New Developments in the Management of Diabetic Retinopathy

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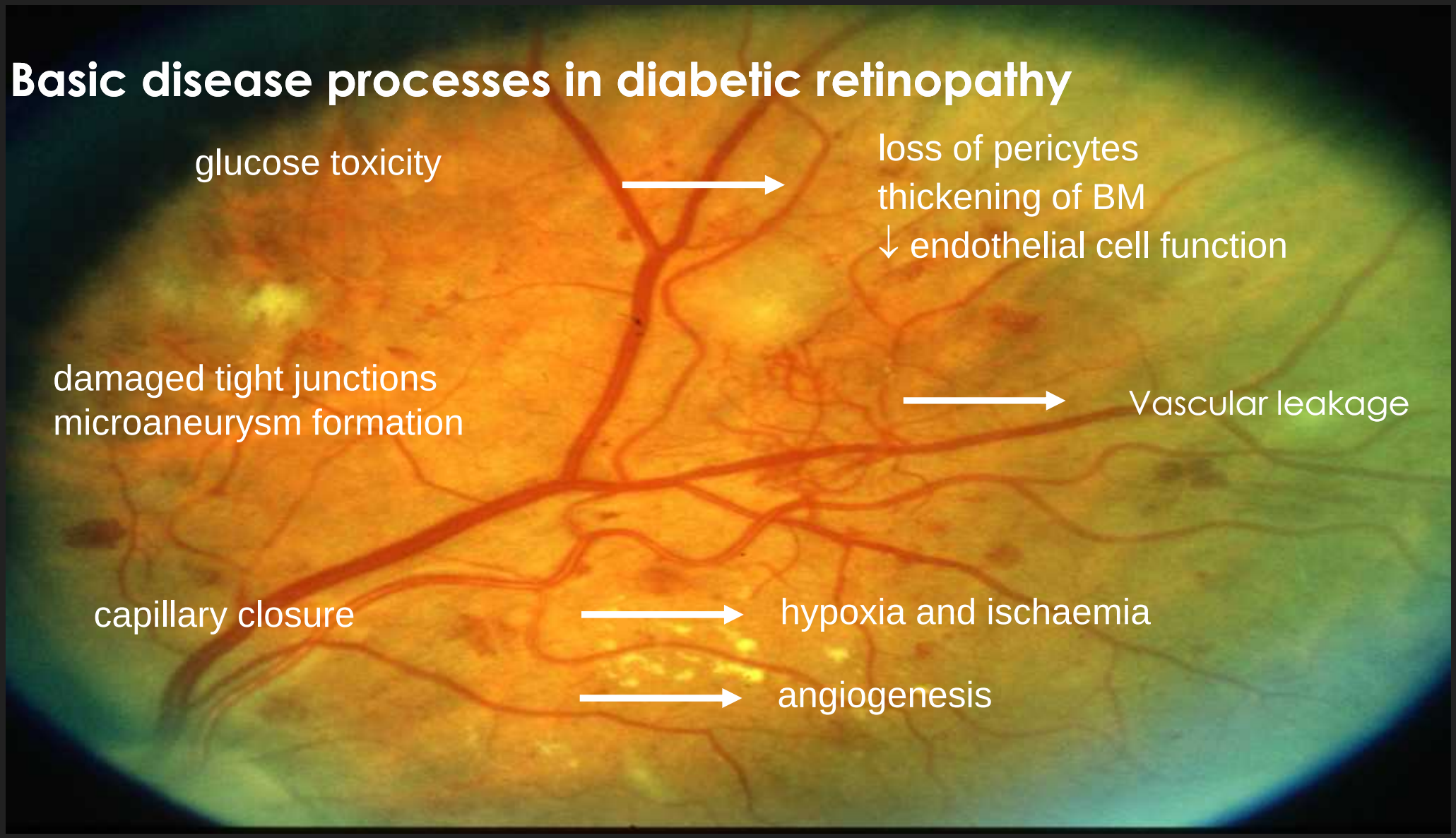
Overview

- Diabetic Macular Oedema
- Diabetic Retinopathy

  - Pathogenesis
  - Past and current treatments
  - Latest developments in treatments
  - Advances in imaging and screening


Basic disease processes in diabetic retinopathy
glucose toxicity
loss of pericytes
thickening of BM
↓ endothelial cell function
damaged tight junctions
microaneurysm formation
Vascular leakage
capillary closure
hypoxia and ischaemia
angiogenesis

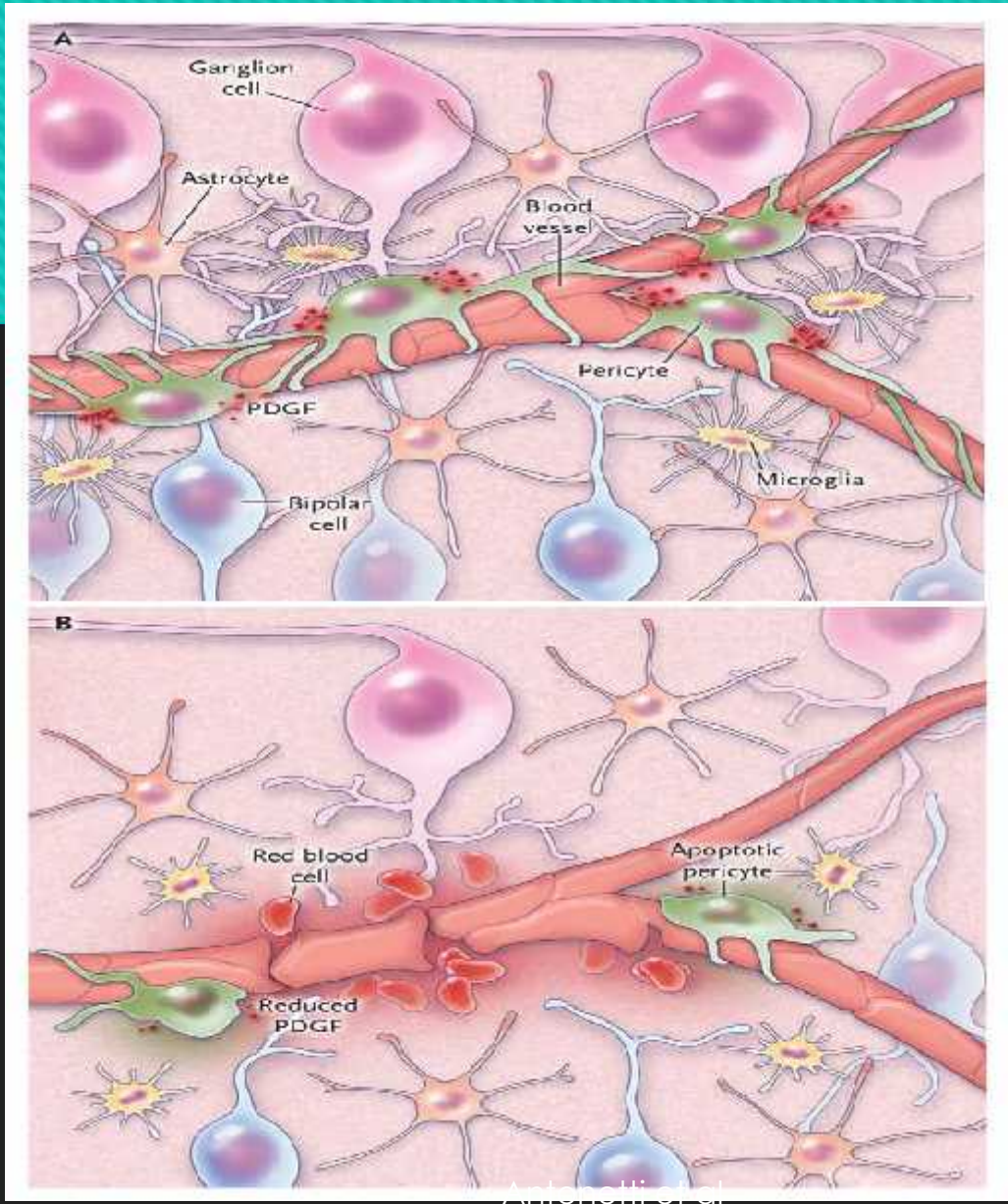
Neurodegeneration

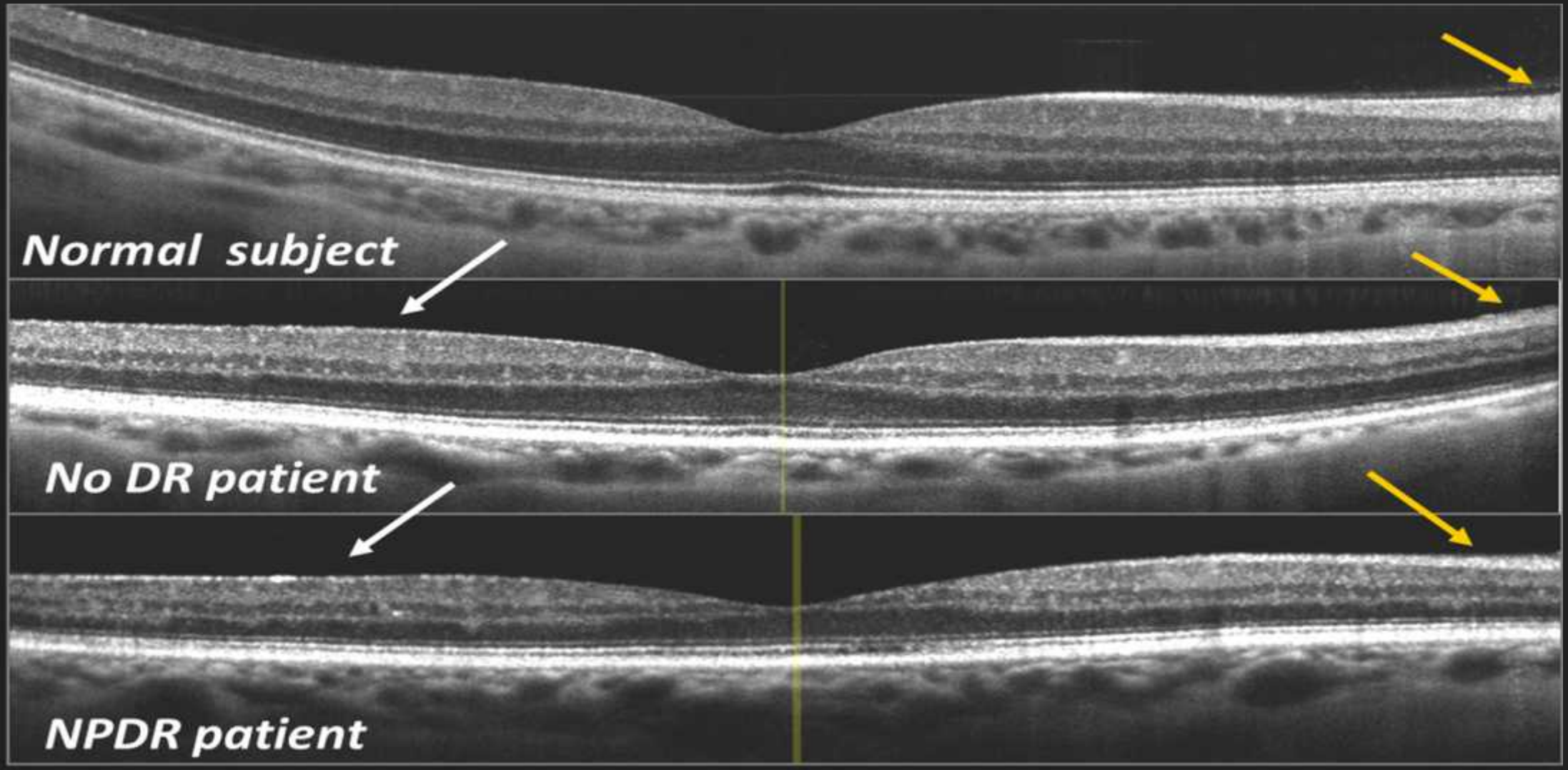
- **Neural degeneration occurs in DR:**
  - Before vascular damage
  - Contributes to vascular damage

- Increased glial apoptosis
- Glial dysfunction
  - glutamate accumulation/inflammation

Release of pro-inflammatory cytokines

Leucostasis and vascular occlusion





1. Barber AJ et al. *Invest Ophthalmol Vis Sci* 2011;52:1156–63. 2. van Dijk HW et al. *Invest Ophthalmol Vis Sci* 2010;51:3660–5. 3. Vujosevic S et al. *J Diabetes Res* 2013;2013:491835. doi: 10.1155/2013/491835.

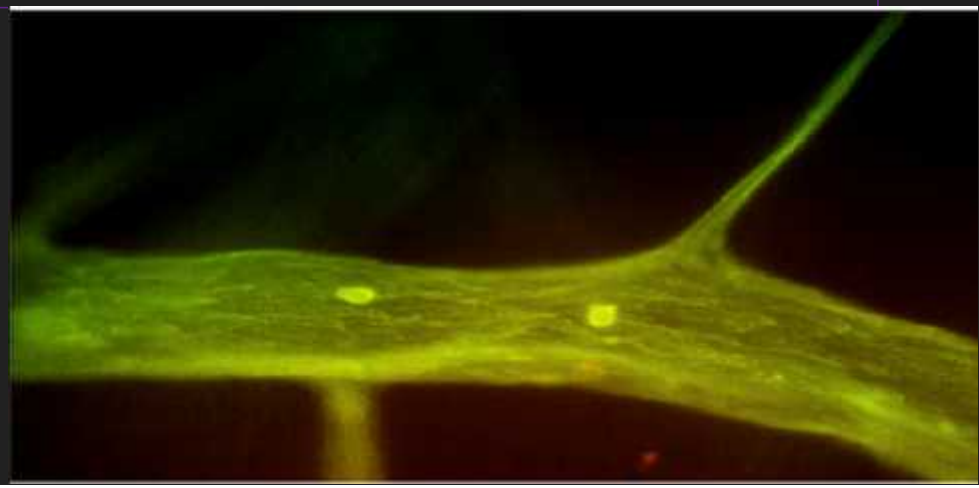
Inflammation in DR

Vitreous profile in patients with diabetic retinopathy

- **VEGF-A**
- Erythropoietin
- **IL-1**b
- **IL-6**
- **IL-8**
- **MCP-1**
- **IP-10**
- **IFN-¥**
- **TNF-**a
- PDGF
- PGE2
- ICAM-1

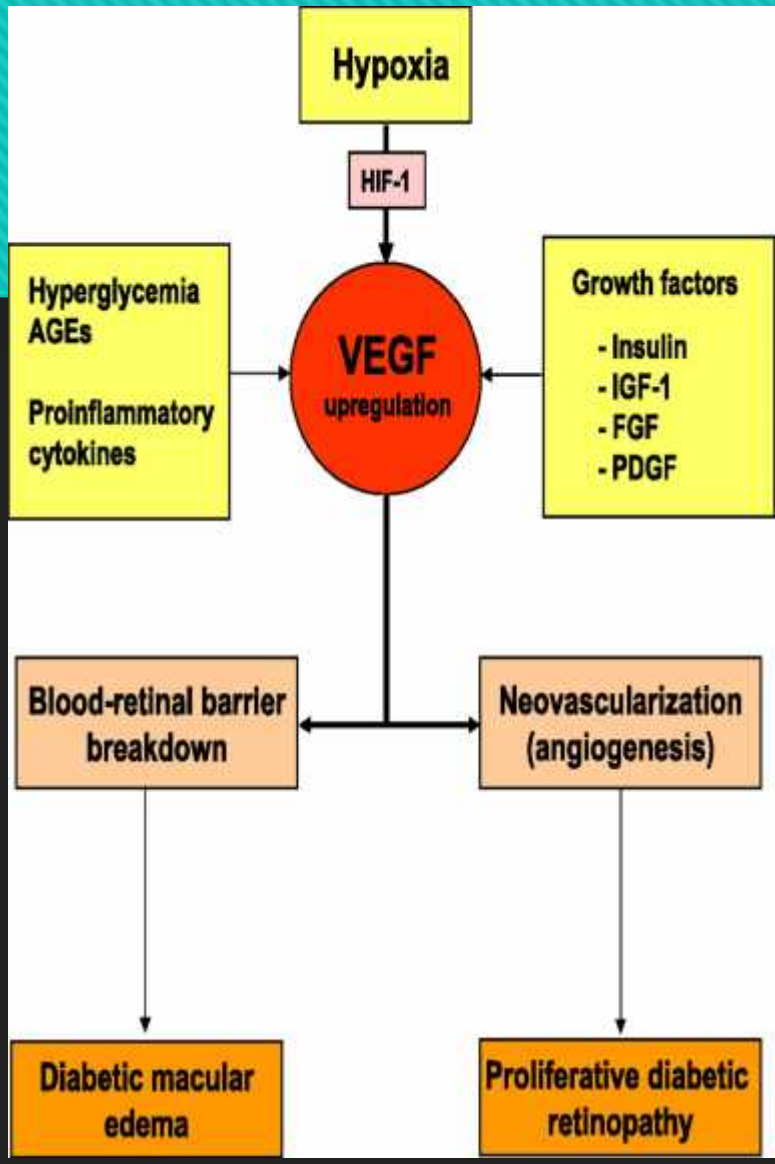
- TGF-β
- sVEGFR-1
- PEDF
- **IL-10, IL-12,** Il-13

The balance of cytokines and chemokines is altered in the ocular media of diabetes patients



Vascular Endothelial GF

- GF required for normal vascular development
- Hypoxia is the most important trigger for VEGF upregulation
- Overexpression leads to BRB disruption + neovascularisation

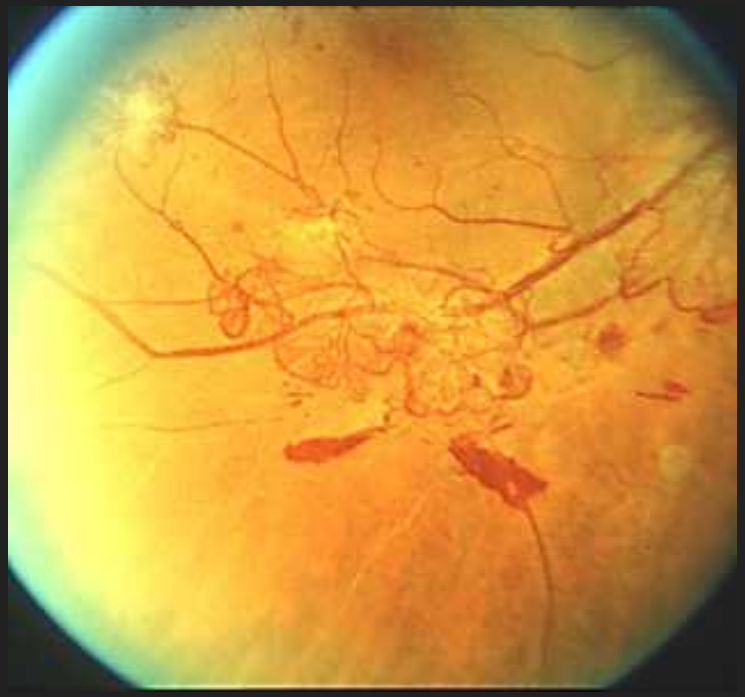


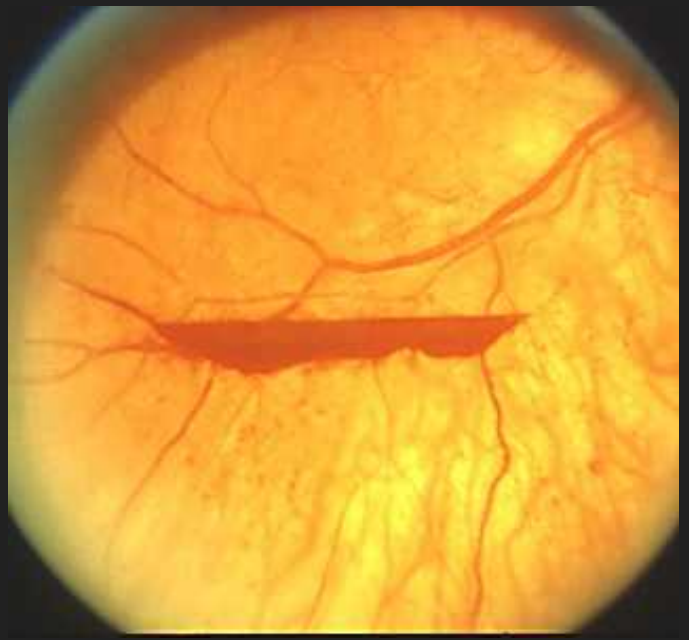
Diabetic retinopathy-current treatments

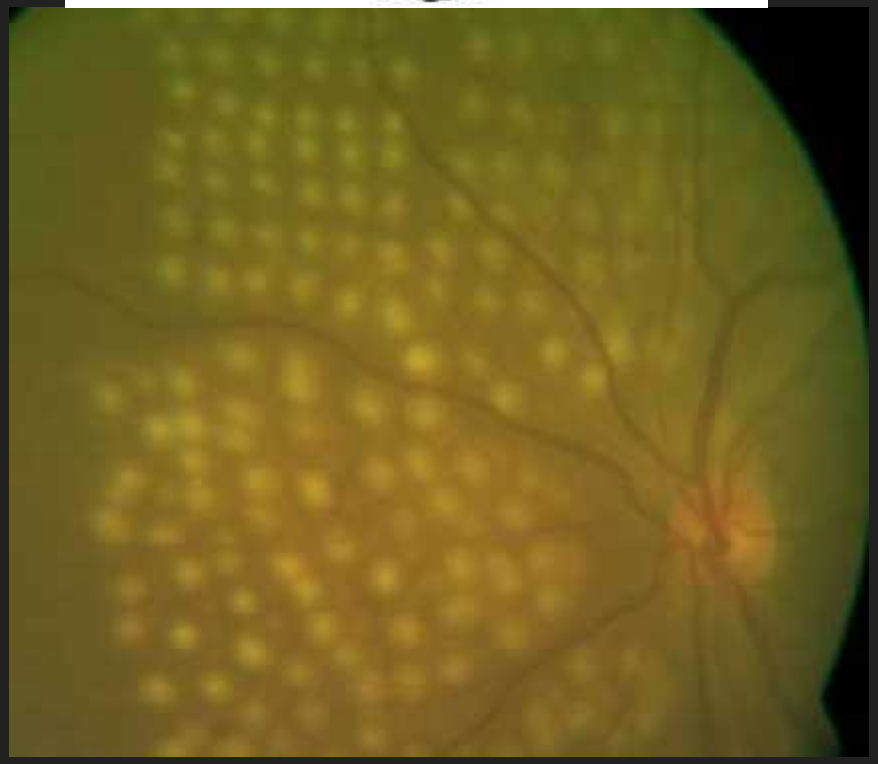
4

2

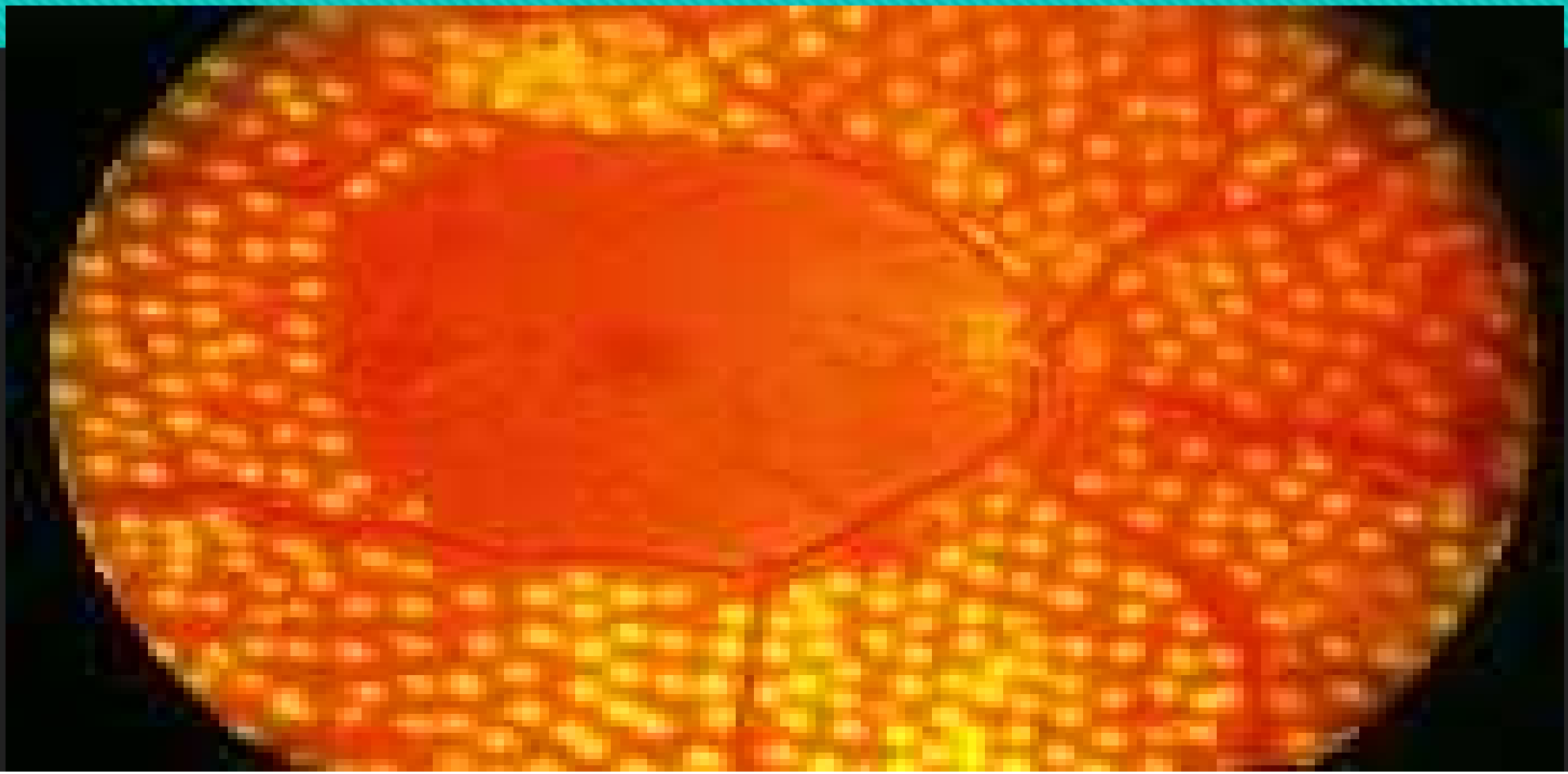
1







PRP

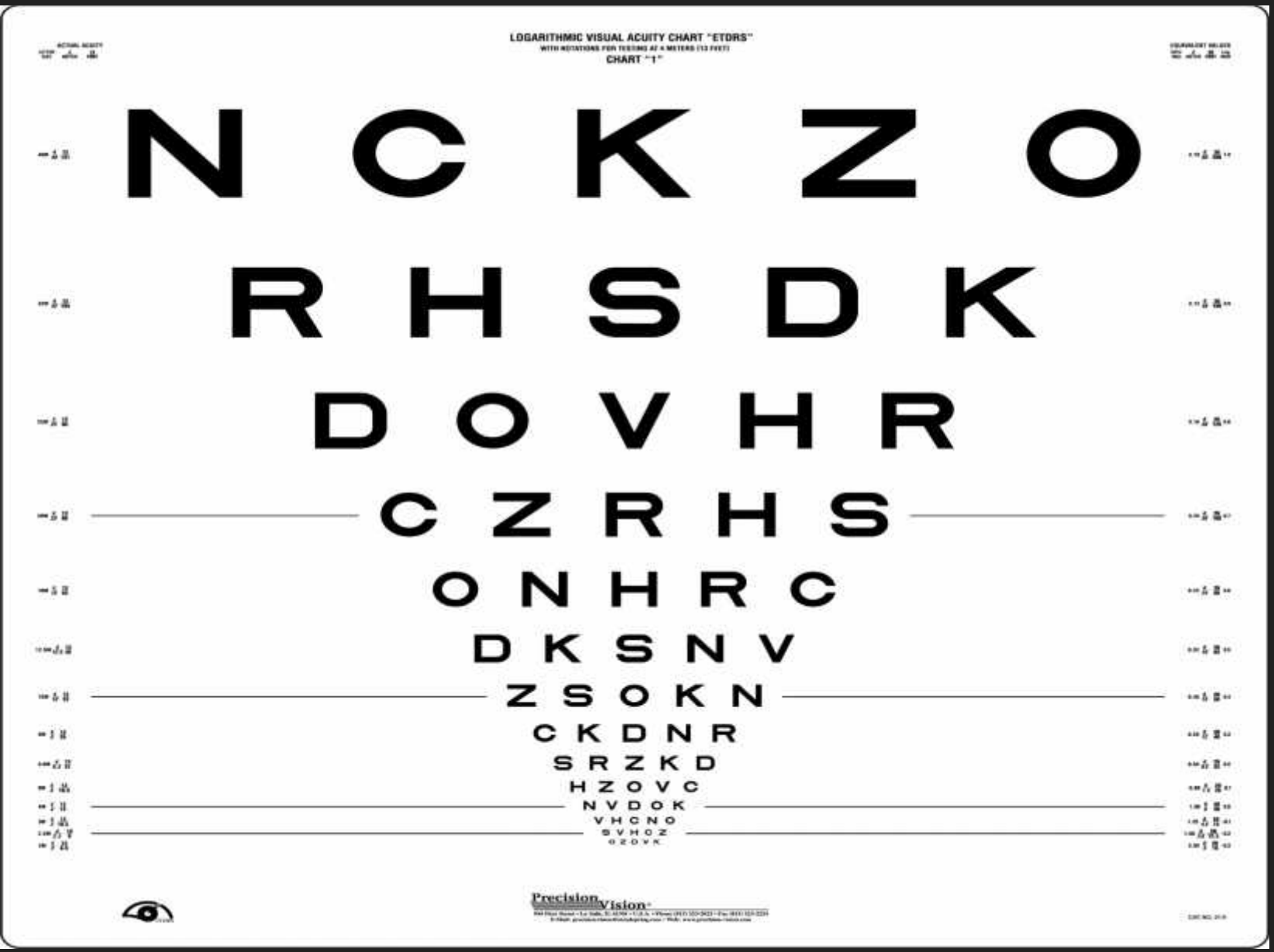


How PRP works

- Thermal coagulation of RPE and adjacent retina
- Hypoxic retina produces VEGF stimulating NV growth
- Laser kills hypoxic retina and stops VEGF production
- Remaining retina is better perfused.

Risks of PDR

- Inherently destructive treatment
- Loss of peripheral vision/driving fields
- Reduced night vision
- Central foveal burn
- Exacerbates macular oedema



Change in 5 letters is meaningful to patients

The Diabetic Retinopathy Clinical Research Network

Prompt PRP
vs.
Ranibizumab + Deferred PRP
for PDR Study

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

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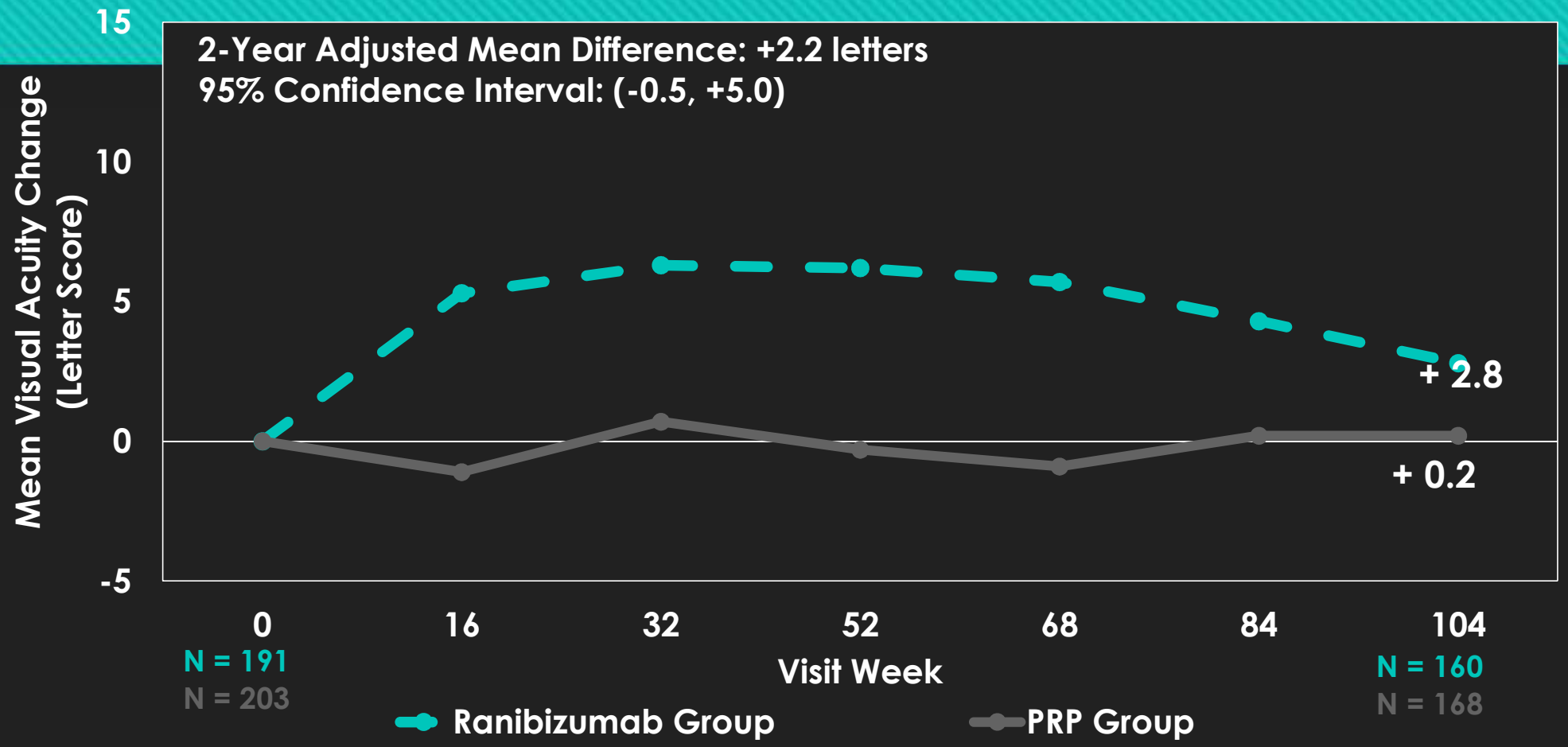
Mean Change in Visual Acuity



Discussion

- Treatment with 0.5-mg ranibizumab met primary non-inferiority outcome for VA being no worse than PRP

- Summary of Ranibizumab group results vs. PRP:
  - Mean change in VA from baseline to 2-years with ranibizumab no worse than with PRP
  - Superior mean visual field outcomes
  - Decreased occurrence of vitrectomies
  - Decreased development of central involved DMO

CLinical efficacy of intravitreal Aflibercept versus panRetinal photocoagulation for best corrected visual acuity In patients with proliferative diabetic reTinopathY without macular oedema at 52 weeks (CLARITY): a multicentre, single-blinded, randomized, controlled, phase 2b, non-inferiority trial.

Sobha Sivaprasad,

Philip Hykin, Toby Prevost, Joana Vasconcelos, Amy Riddell, Caroline Murphy, Joanna Kelly & Jim Bainbridge on behalf of the CLARITY Study Group, UK

The full CLARITY study report is published in *The Lancet*
http://dx.doi.org/10.1016/S0140-6736(17)31193-5

KING'S College LONDON

CLARITY Funded by NHS National Institute for Health Research

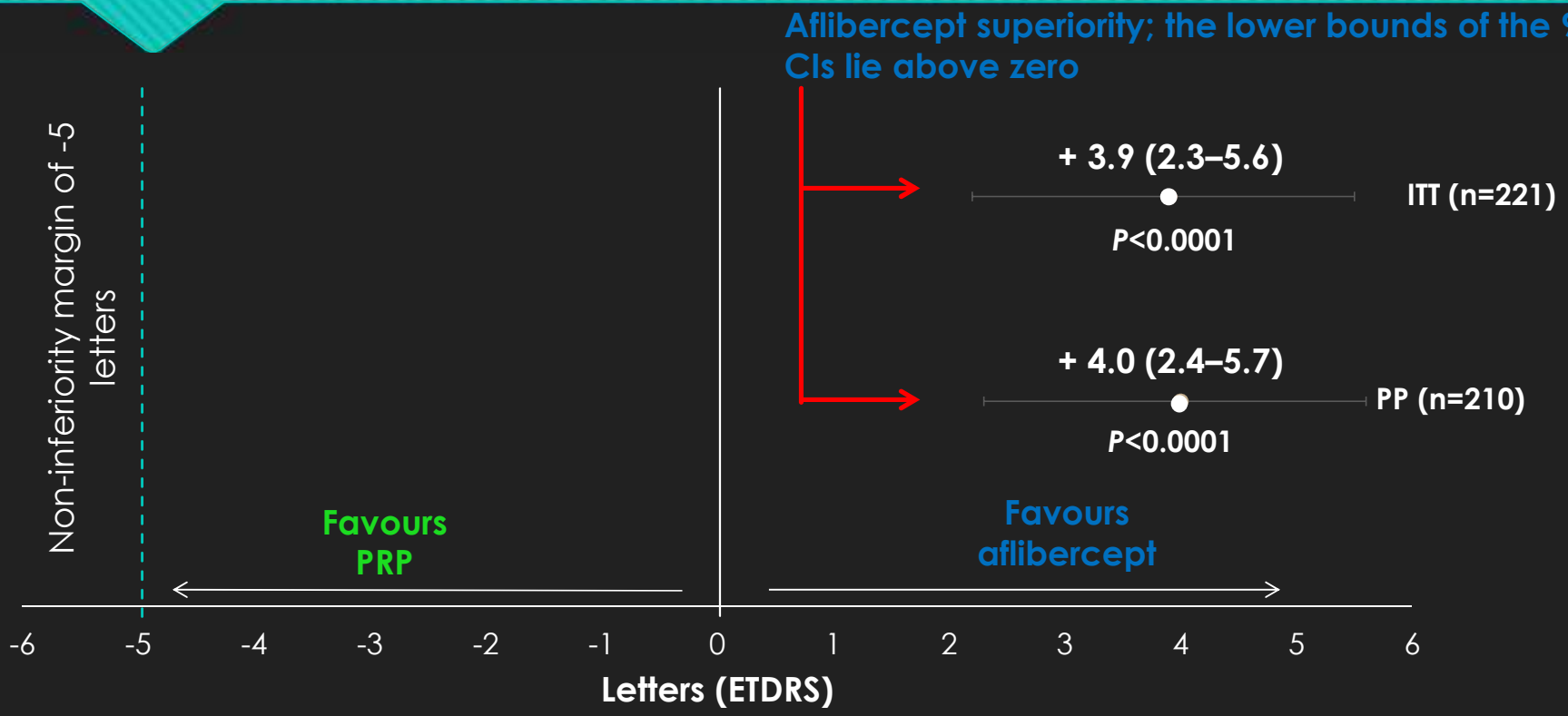
Moorfields Eye Hospital

CLARITY: Primary Objective

To determine if visual acuity at 52 weeks in patients with active proliferative diabetic retinopathy (PDR) treated with aflibercept is non-inferior to those treated with panretinal photocoagulation (PRP)

PDR, proliferative diabetic retinopathy; PRP, panretinal photocoagulation.

Primary outcome: Adjusted difference in mean BCVA change was both non-inferior AND superior with aflibercept therapy compared to PRP at week 52



CI, confidence interval; ETDRS, Early Treatment Diabetic Retinopathy Study; ITT, intention to treat; PDR, proliferative diabetic retinopathy; PP, per protocol; PRP, panretinal photocoagulation; BCVA, best corrected visual acuity.

Secondary outcome measures

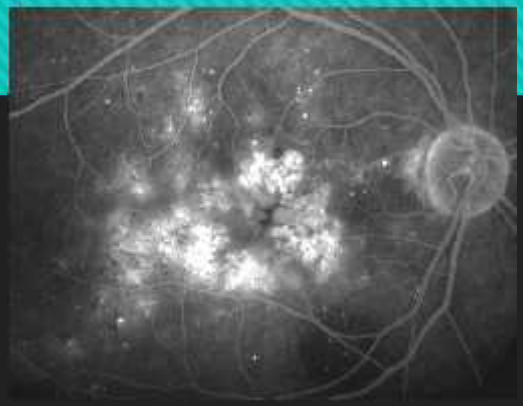
- 11% AFL vs 29% PRP developed DMO
- 64% AFL vs 34% had complete regression of NV
- 9% AFL vs 18% PRP developed VH
- 1% AFL vs 6% required vitrectomy
- AFL has a lower risk of visual field loss than PRP

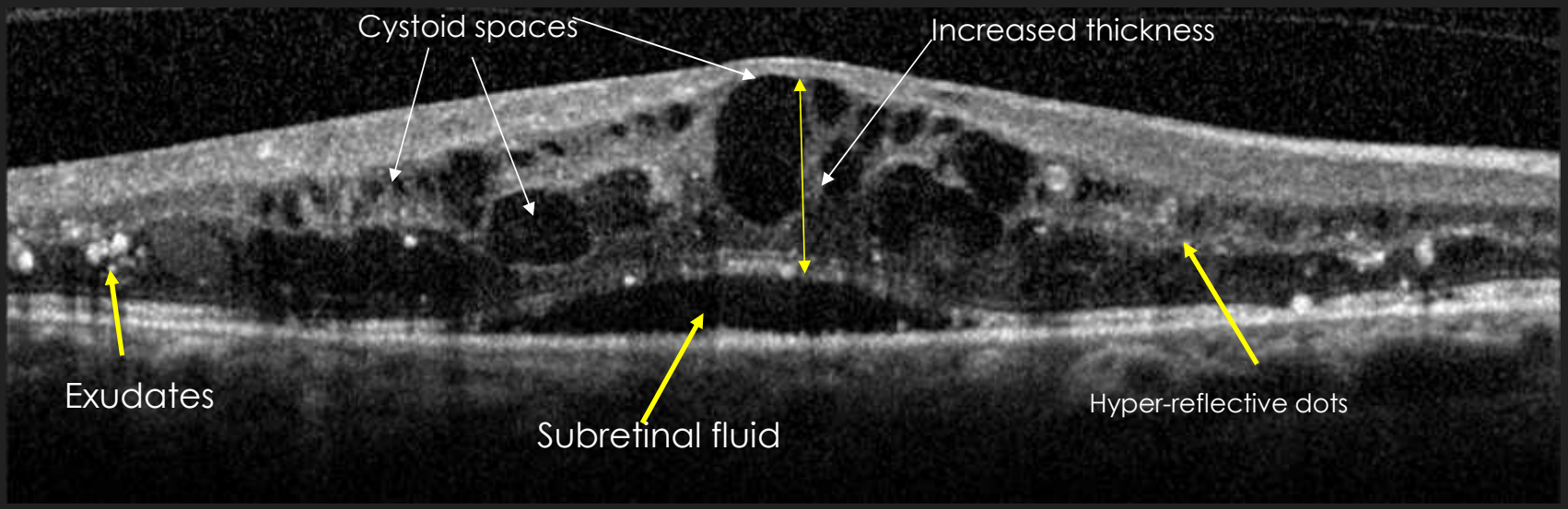
Summary of anti-VEGF in PDR

- Non inferior to PRP at up to 2 years-what happens after
- More expensive
- More visits/ capacity/ patient compliance
- However
  - Less destructive
  - Better VF and night vision
  - Less DMO
  - Less progression of DR/More regression of PDR

- Current position
  - Still using PRP
  - Can delay PRP if patient also has macular oedema
  - Use if progression despite full laser

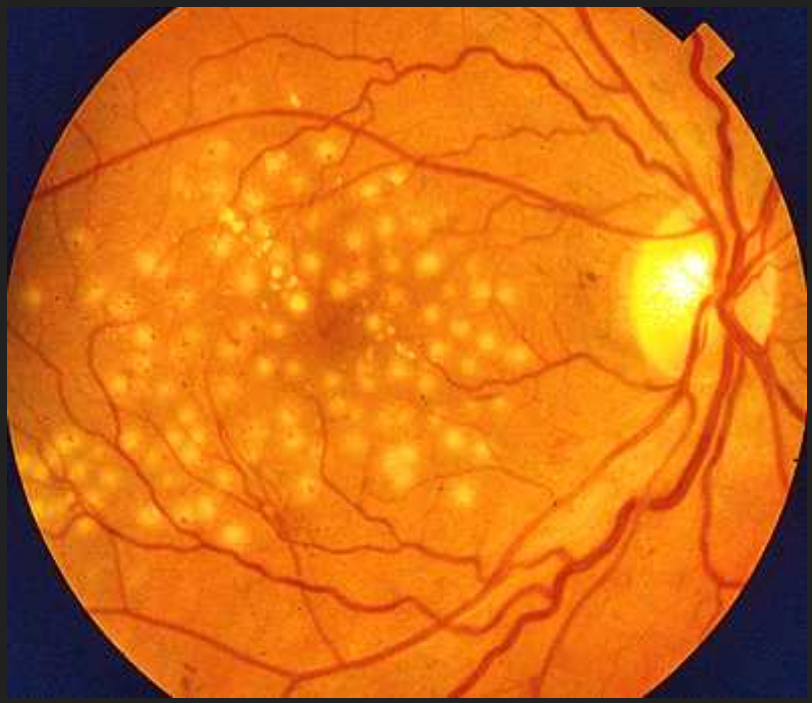
Diabetic Macular Oedema-Current Treatments

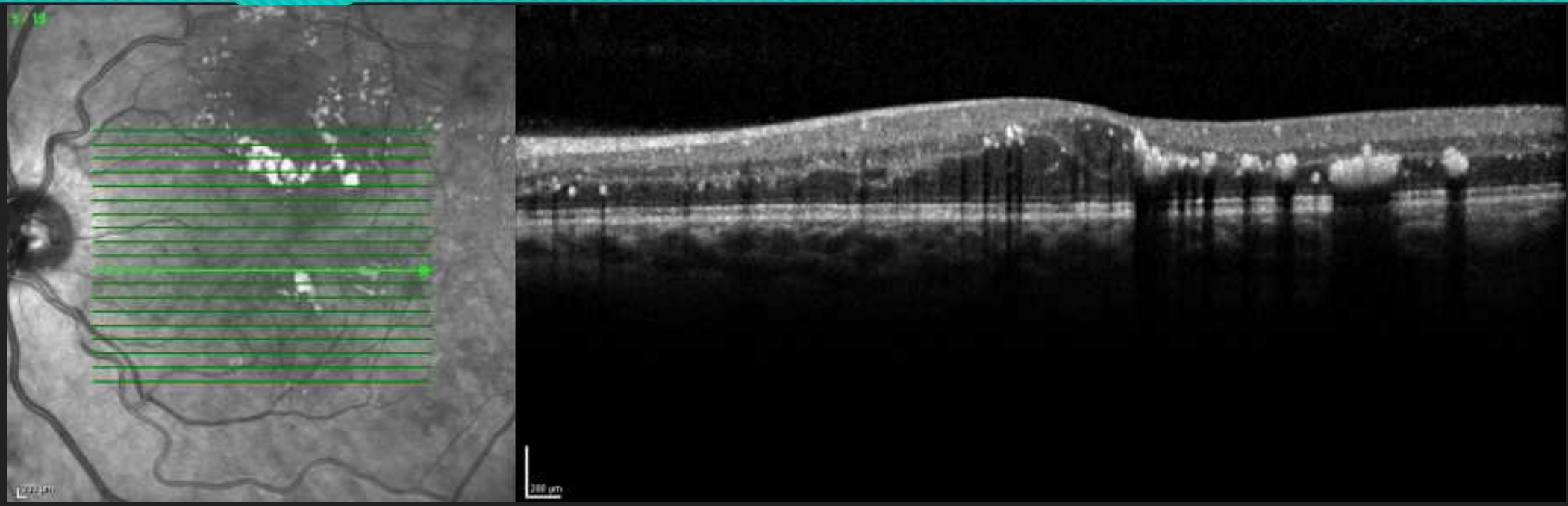


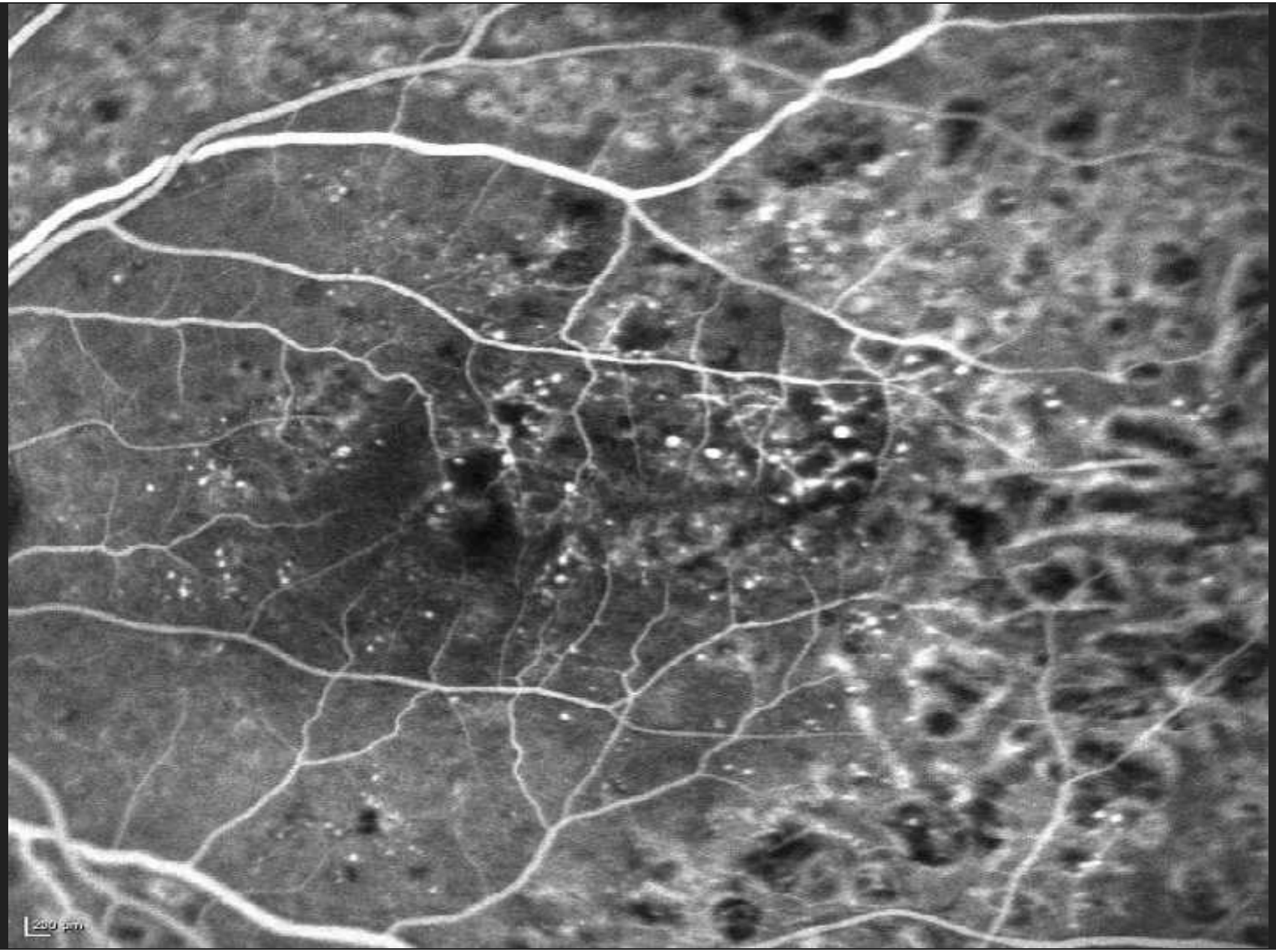


Diabetic Macular Oedema

- Leading cause of visual impairment in DR
- Macular laser was standard treatment -2010
  - Closes down leaking microaneurysms
  - Stimulates RPE pump







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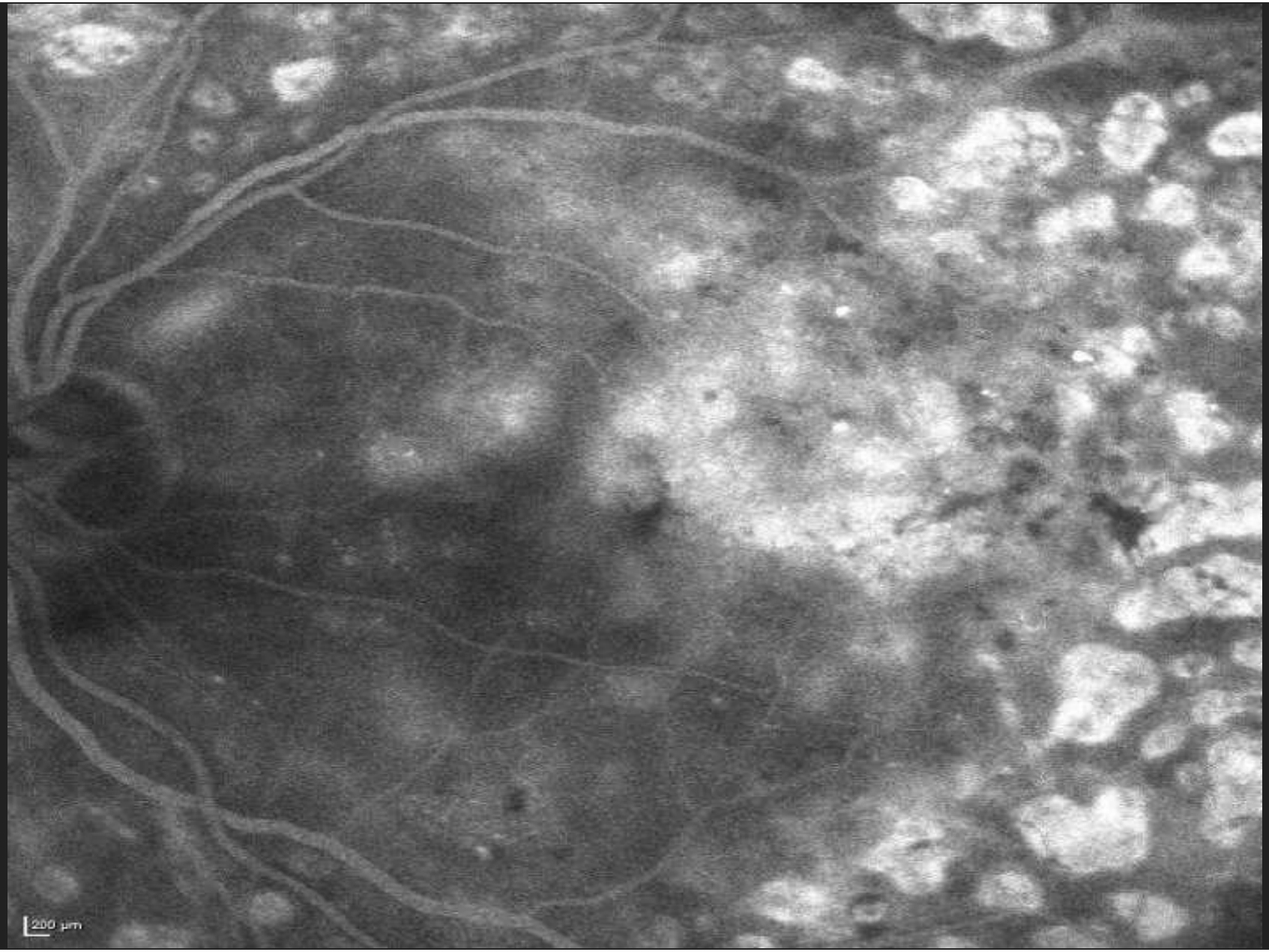


10min 54sec

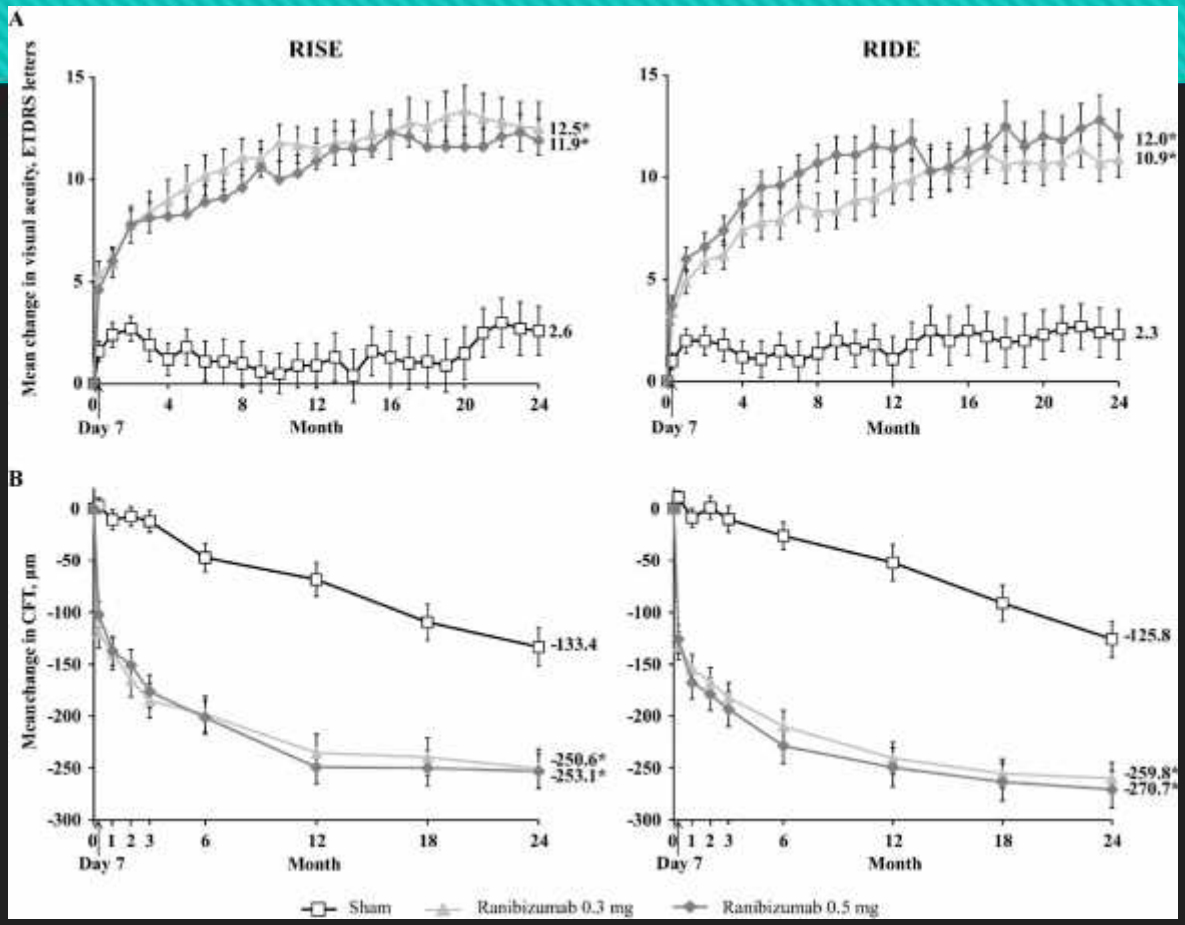
- Only gives stability, no improvement
- Destructive treatment, risks
  - Foveal burn
  - Paracentral scotomas
  - Choroidal NV

Background
Anti-VEGF Therapy for DMO

VEGF levels are increased in the retina and vitreous of eyes with diabetic retinopathy

Therapy that inhibits VEGF may represent a useful therapeutic modality which targets the underlying pathogenesis of DMO

RISE/RIDE study

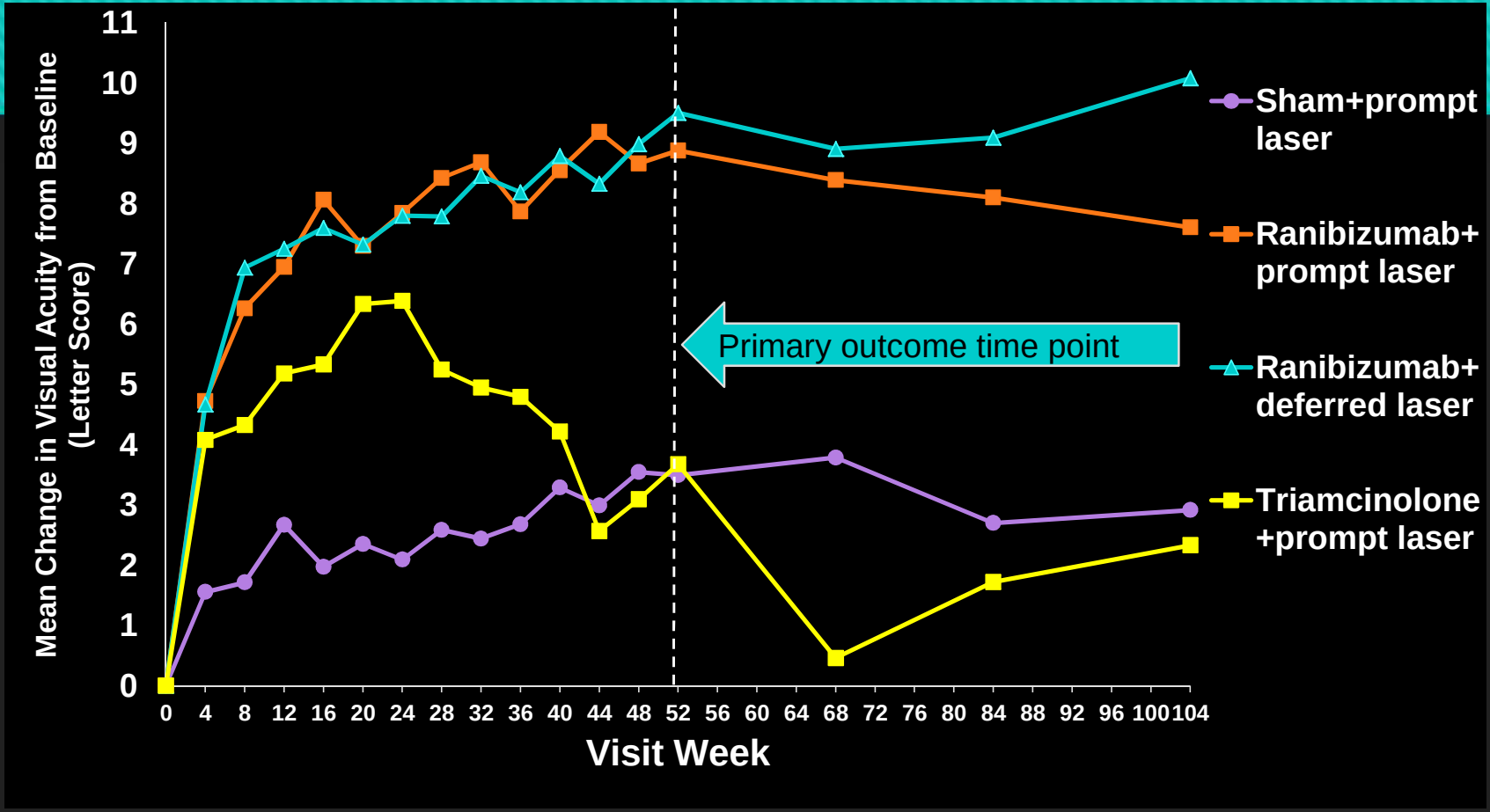


Ophthalmology 2012 119, 789-801DOI: (10.1016/j.ophtha.2011.12.039)

DRCR.net Protocol I

- Compared Ranibizumab vs Ranibizumab plus laser vs IV triamcinolone to laser alone
- Primary outcome measure was change in VA from baseline to 1 year

Mean Change in Visual Acuity (Letter Score) at Follow-up Visits



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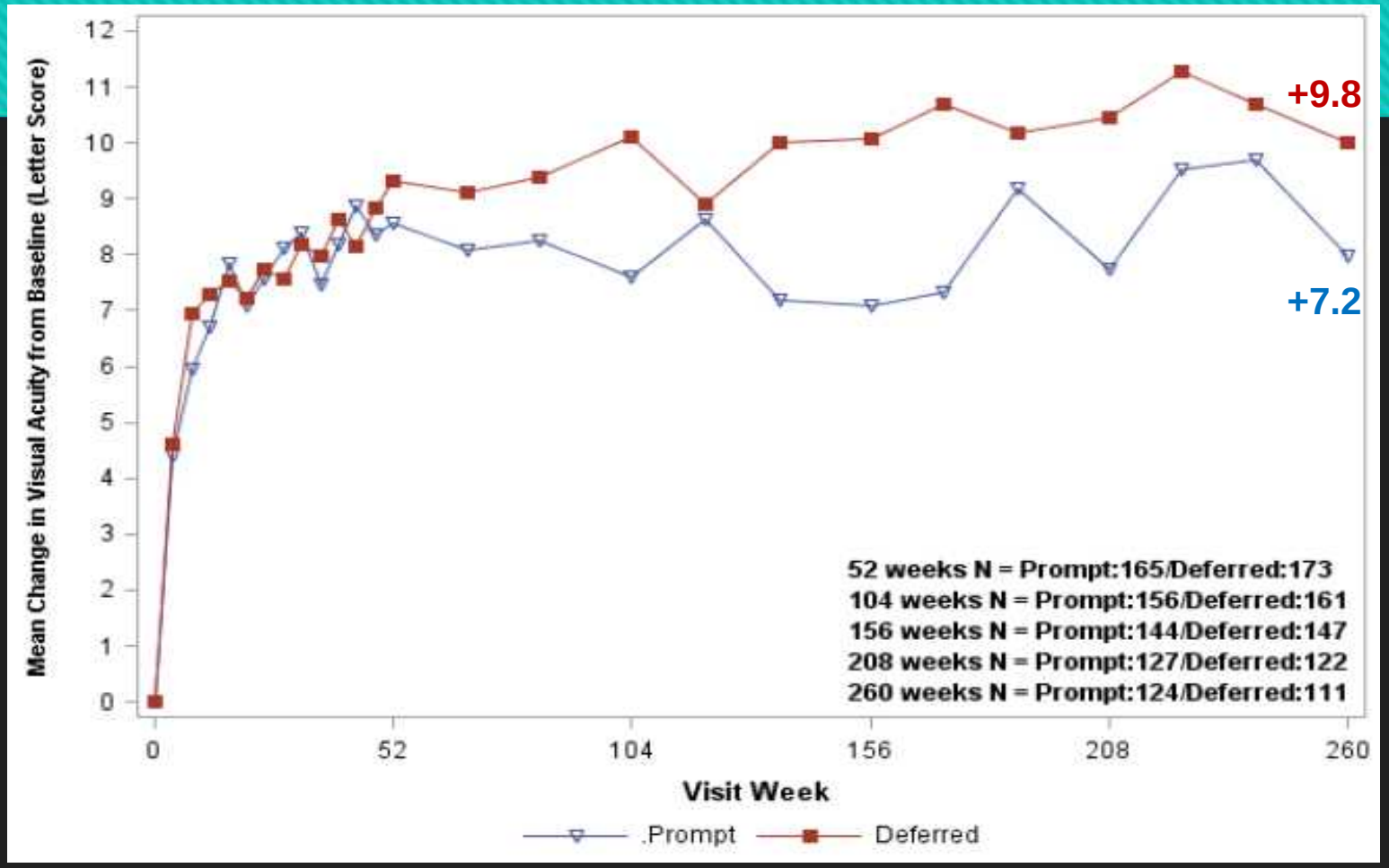
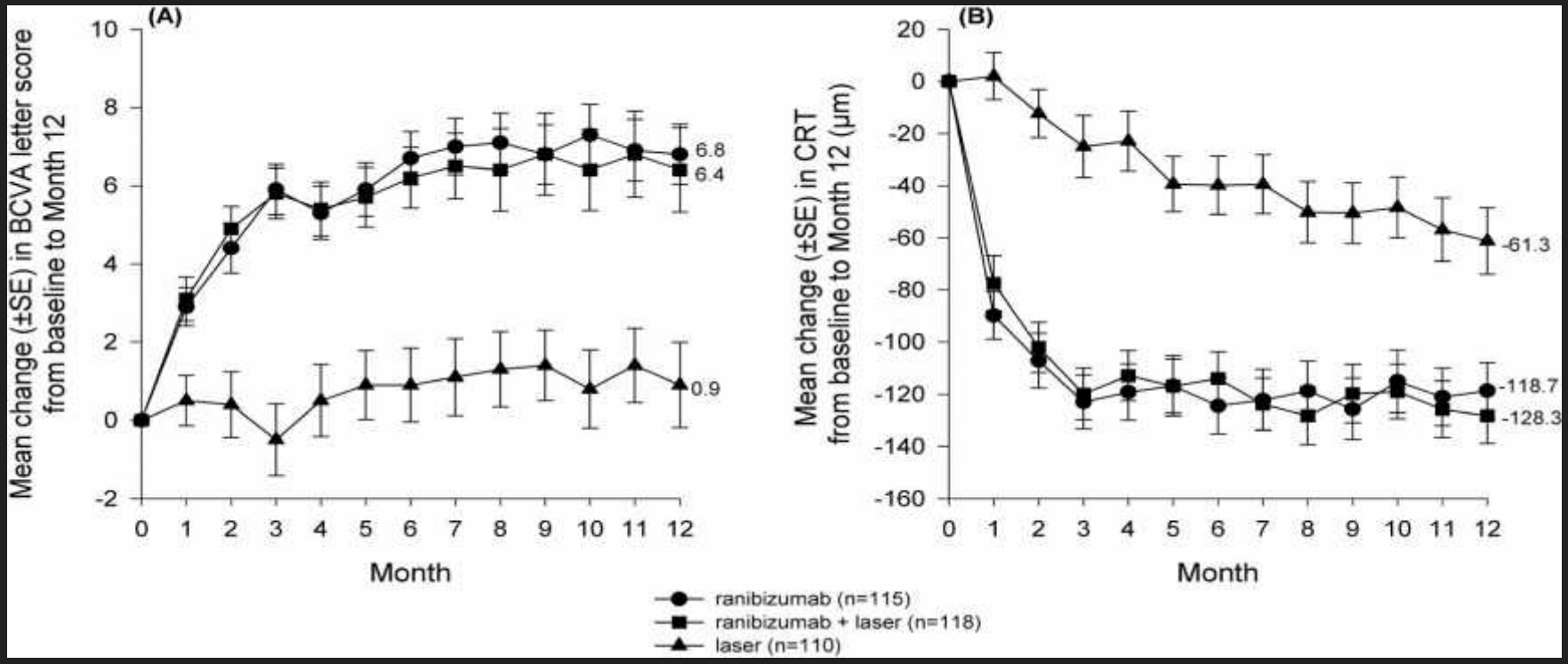


Injections Prior to 5 Year

	Ranibizumab + Prompt Laser N=124	Ranibizumab + Deferred Laser N=111
Median # of injections in year 1	8	9
Median # of injections in year 2	2	3
Median # of injections in year 3	1	2
Median # of injections in year 4	0	1
Median # of injections in year 5	0	0
Median # of injections prior to 5 year visit	13	17
% of eyes that received ≥1 injection in year 4	46%	55%
% of eyes that received ≥1 injection in year 5	38%	48%

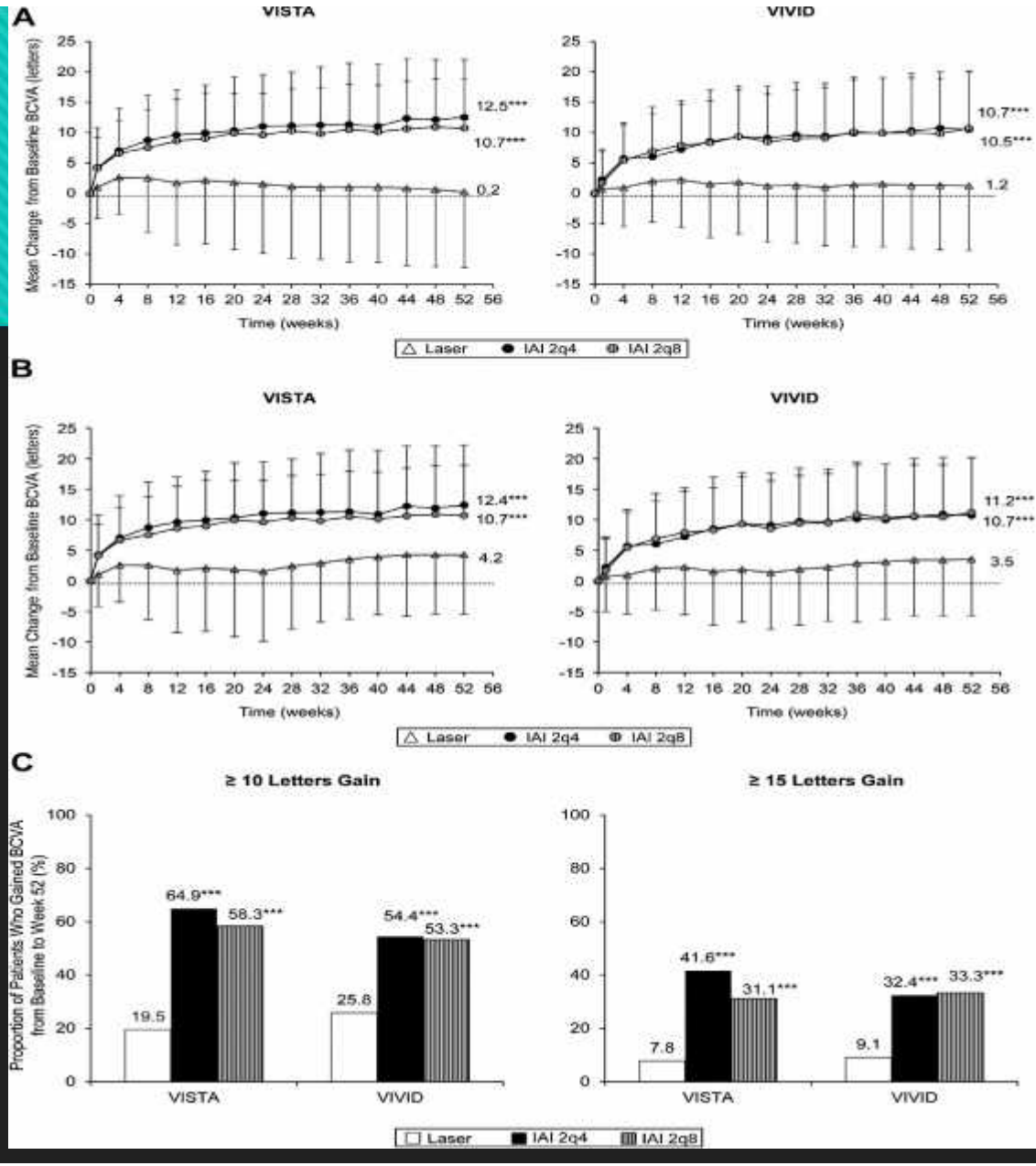
RESTORE-Ranibizumab vs Ranibizumab + Laser vs Laser



RESTORE,Ophthalmology 2011 118, 615-625DOI: (10.1016/j.ophtha.2011.01.031)

Aflibercept

- Binds to VEGF A and B and PLGF
- Higher affinity to VEGF A than Ranibizumab
- Longer half life in eye
- Aflibercept superior to laser at 12 months
  - And up to 148 weeks
  - Dosing every 2 months=monthly
  - Improvement in DR score



Diabetic Retinopathy Clinical Research Network

Aflibercept, Bevacizumab, or Ranibizumab for DME: Two-year Results

Supported through a cooperative agreement from the

National Eye Institute; National Institute of Diabetes and Digestive and Kidney Diseases; National Institutes of Health, Department of Health and Human Services EY14231, EY14229, EY018817

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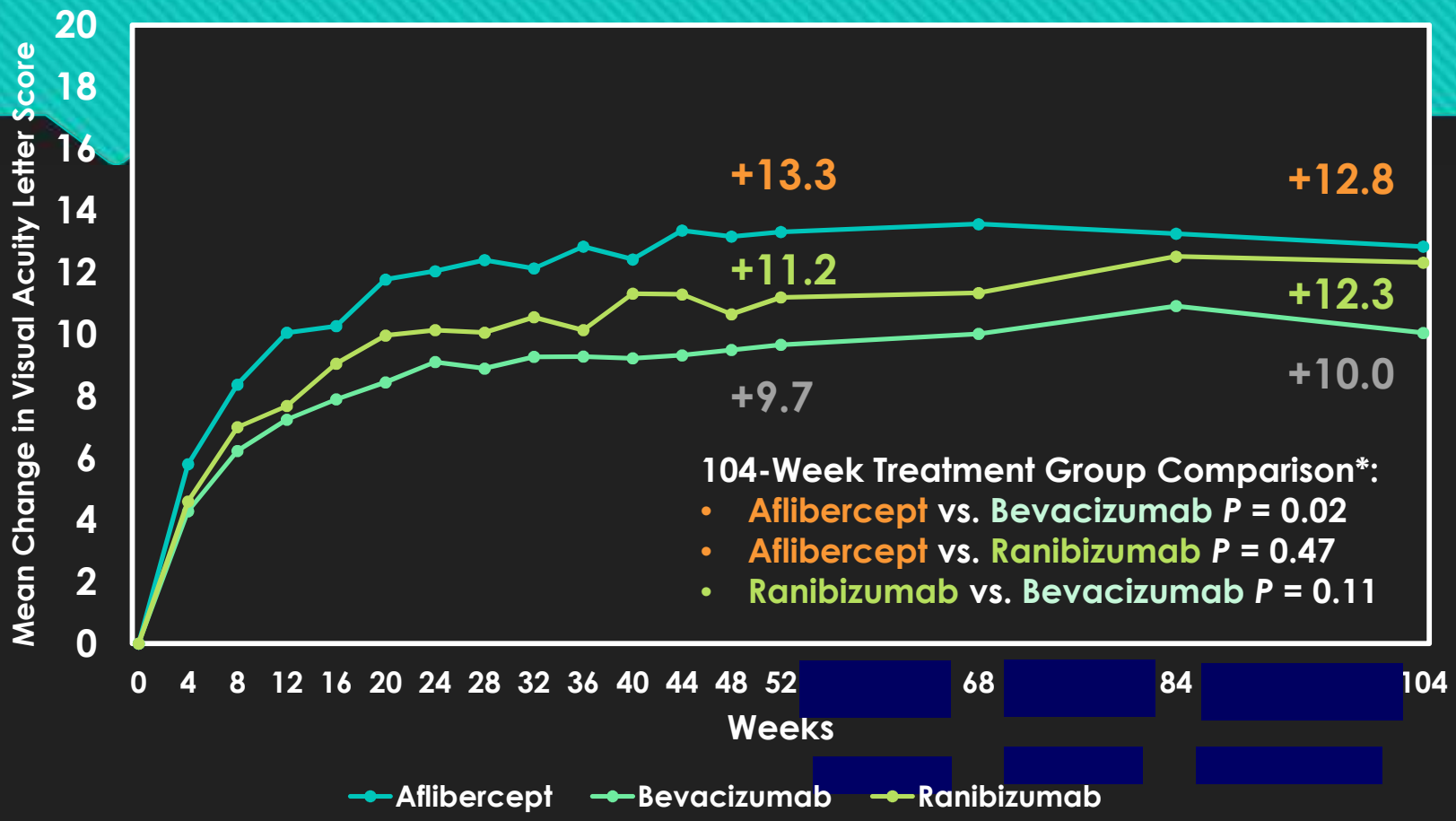
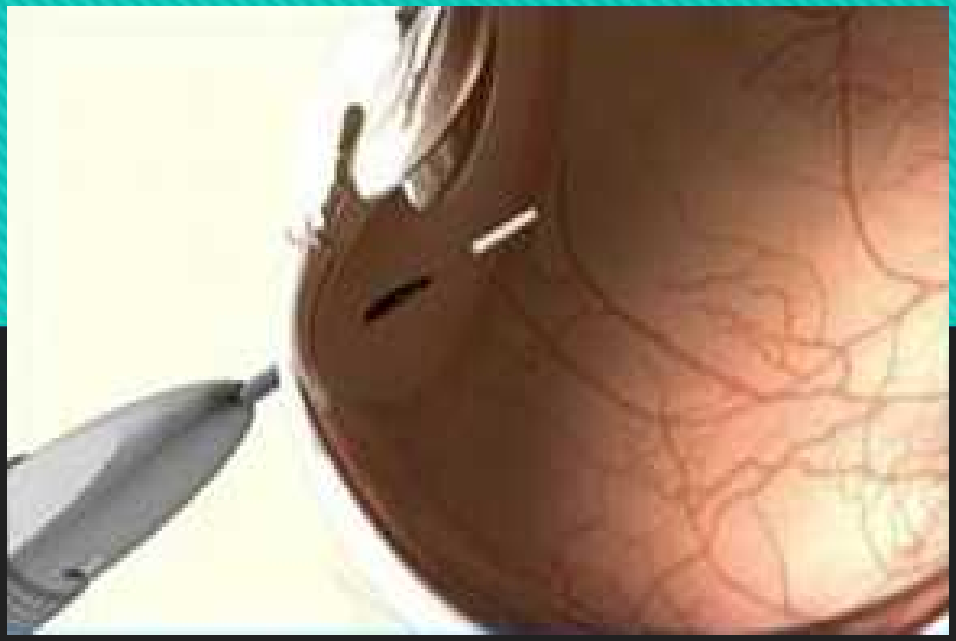
Mean Change in Visual Acuity Over 2 Yrs



Steroid therapies

- Ozurdex-dexamethasone implant-6 months
- Iluvien –flucinolone acetonide implant -3 years
  - Pseudophakic patients only-NICE
  - Risk of IOP rise
- Reserved as second line



Novel Treatments

- Bi-specific antibodies in phase 2 study (BOULEVARD)
  - simultaneous VEGF and angiopoietin 2 inhibition
- Drug delivery systems
- 2 studies evaluating anti VEGF in pre-proliferative DR

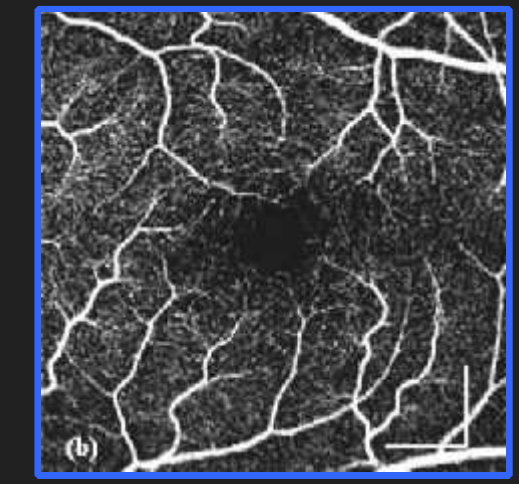
New Imaging Modalities

- Optical coherence tomography (OCT)
- OCT A
- Wide-field angiography

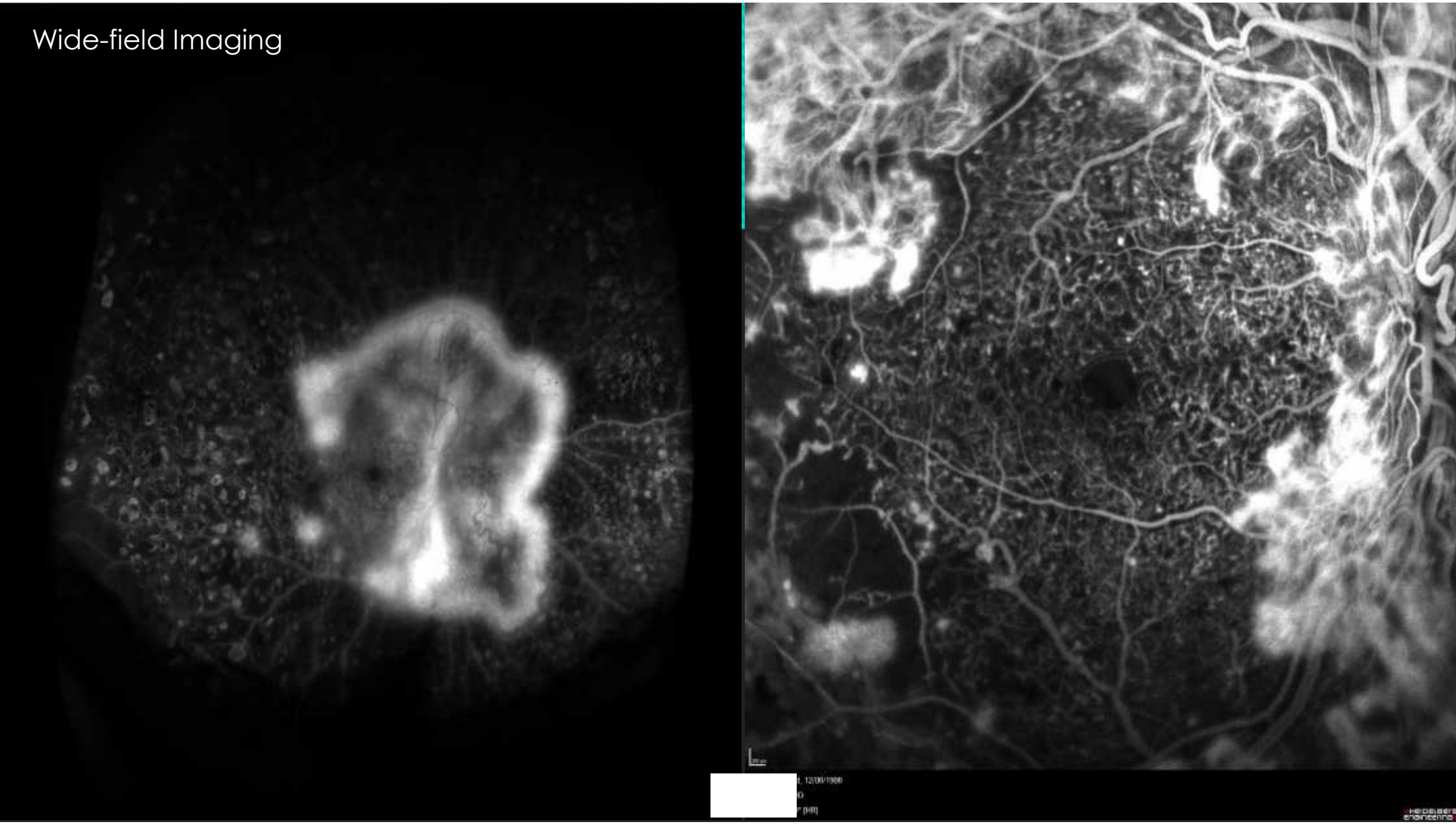
OCT Angiography

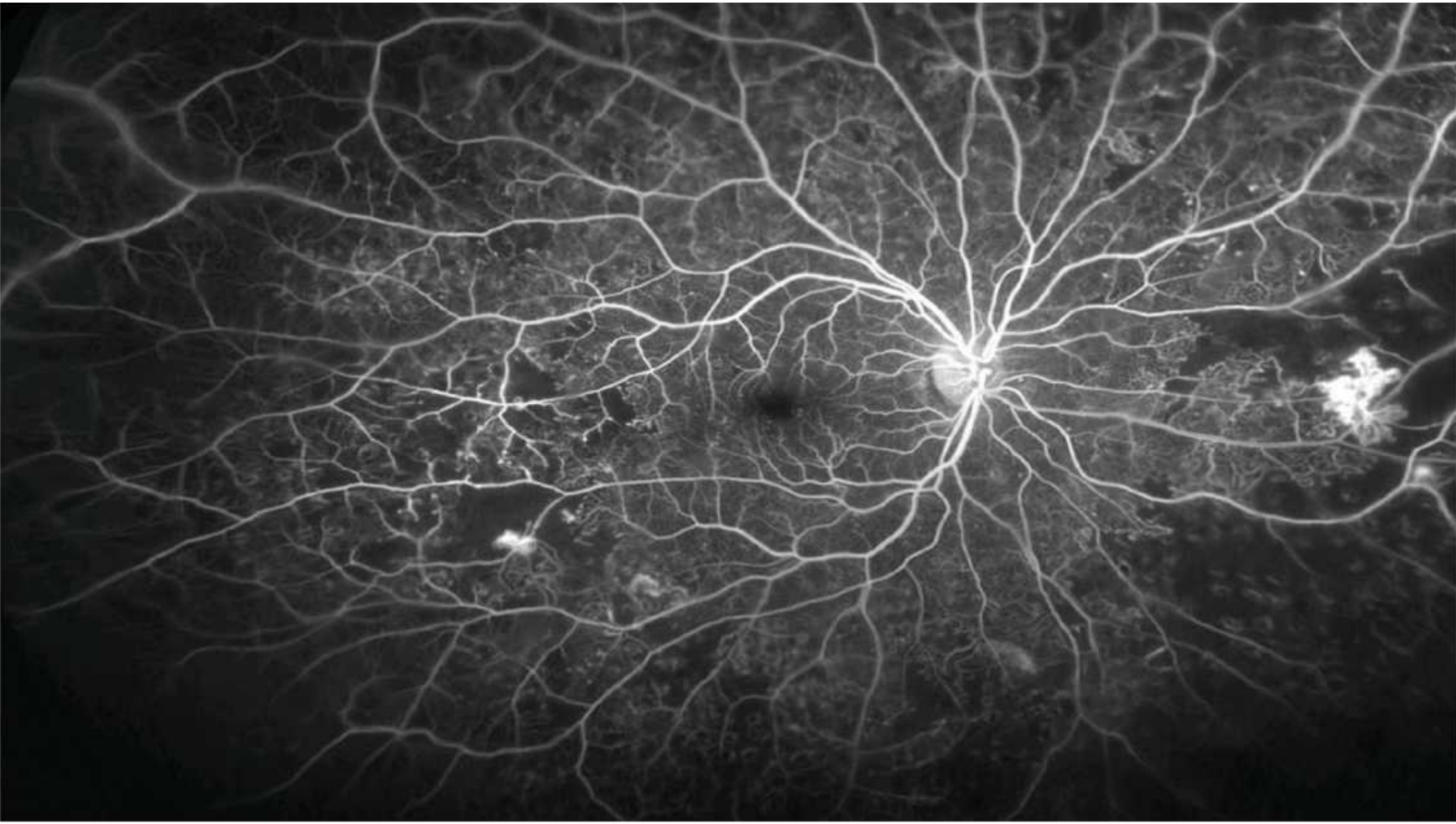
- **Advantages**
- cross-sectional imaging
- high resolution
- non-invasive
- fast

- **Disadvantages**
- small field of view (10-20 degrees / 3x3, 6x6mm)
- no dynamic leakage information



Wide-field Imaging



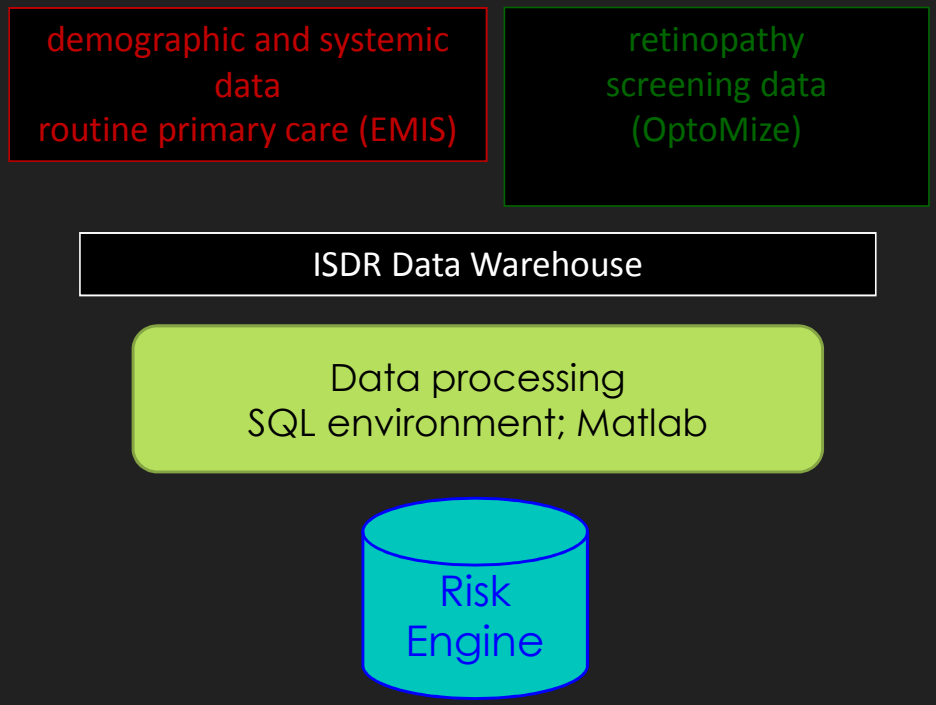


Developments in screening

- Well established –local programmes covering the country since 2008
- Effective- only country where DR no longer the commonest cause of VA impairment in working age population-first time for 50 years
- Expensive-80 million/year, increasing demand
  - Extended screening intervals
    - No retinopathy on 2 consecutive screens-low risk-2 yearly intervals
    - Introduced when software developed
  - Personalised risk based screening
  - Automated grading software –being evaluated

Individualised variable interval risk based screening

Harding SP, Broadbent DM, et al. Programme Grant for Applied Research (RP-PG-1210-12016) £2.08m

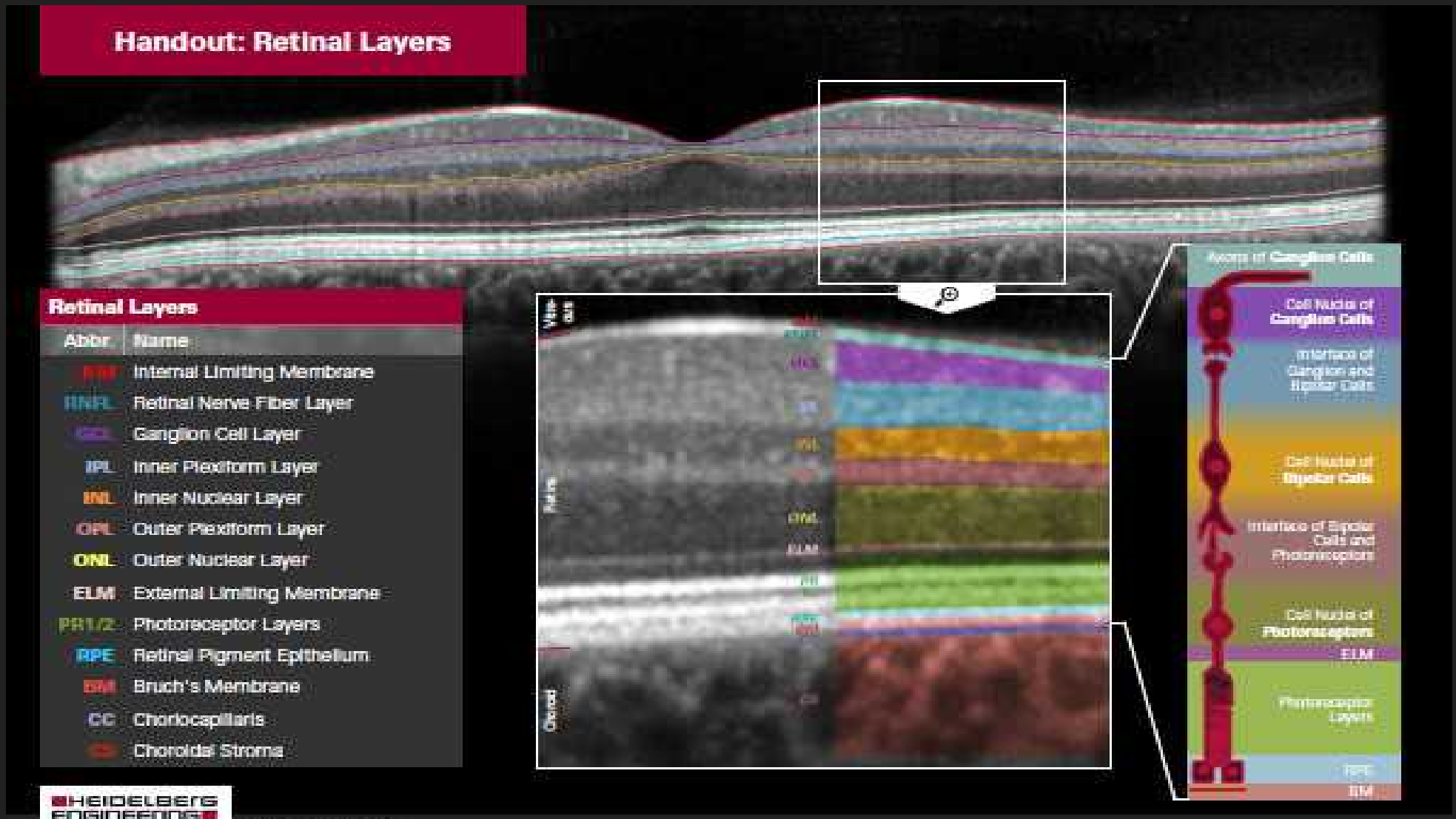


- past and present DR, age, duration of DR, HbA1c, sBP, TC
- 6, 12, 24 month interval

Summary

- Past 6 years huge developments in management
- Anti VEGF revolutionised treatment and outcomes for patients with diabetes
- We can now make significant improvement to quality of life
  - But the treatment is intensive
- Future bright

Handout: Retinal Layers



Retinal Layers

Abbr.	Name
ILM	Internal Limiting Membrane
RNFL	Retinal Nerve Fiber Layer
GCL	Ganglion Cell Layer
IPL	Inner Plexiform Layer
INL	Inner Nuclear Layer
OPL	Outer Plexiform Layer
ONL	Outer Nuclear Layer
ELM	External Limiting Membrane
PR1/2	Photoreceptor Layers
RPE	Retinal Pigment Epithelium
BM	Bruch's Membrane
CC	Choriocapillaris
CS	Choroidal Stroma

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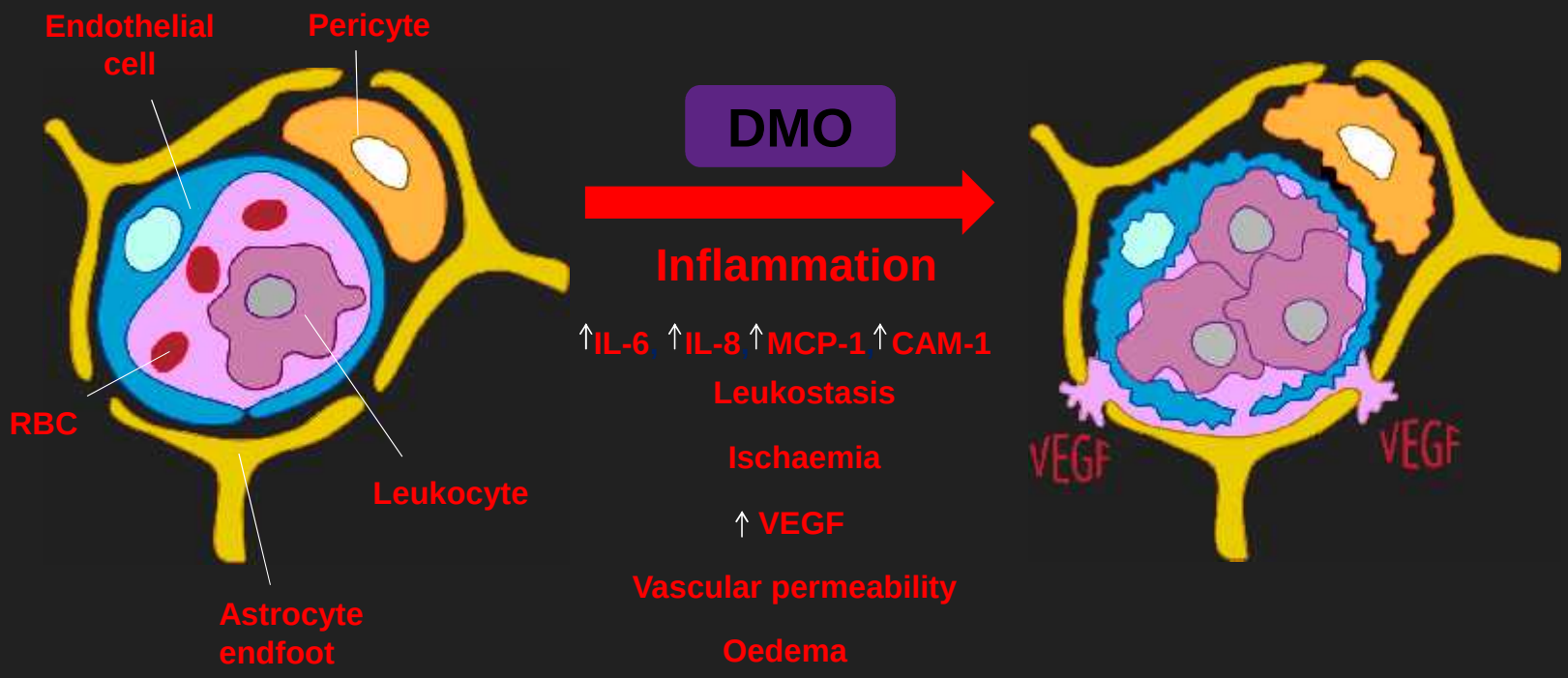
Other treatment options

- Fenofibrate
  - Field study (Fenofibrate vs placebo-5yrs)–significantly lower requirement for laser for DR/DMO in main study
  - Substudy –significantly lower requirement for laser, and also if existing DR-less progression of DR
  - Findings were independent of the effect on lipids-no diff at end of study in both groups
    - PPAR agonists may inhibit VEGF and ICAM
  - Limitations
    - Laser tertiary outcome, some data retrospective, only patients In substudy had photographs, numbers of all events was small
  - ACCORDeye-fenofibrate plus simvastatin reduced progression of DR at 4 years (6.5% vs 10.2% with placebo)

Pathogenesis of DMO



Automated grading

- Others in development: VisionQuest, Singapore, Liverpool

- EyeArt and Retmarker meet NDESP criteria

  - *Egan et al #1002 ARVO 2016*