

Macular Edema

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Member of Advisory Boards:

Alcon, Alimera, Allergan, Astellas, Bayer, GeneSignal, GSK,
Novartis, Pfizer

Macular Edema

1. Definition – Classification
2. Frequency – Morbidity (DR, VO)
3. DR Clinical Evaluation – Macular Edema as complication
4. Biomarkers of Progression
5. Pathogenesis
6. Treatment of Macular Edema

1. Definition / Classification

Non specific sign of ocular disease

Wide variety of situations:

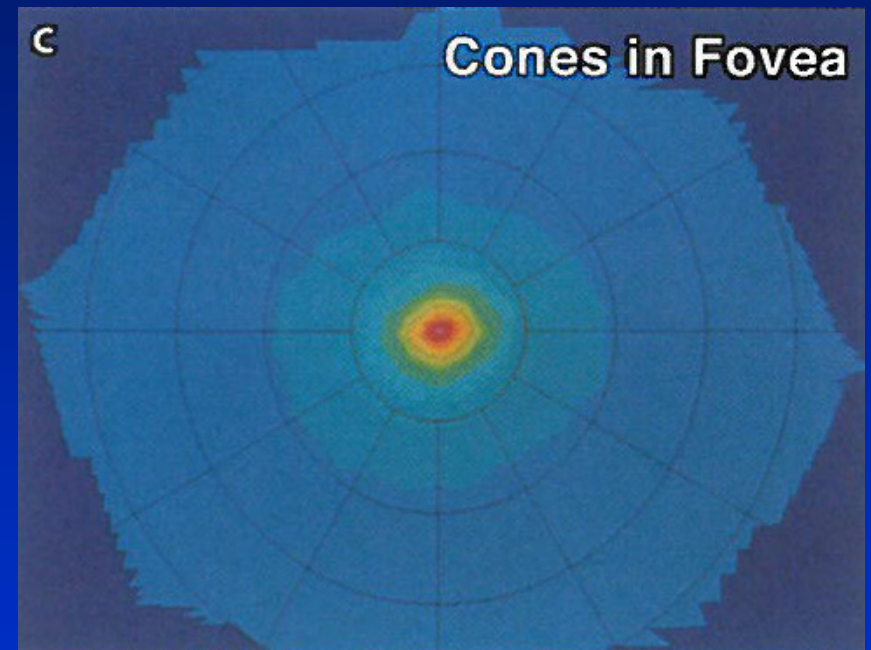
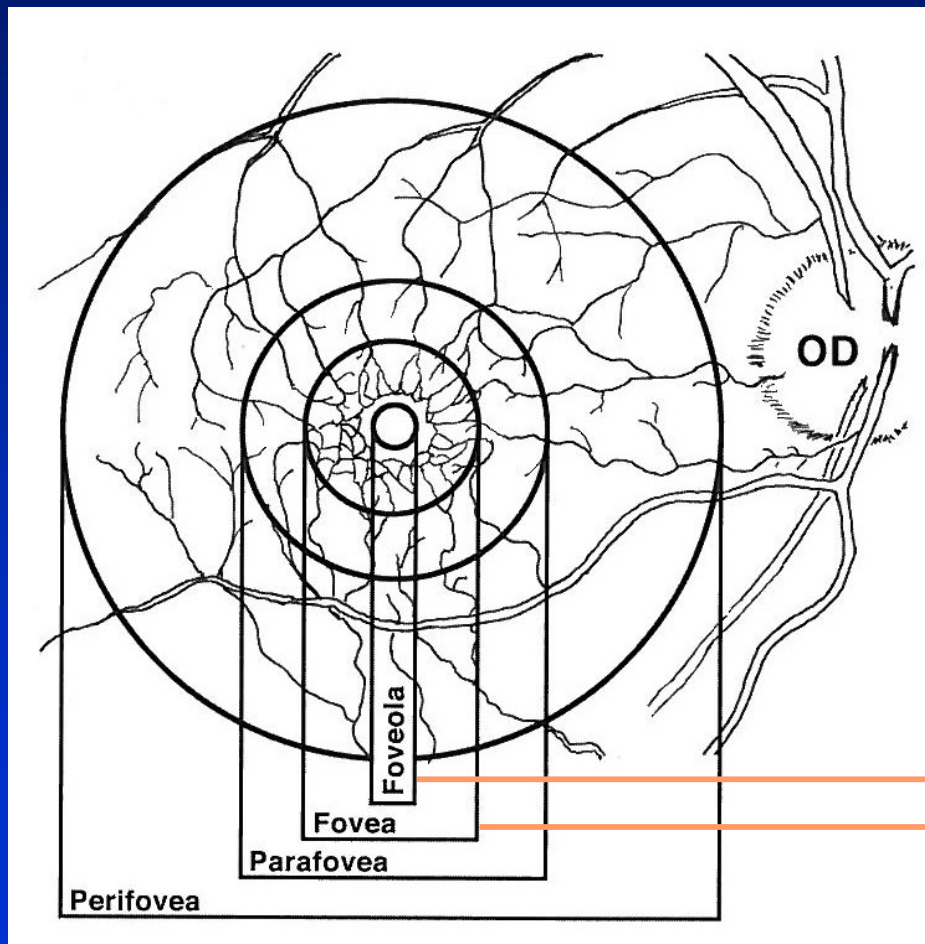
Diabetes, venous occlusions, trauma, uveitis, surgery, age-related macular degeneration, etc.

Retinal Edema = Increased thickening of the retina

Intracelullar

Extracelullar – due to a breakdown
of the Blood-Retinal Barrier

Fovea - Macula

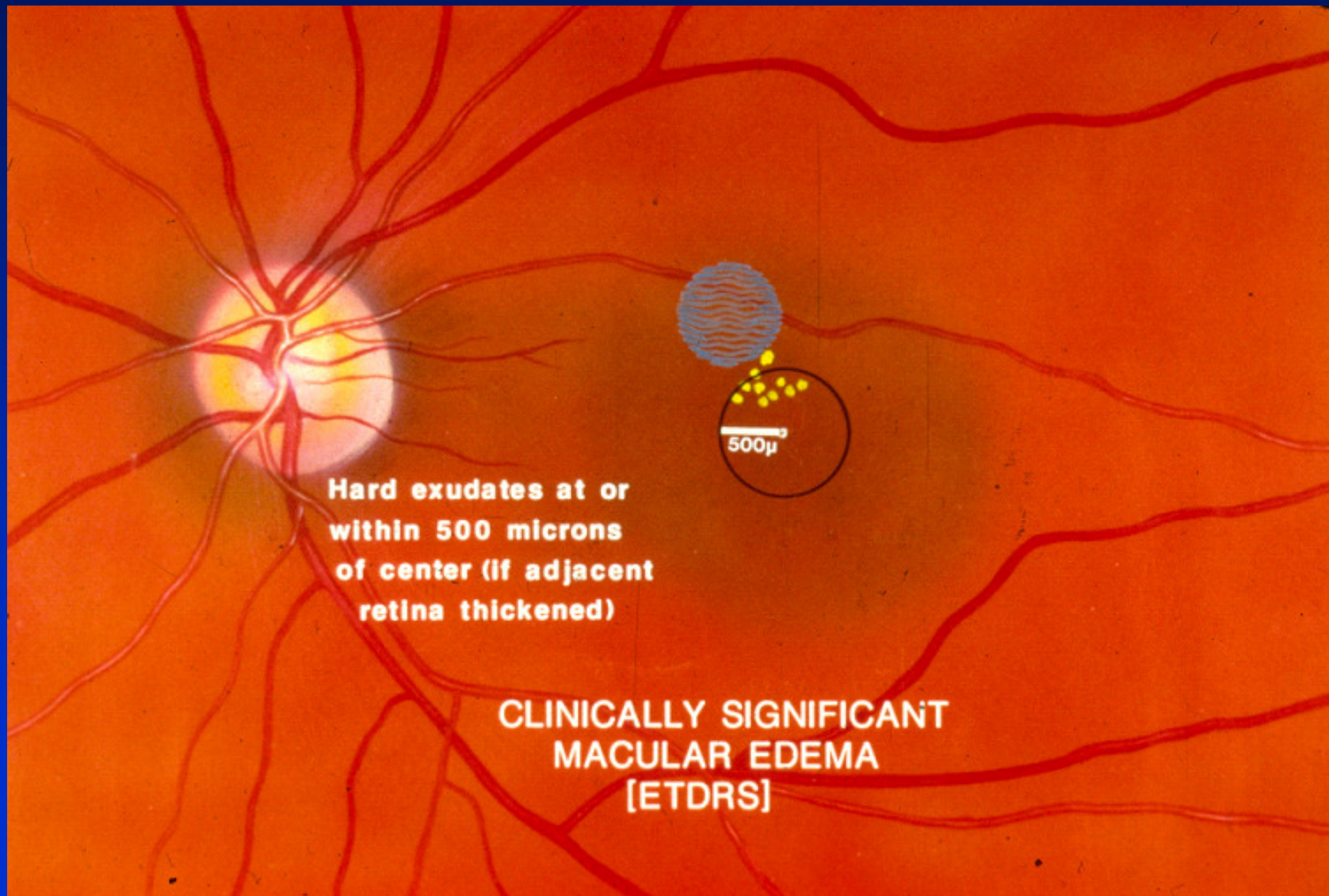


Clinically Significant Macular Edema (ETDRS)

Relevance for Visual Acuity - **Location**

1. thickening of the retina at or within 500 μm of the center of the macula;
2. hard exudates at or within 500 μm of the center of the macula (if associate with thickening of the adjacent retina);
3. zone(s) of retinal thickening of 1 DD or larger, any part of which is within 1 DD of the center of the macula.

Clinically Significant Macular Edema



Clinical Evaluation of DME

Replaced by **objective** measurements

Subjective

Ophthalmoscopy

Slit-lamp

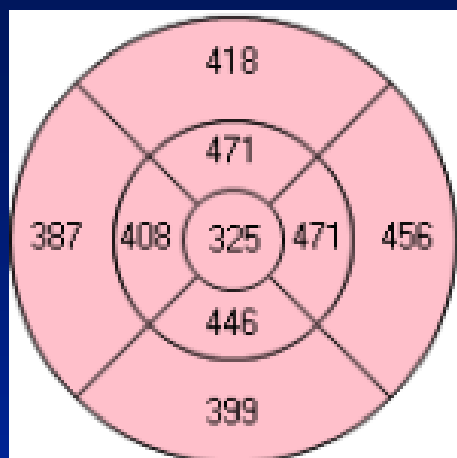
Stereo photography

Objective

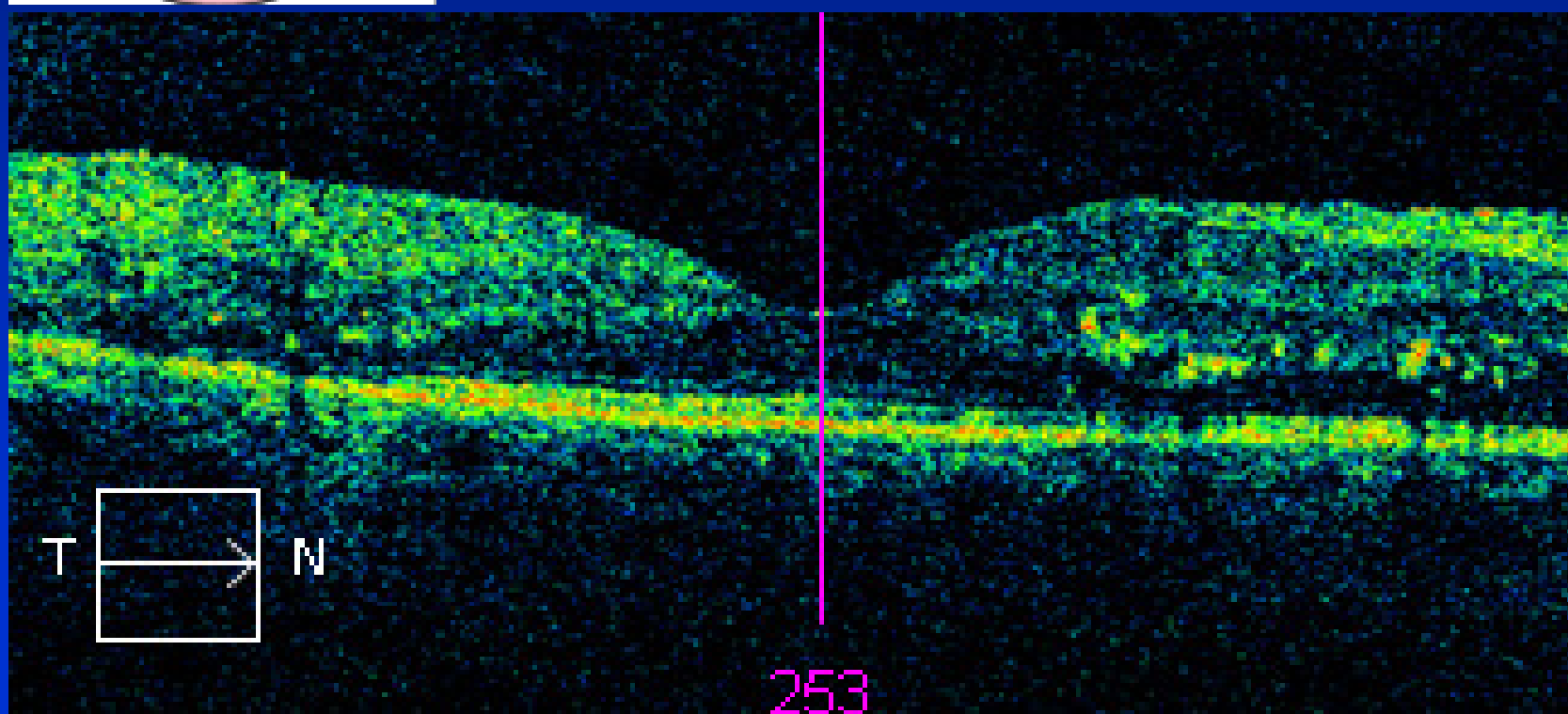


Essential – Location of edema vs. fovea

Amount of Edema



	Central Subfield Thickness (μm)	Cube Volume (mm ³)	Cube Average Thickness (μm)
ILM - RPE	325	14.7	409

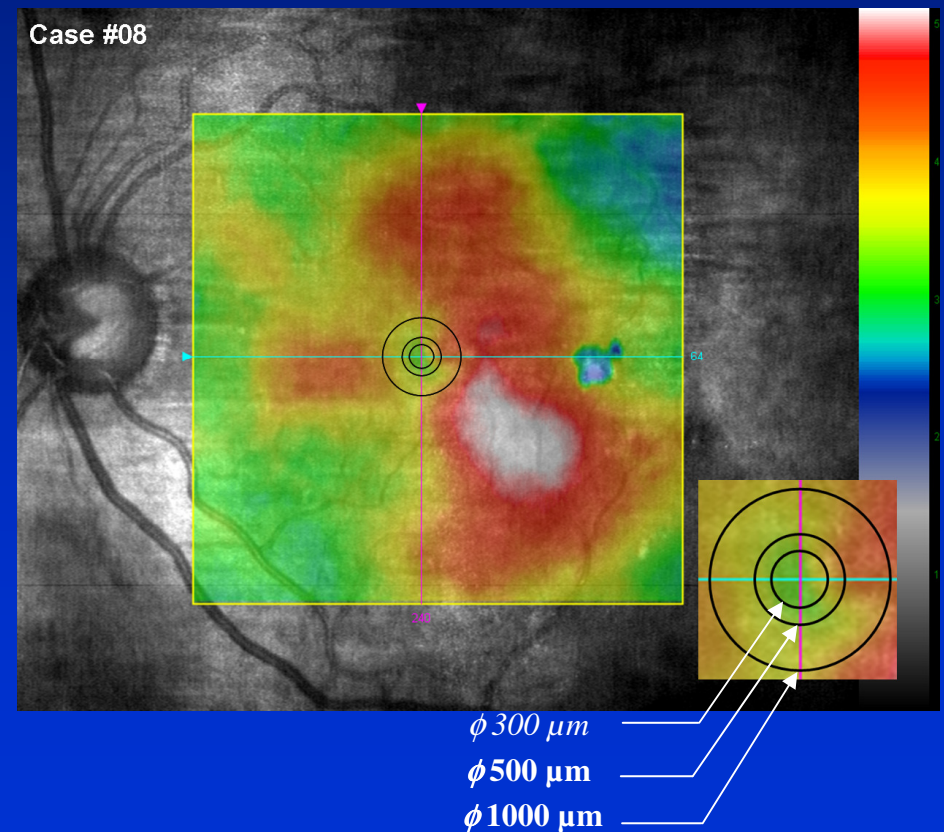


Location vs. Fovea

Mapping CSME

With or Without Central Involvement (500 μm)

Fundus Photography
OCT – High Definition
- Spectral Domain



Proposed ME classification

The proposed classification for DME in an individual patient comprises:

1. Location of edema

- Central-involved DME *or*
- Peri-central inner-involved DME *or*
- Peri-central outer-involved DME

2. Amount of edema

- Mean thickness, volume and/or logOCT of location **PLUS** total volume of all 9 ETDRS subfields

3. Vitreoretinal interface abnormalities

- Present/absent
 - Epiretinal membrane: present/absent/indeterminate
 - Posterior hyaloid detachment: present/absent/indeterminate

4. Hard exudates

- Present/absent in central subfield

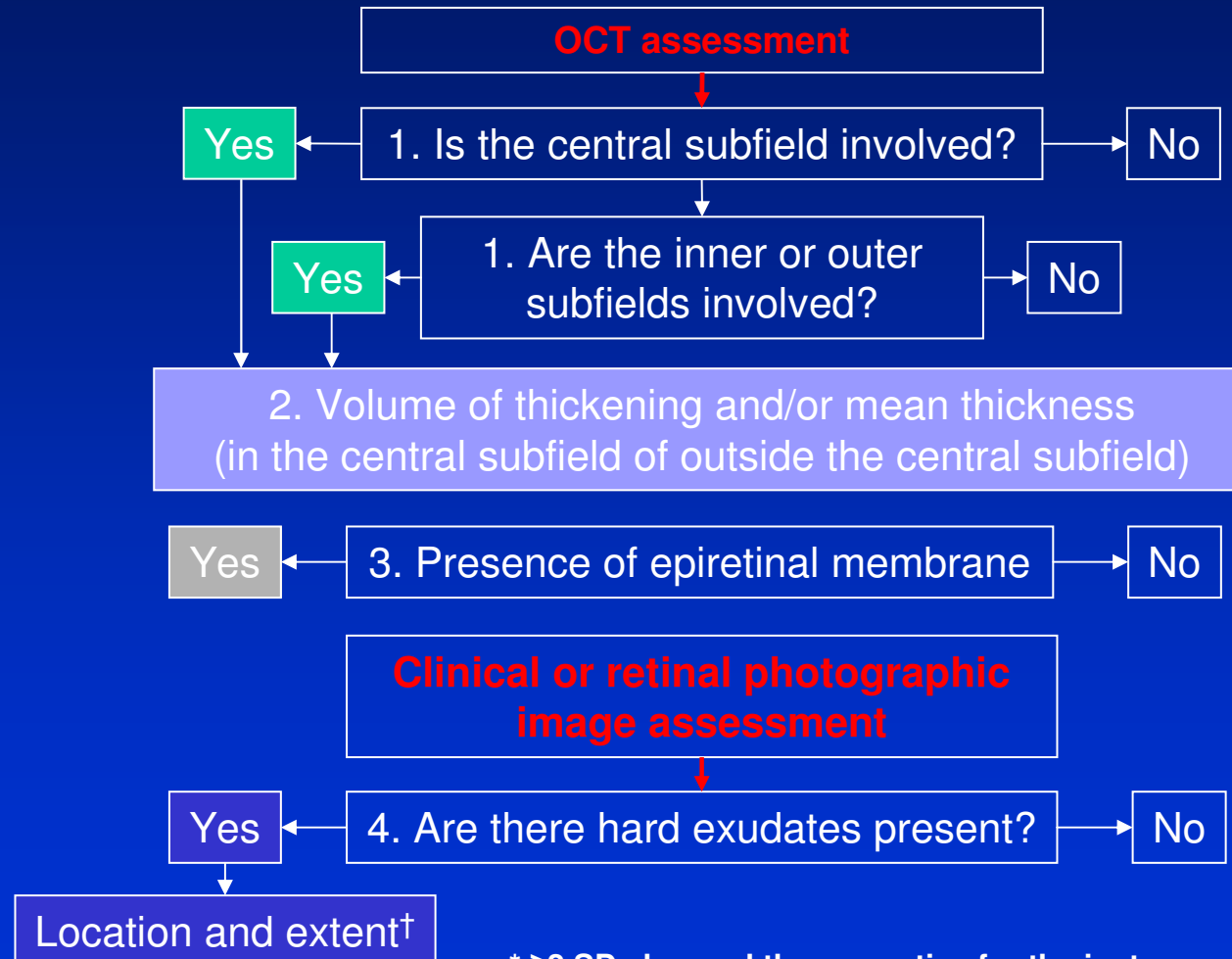
ME classification

1. Location

2. Amount of edema

3. Vitreo-retinal interface abnormalities

4. Hard exudates



* ≥ 2 SDs beyond the normative for the instrument

[†] ETDRS/Wisconsin Reading Centre descriptions

2. Frequency – Morbidity

- Diabetic retinopathy (DR) is a major cause of blindness and the primary cause of blindness in working-age individuals in developed countries¹
- DME is a common manifestation of DR^{1,2}
- DME is the main cause of visual impairment in patients with Type 2 diabetes^{1,2}
- Although DME does not cause total blindness, it frequently leads to a severe loss of central vision¹

DME, diabetic macular edema
DR, diabetic retinopathy

1. Simo R and Hernandez C. *Diabetologia* 2008;51:1574–1580.
2. Simo R and Hernandez C. *Diabetes Care* 2009;32:1556–1562.

Epidemiological trends in diabetes and DME

- Prevalence of diabetes expected to approximately double globally between 2000 and 2030¹
- Number of diabetes cases estimated to reach 300 million worldwide by 2025^{2,3}
- Burden of DME likely to increase due to predicted rise in diabetes prevalence³
- In the UK, prevalence of DME⁴:
 - Estimated to be 187,842 in 2010
 - Expected to increase to 235,602 in 2020

1. Wild S *et al. Diabetes Care* 2004;27:1047–1053.

2. King H *et al. Diabetes Care* 1998;21:1414–1431.

3. Chen E *et al. CMRO* 2010;26:1587–1597.

4. RNIB and EpiVision. 2009; Future sight loss UK (2): An epidemiological and economic model for sight loss in the decade 2010-2020. Full report
http://www.rnib.org.uk/aboutus/Research/reports/2009andearlier/FSUK_2.pdf

Venous Occlusions - Frequency

- Macular Edema - 5-15% BRVO
(over 1 year period)
 - 18% achieves resolution by 4.5 months
 - 41% achieves resolution by 7.5 months

3. Clinical characterization

Diabetic retinopathy: a progressive disease

Nonproliferative DR (NPDR)

- Microaneurysms, intraretinal haemorrhages
- Barrier breakdown (leakage) – exudates
- Capillary closure
- Complication – **DME**

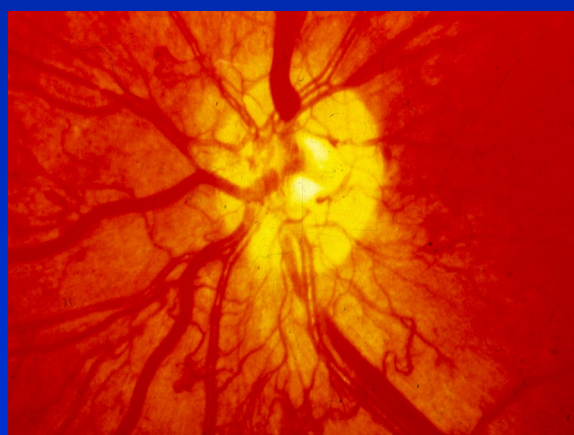


Symptoms

- None
- Vision loss
- Glare

Proliferative DR (PDR)

- Neovascularisation
- Vitreous/preretinal haemorrhage

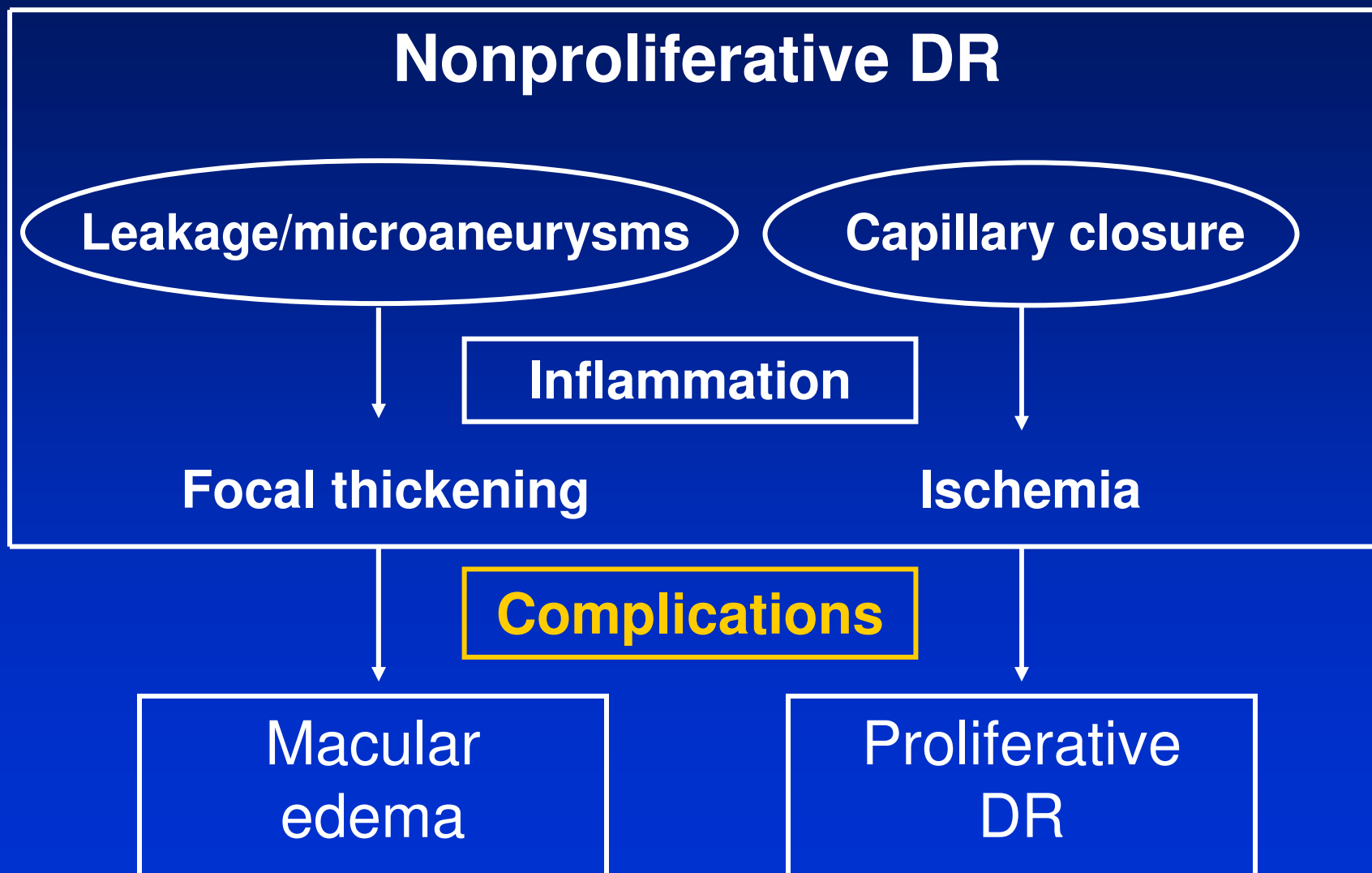


- None
- Vision loss
- Floaters

1. Wilkinson CP *et al. Ophthalmology* 2003;110:1677–1682.

2. Falcão M *et al. Open Circulation and Vascular Journal* 2010;3:30–42.

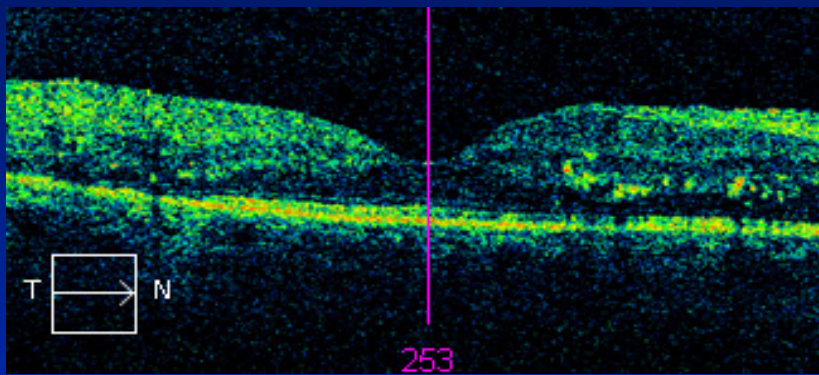
Diabetic retinopathy (DR)



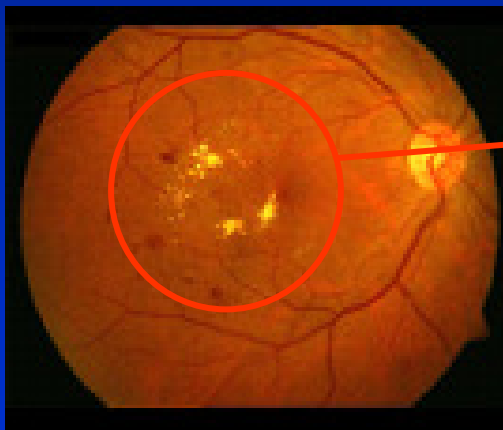
1. Cunha-Vaz J. *Dev Ophthalmol* 2007;39:13–30.

What is Diabetic Macular Edema?

- DME can develop at any stage of DR and is the most common cause of visual loss in nonproliferative DR¹



- Retinal **thickening** due to accumulation of fluid



- Accumulation of **hard exudates**²
- **Microaneurysms** in the central 1000μ

- Severity of DME is based on distance of retinal thickening and/or exudates from the macular centre² - **Location to fovea**

1. Lang GE. *Dev Ophthalmol* 2007;39:48–68.

2. Wilkinson CP *et al. Ophthalmology* 2003;110:1677–1682.

Evolution of DR: general clinical impression

- Different evolution in different patients with similar metabolic control and duration of disease
- Not all patients develop persistent macular edema
- Not all patients develop neovascularization

NPDR phenotypes: type 2 diabetes

Phenotype A	▪ Slow progression (<2 red dots/year) ▪ Accelerated ageing process (diabetes)
Phenotype B	▪ Rapid progression (>2 red dots/year) ▪ Increased flow ▪ Alterations of BRB – leakage ▪ Increased retinal thickness – edema ▪ Haemodynamic changes predominate
Phenotype C	▪ Rapid progression (>2 red dots/year) ▪ Decreased flow ▪ FAZ outline changes ▪ Thrombotic changes predominate

BRB, blood retinal barrier
FAZ, foveal avascular zone

1. Cunha-Vaz J. *Development Ophthalmology* 2007;39:13–30.

4. Biomarkers of Progression

Microaneurysm Turnover

- Evaluation of Progression by counting microaneurysms (red dots) in sequential visits and identifying their exact location in the retina
 - Identifying new microaneurysms (formation rate)
 - Disease activity + Leakage
 - Identifying disappearing microaneurysm (disappearance rate) – Capillary Closure

Microaneurysm turnover

Methods

MA Turnover - “Retmarker^{DR}”

Baseline

6-month

12-month

18-month

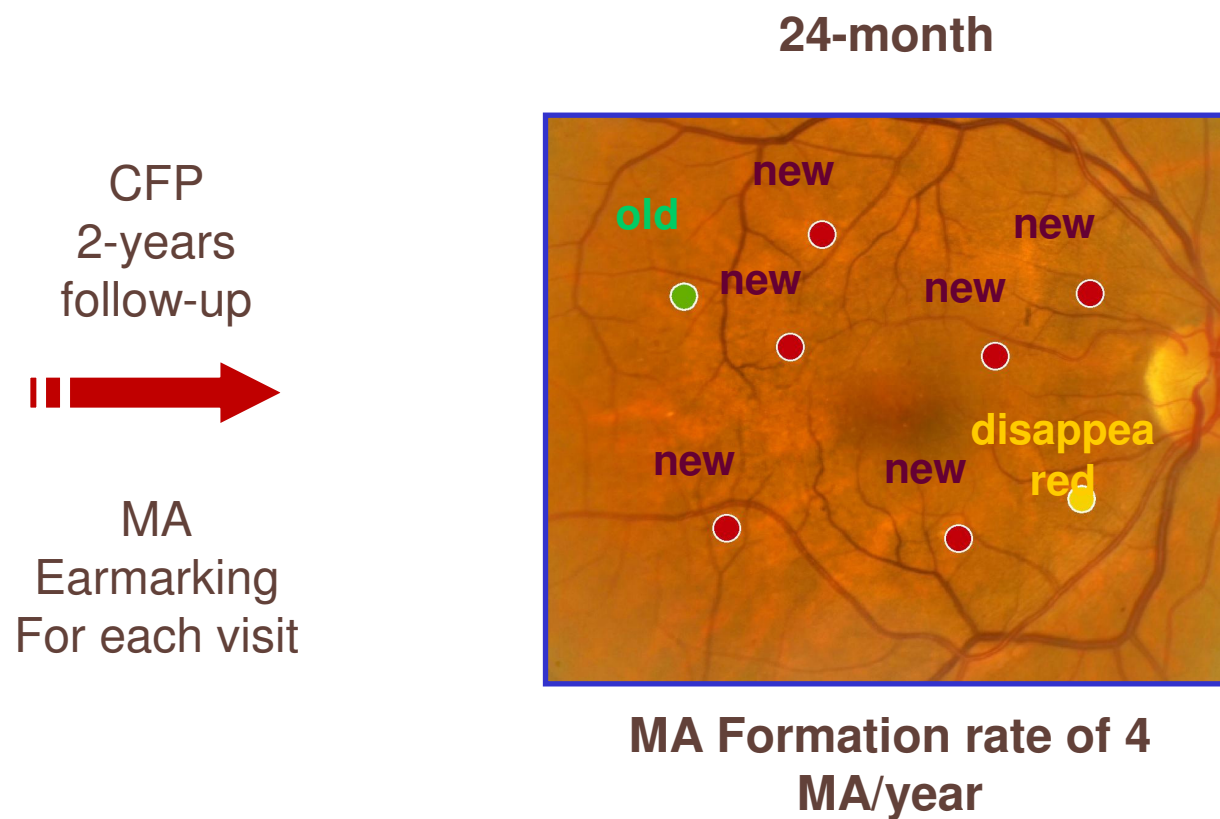
24-month



Microaneurysm turnover

Methods

MA Turnover - “Retmarker DR”



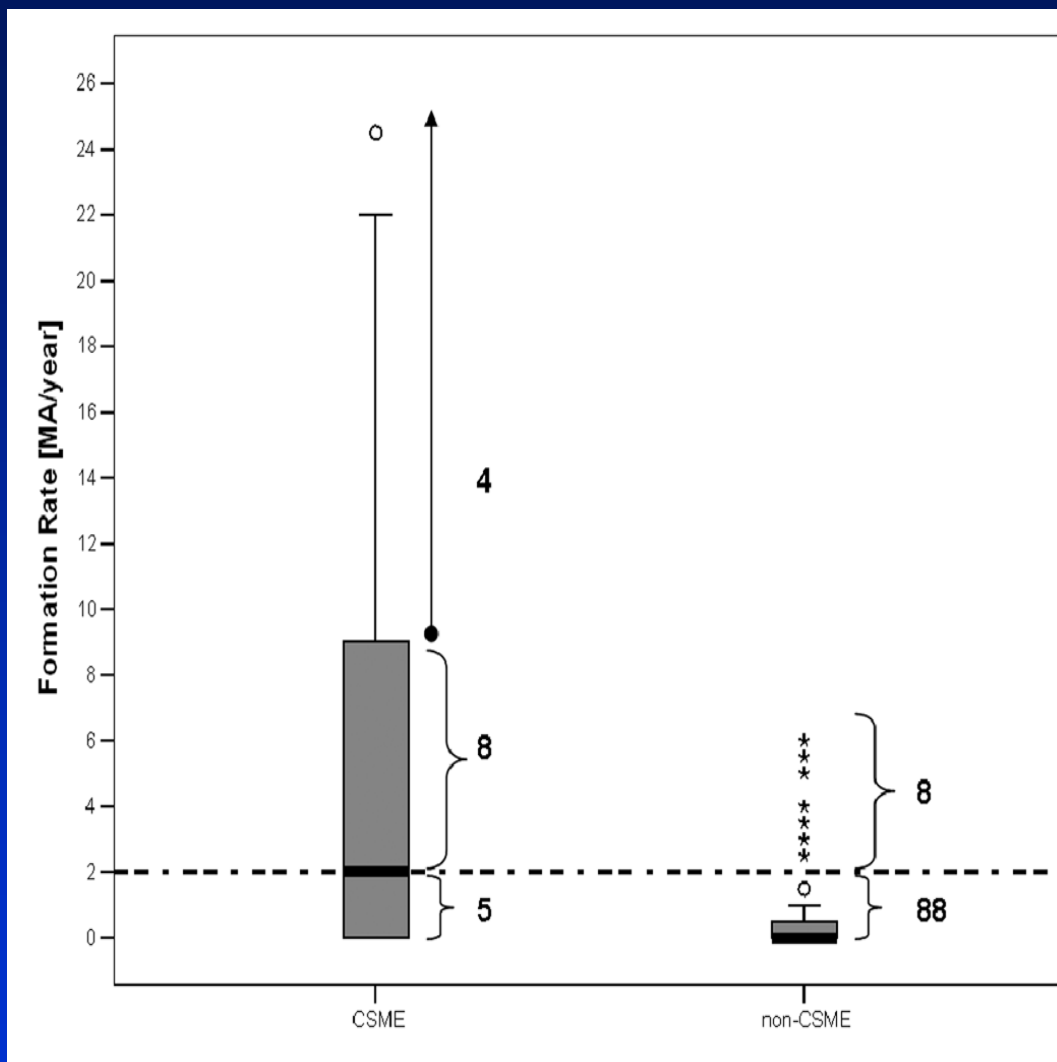
Microaneurysm turnover Results

■ 17 patients with **CSME**
(10-Year follow-up of 113 patients)

◆ Higher MA turnover
 $p < 0.001$

◆ MA turnover ≥ 2 MA/Y

12/17 (70.6%) vs 8/96 (8.3%)
 $P = 0.002$ vs $p = 0.647$



Findings confirmed by Michael Ulbig et al., Munich, Germany.

EVICR.net (European Vision Institute Clinical Research Network)

- **Network of European certified clinical trial sites (75) from 16 European countries**
- **Centralized infrastructure**

6 Scientific Sections:

- ⇒ AMD and Retinal Dystrophies
- ⇒ Diabetic Retinopathy
- ⇒ Glaucoma
- ⇒ Cornea, Cataract & Refractive Surgery
- ⇒ Ocular Surface & Inflammation
- ⇒ Reading Centres

2. Protocol nº ECR-RET-2010-02

Title: Identifying progression of retinal disease in eyes with NPDR in diabetes type 2 using non-invasive procedures

ClinicalTrials.gov Identifier: NCT01145599

Principal Investigator: J. Cunha-Vaz

Nº Centres involved: 18 (450 patients)

- One year follow-up (0, 3, 6, 12 months)
- Centralized Reading Centre (CORC)

Progression to DME

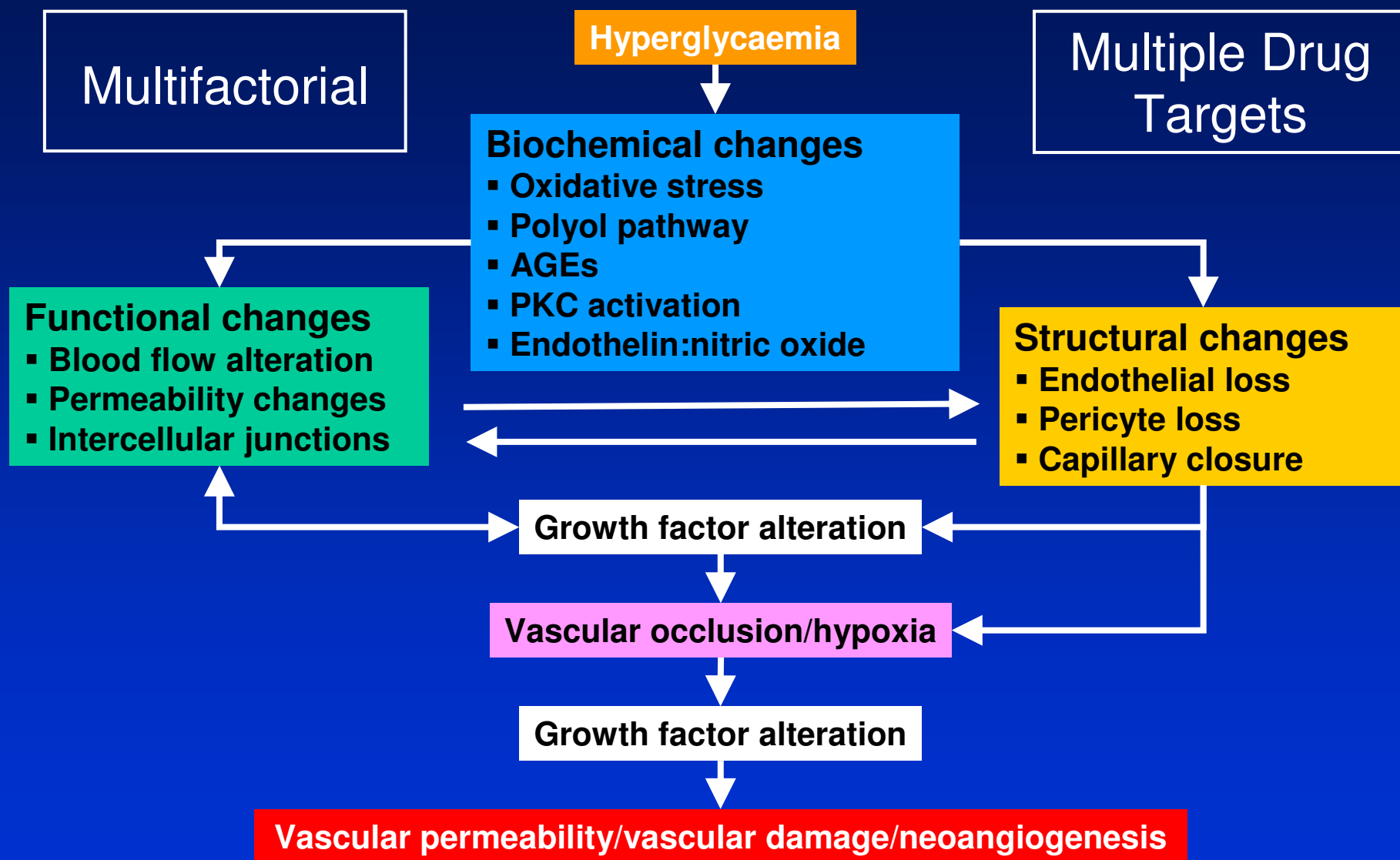
- **Microvascular disease activity**
 - **Microaneurysm Turnover**
 - **Fundus Photography**
 - **Retmarker**
- **Increase in Retina Thickness**
 - **OCT**
- **Association with vision loss (photoreceptors status)**
 - **OCT**
- **BCVA** -

5. Macular Edema - Pathogenesis

- Breakdown of Blood-Retinal Barrier -

- 1. Diabetes - Multifactorial changes in the inner BRB**
- 2. Venous Occlusion – Hemodynamic factors**
- 3. Associated role of inflammation and outer BRB**

Pathogenesis of diabetic retinopathy



AGE, advanced glycation end-product
PKC, protein kinase C

Adapted from Kahn ZA and Chakrabarti S.
Experimental Diabetes Res 2003;4:287–301.

Diabetic Macular Edema – Key points

- DME is a major cause of visual impairment in patients with diabetes
- Burden of DME likely to increase as prevalence of diabetes expected to rise by ~50% globally from 2000 to 2030
- Several biochemical factors and pathways are implicated in the development of DR and DME (complex association to mechanisms)
- VEGF plays a major role in the pathogenesis of DR complications
- The pathogenic profile varies among patients, leading to differing disease characteristics, requiring personalised strategies to manage the disease effectively

6. Treatment of Macular Edema

Systemic

Metabolic control

Blood Pressure

Lipid Lowering

Local

Laser: Conventional vs subthreshold

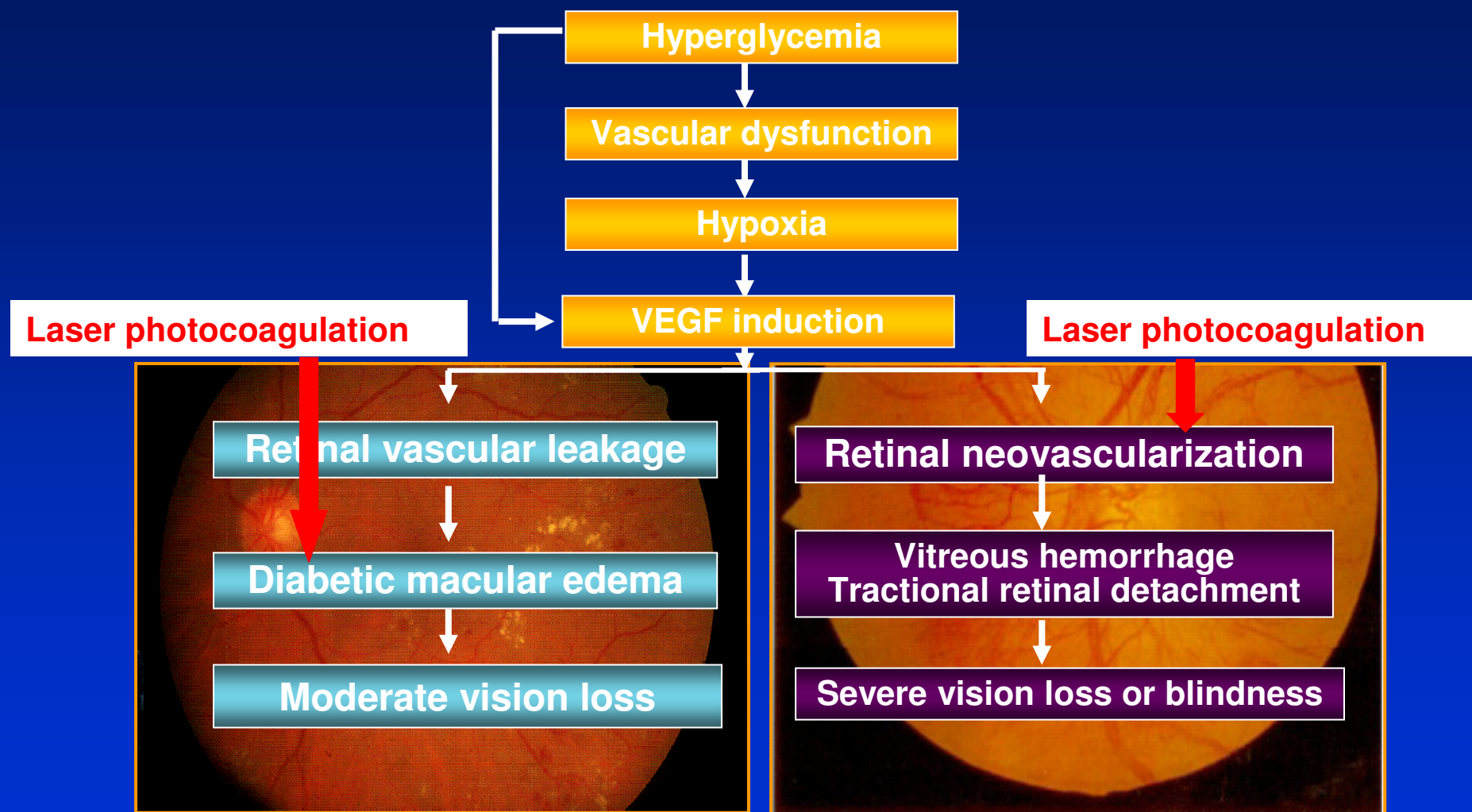
Intravit. Antiangiogenics: Lucentis, etc

Intravit. Steroids: Osurdex, Iluvien, etc

Combination Tx

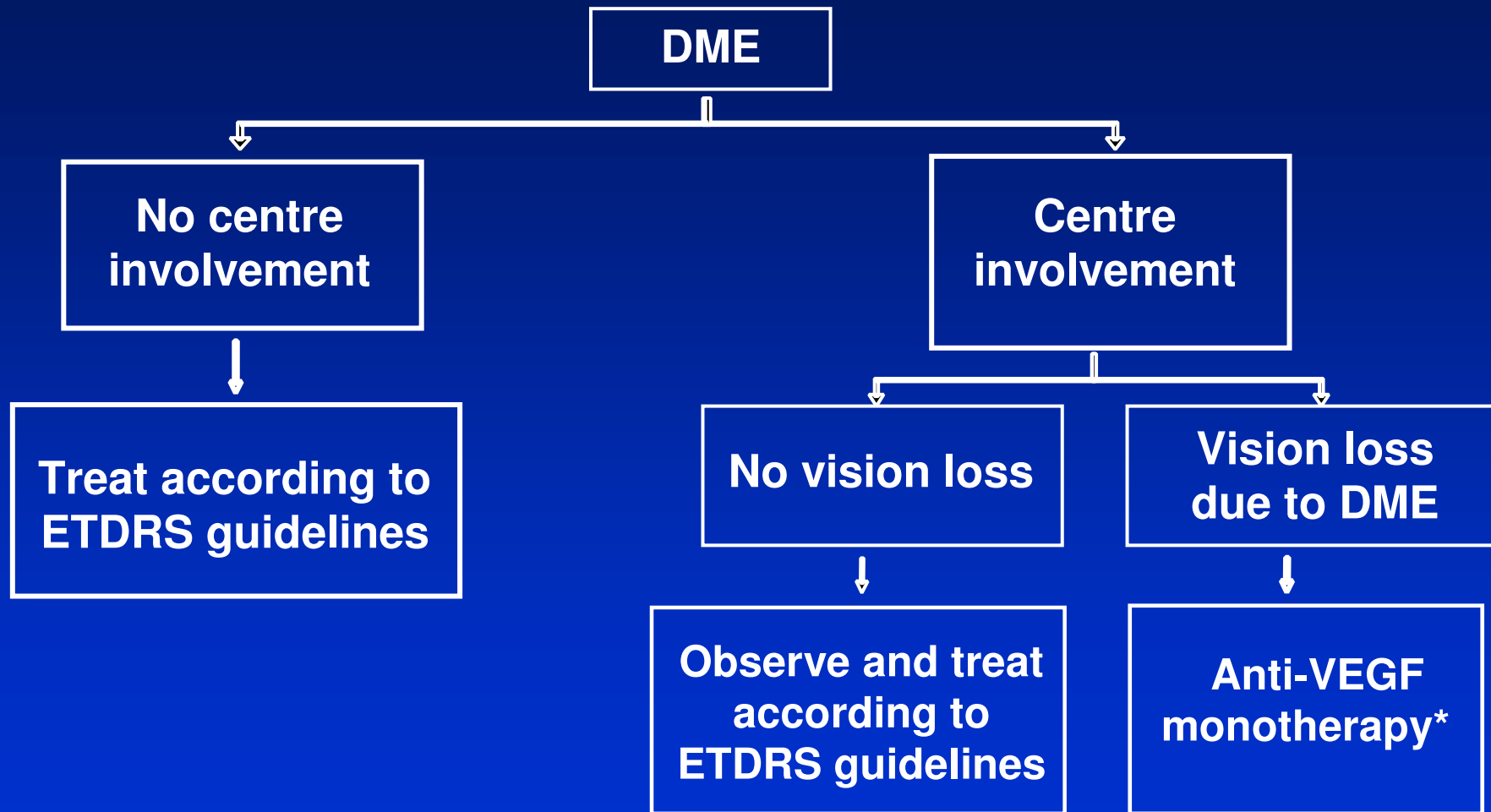
Vitreectomy – ILM (?)

Laser Management of DR



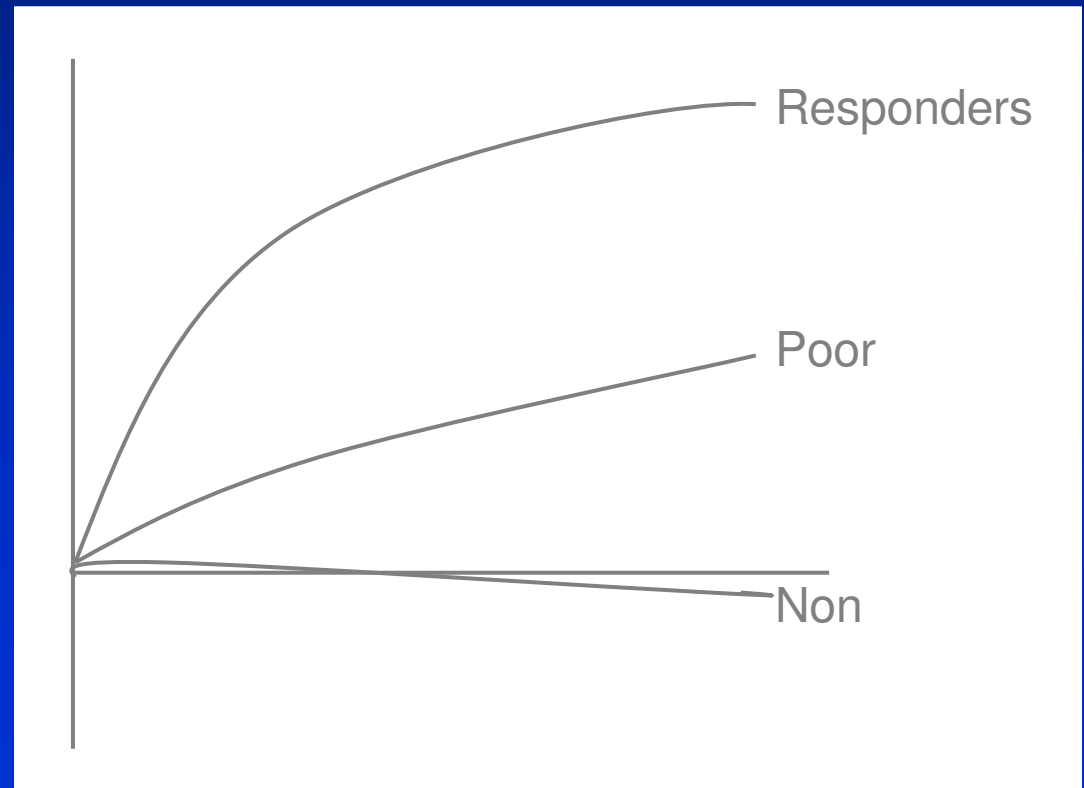
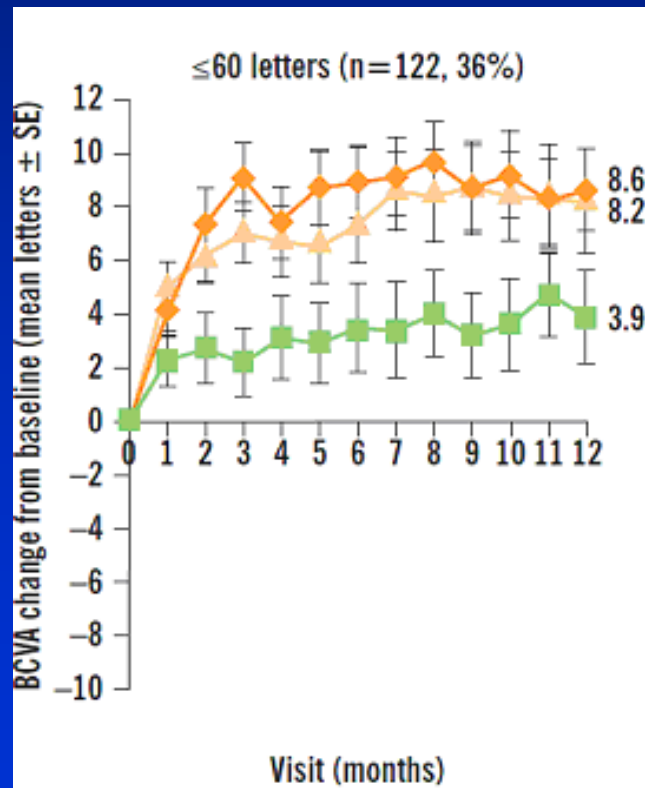
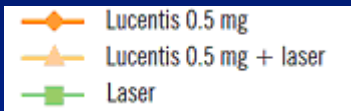
Adapted from Sheetz MJ, King G. JAMA 2002;288:2579-2588.

Present view of DME treatment



Different Responders to Anti-VEGF Treatment

Visual Acuity – recovery of photoreceptor function



Combination treatments for DME

Anti-VEGF Loading dose 3-4 injections

Laser After 1st injection (one week)

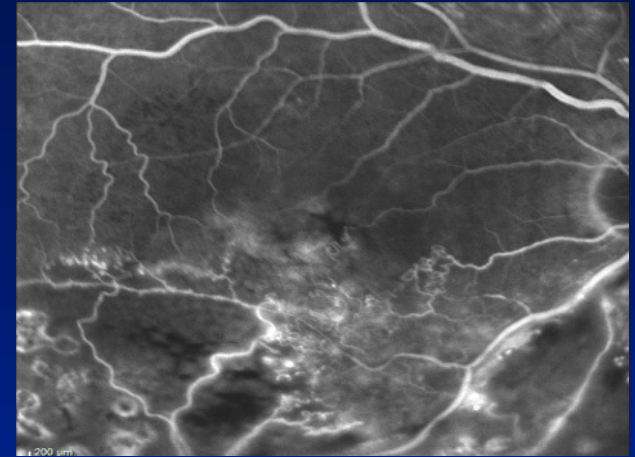
Steroids for non-responders to anti-VEGF treatment

Characterization of Responders

Predominant Disease Mechanism

Leakage	Inflammation	Ischemia
Edema OCT	Disease Activity MA Turnover + chronicity	Ischemia Ganglion Cells OCT

Treatment Macular Edema in Retinal Vein Occlusions



Macula perfused

- Intravitreal steroids
- Anti-VEGF

Macular ischemia

- Intravitreal steroids
- Anti-VEGF

Neovascularization

- Scatter laser to area of ischemia
- Consider
 - Intravitreal Steroids
 - Anti-VEGF

Consensus Management VO. Ophthalmologica 2011,226(4).

Macular Edema Treatment

Depends of response to treatment

Visual Acuity Improvement

Photoreceptors status

Retinal Tickness (Edema)

Leakage intra-retinal fluid

subretinal fluid (VA)

Macular Edema

1. Definition based on OCT (non-invasive, objective)
2. Increasing frequency
3. Different patients - Different rates of progression
4. Microaneurysm Turnover - Biomarker in diabetes
5. Pathogenesis – Complex/Alt of Blood-Retinal Barrier
6. Treatment of Macular Edema – Personalized / Response to Tx

→ Combination Therapy