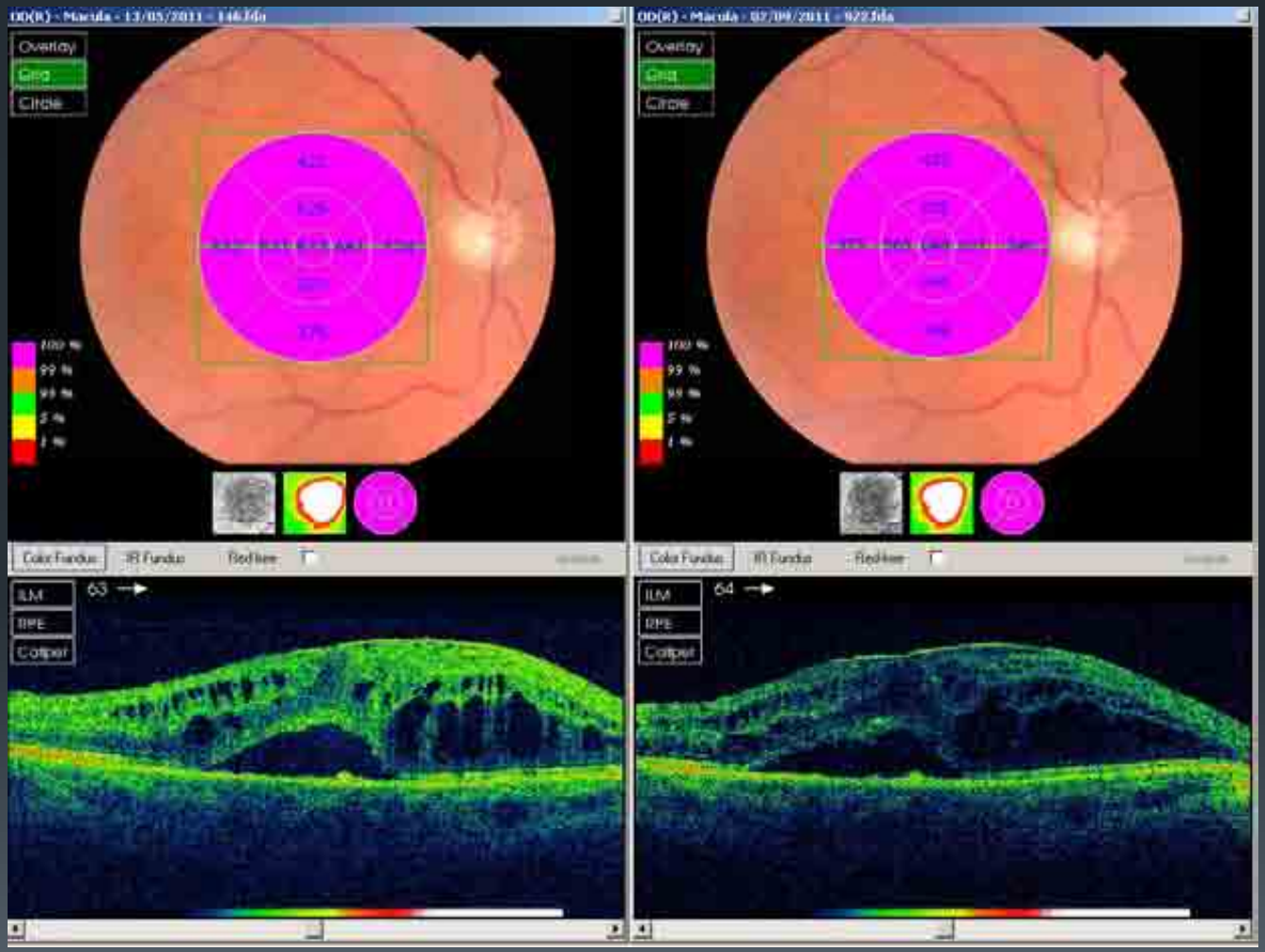
BCVA, best-corrected visual acuity ; PRN, *pro re nata* (as needed)

# Summary of key clinical results at month 12

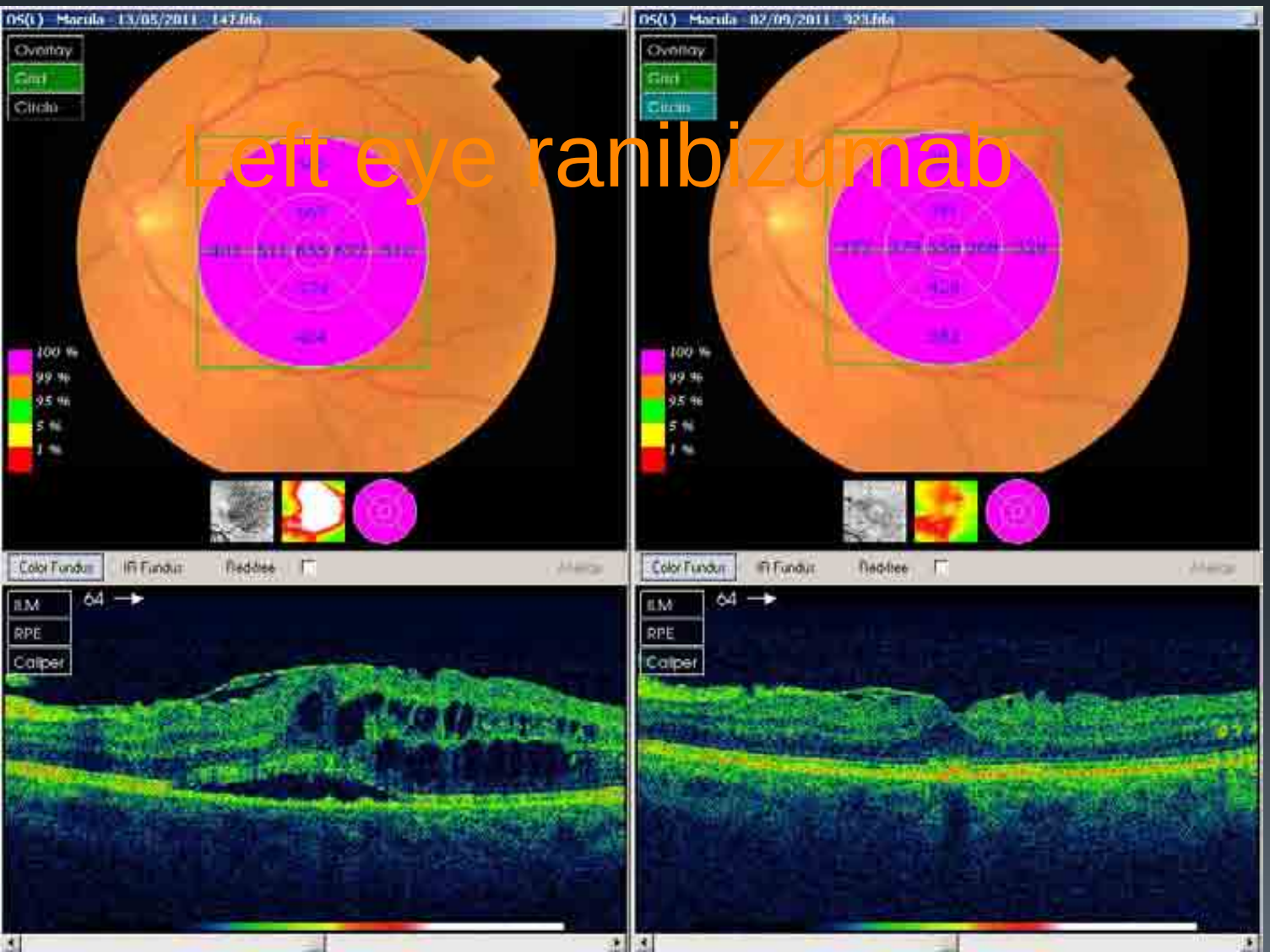



- BCVA improved from a baseline mean of 62.6 letters to 67.8 letters at month 12
  - Mean change: +5.2 letters
- Patients received a median of 7 injections over 12 months (range, 3-9)

BCVA, best-corrected visual acuity



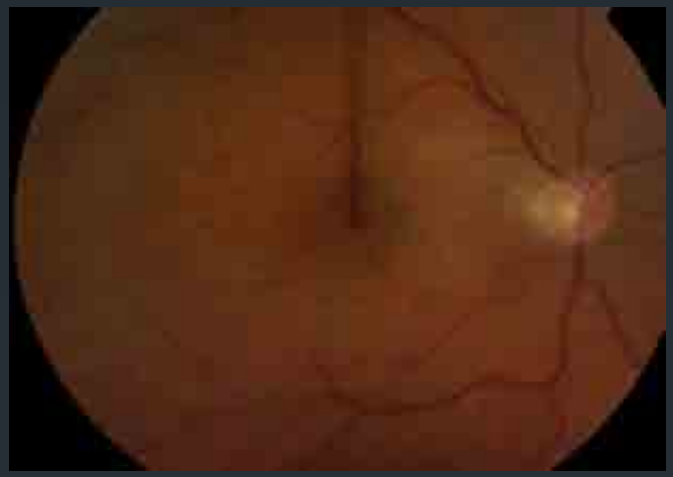

Vision right eye 6/60. Laser ineffective.

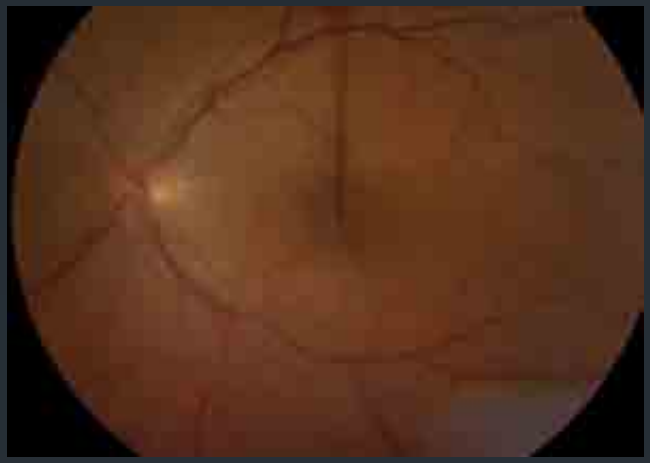



Left eye ranibizumab

Vision improved from 6/36 pt to 6/9. Patient reapplies for driving licence

# PT – what happened after RELIGHT?





| RE | LE |
|---|---|
| 8 Lucentis – treated when NICE approved Lucentis | 12 further Lucentis – treated on compassionate grounds at end of study |
| Vision 6/24-6/60 | Vision 6/9-6/18 |
| Trab working; Field loss stable | Able to drive |

# What have I leant from PT?

- Anti-VEGF's are optimal standard of care if indicated
- Steroids have a role but significant side effects
- Campaign on behalf of our patients
- Clinical trials have an important role in getting access to new treatments for our patients and may enhance future management.

# NICE Guidance

- NICE technology appraisals [TA274] Published date: April 2013

*Ranibizumab is recommended as an option for treating visual impairment due to diabetic macular oedema only if:*

- the eye has a central retinal thickness of 400 micrometres or more at the start of treatment **and**

- the manufacturer provides ranibizumab with the discount agreed in the patient access scheme revised in the context of this appraisal.

# AntiVEGF's in DMO – "a game changer"

- Patients with DMO assessed for diabetic care and control.
- Laser given if indicated – if focal leakage or exudate
- If laser ineffective or if CRT (central retinal thickness)>400um eligible for ranibizumab
- Avastin – issues – unlicensed
- Aflibercept new alternative
- Steroids to be considered if anti-VEGF's c/i , or if longer acting drugs needed.

# Anti-VEGF's in Proliferative Retinopathy

- Stops intra-ocular new blood vessel growth very effectively
- Have been used in patients with vitreous haemorrhage prior to vitrectomy surgery – make operation easier, less bleeding.
- May cause rapid contraction of retinal fibrous tissue – sudden retinal detachment has been reported
- Very effective in cases of neovascular glaucoma (NVI; rubeoosis iridis) because it stops nv growth in anterior chamber angle and buys time to give laser, sort out medication etc
- Currently Lucentis unlicensed for this- so Avastin used because its cheaper.


What does BARS stand for?
Barnes Akathisia Rating Scale
allacronyms.com