Istituto Superiore di Sanità
IV Convegno:

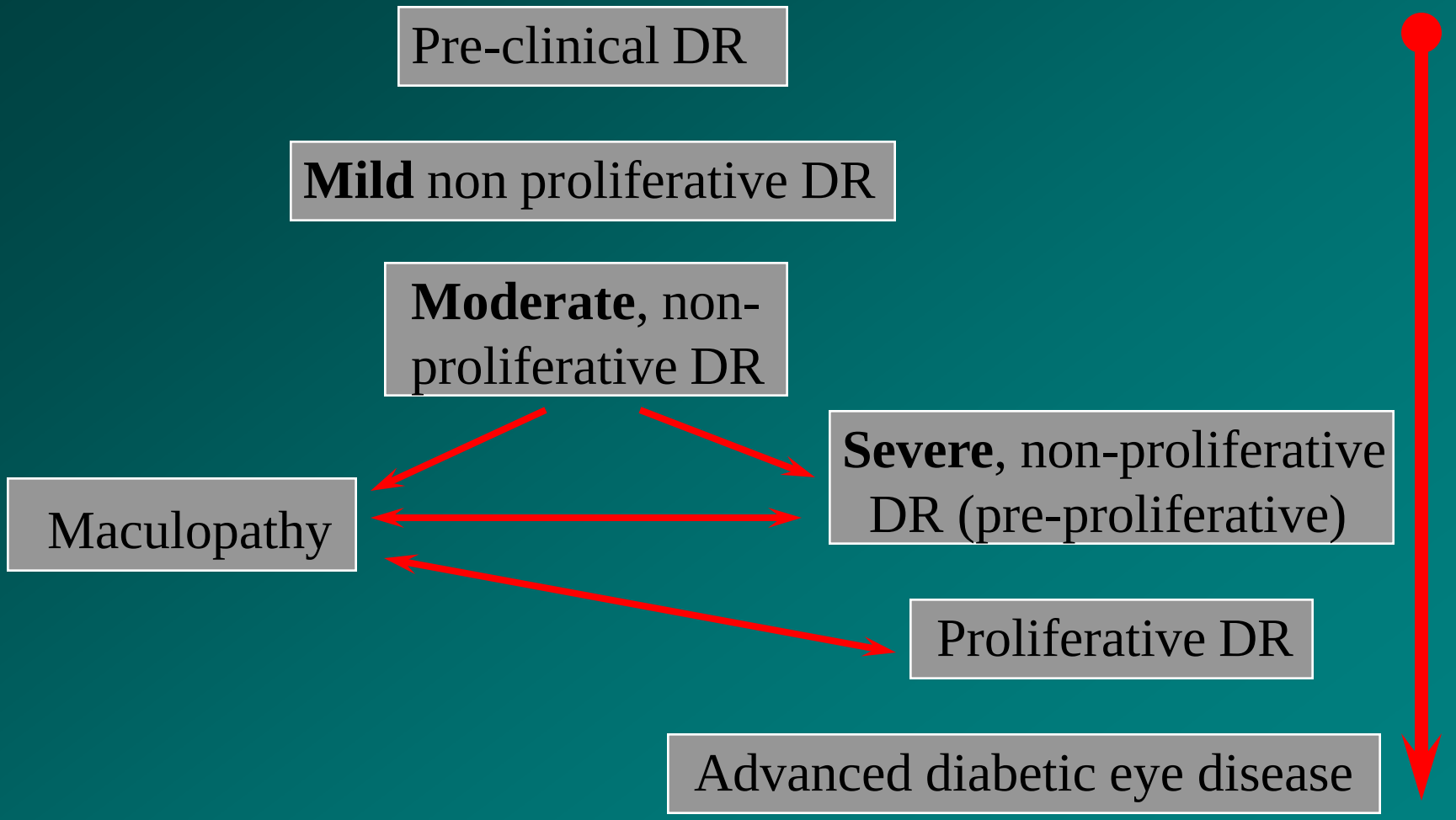
PREVENIRE LE COMPLICANZE DEL DIABETE DALLA RICERCA DI BASE ALL'ASSISTENZA

Roma, 18 febbraio 2009

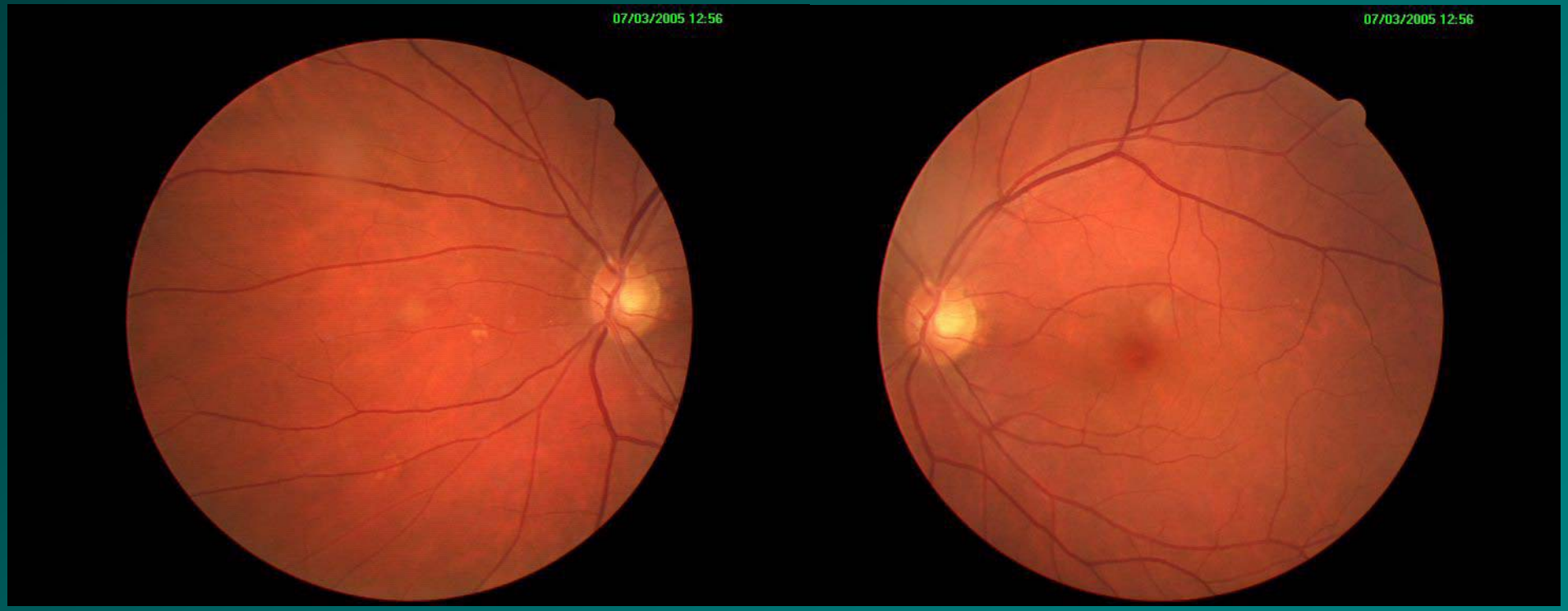
La microangiopatia retinica

Massimo Porta
Dipartimento di Medicina Interna
Università di Torino

Natural history of diabetic retinopathy



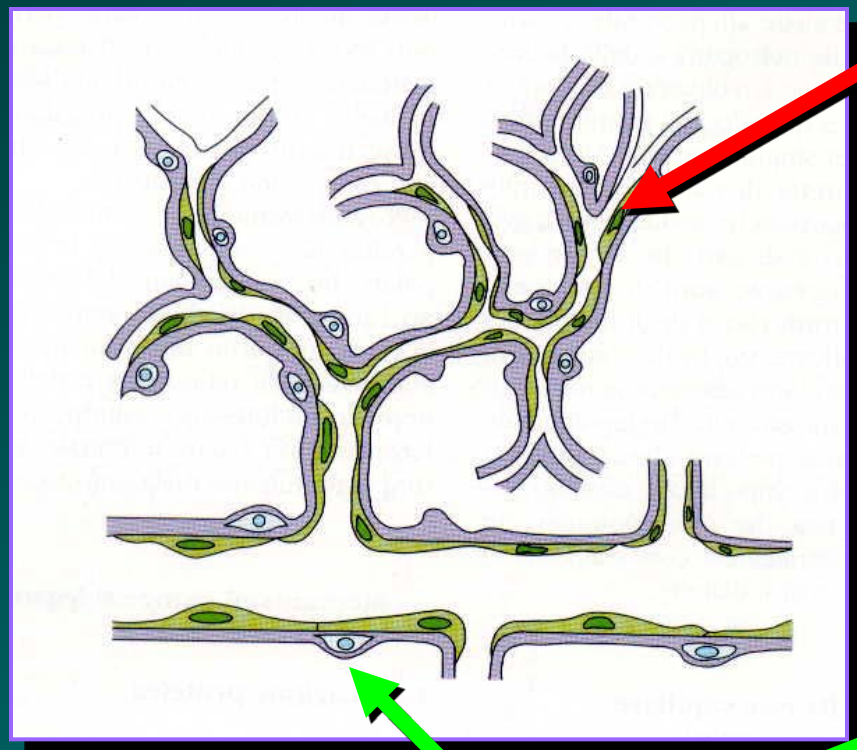
Pre-clinical diabetic retinopathy:



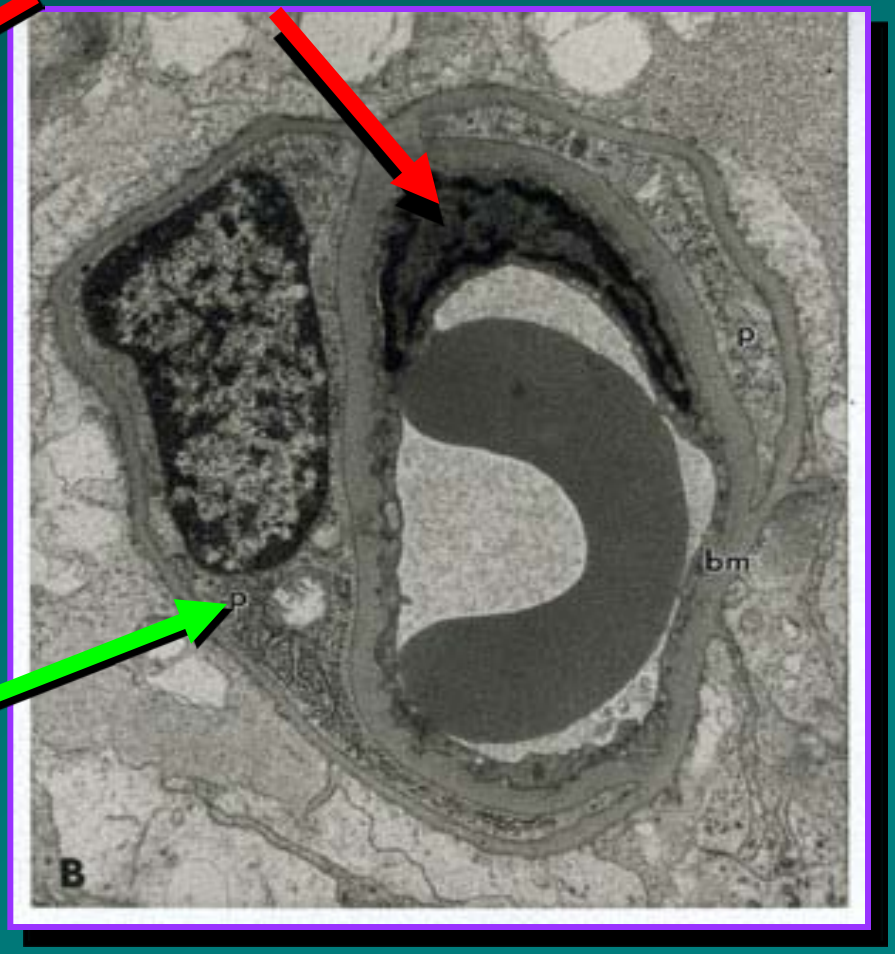
Pre-clinical diabetic retinopathy:

- No lesions observed by ophthalmoscopy or fluorescein angiography
- Altered retinal blood flow
- Histological changes?

HEALTHY RETINAL CAPILLARIES

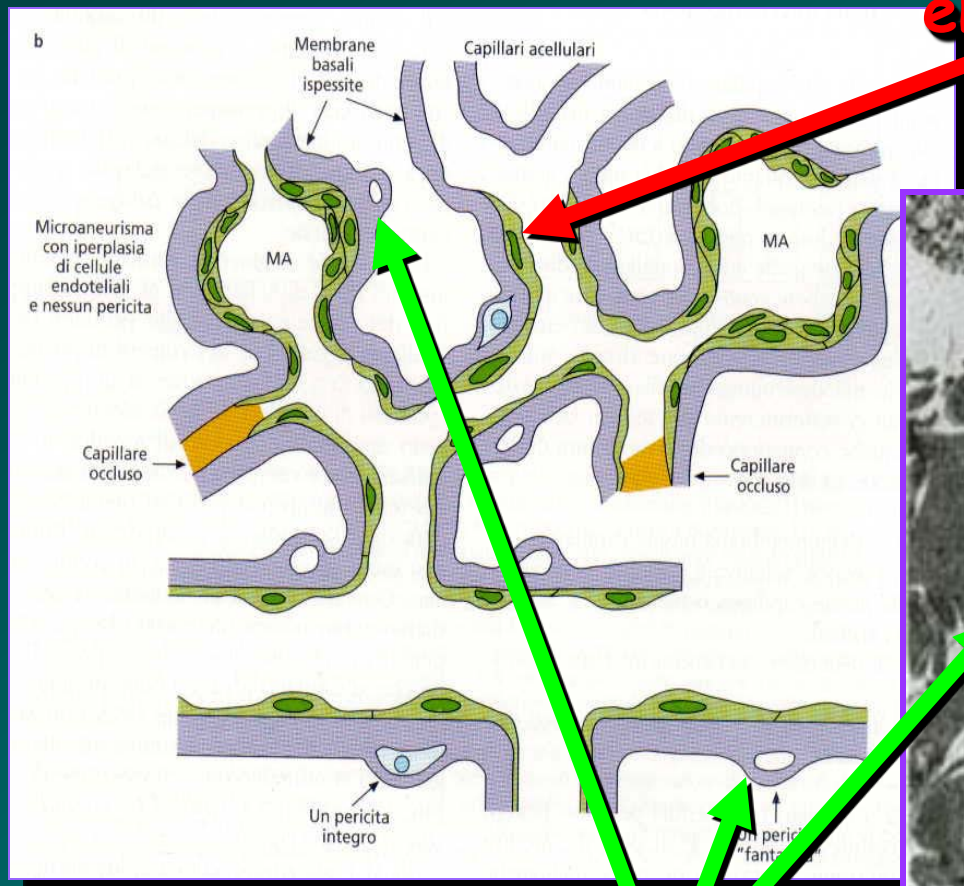


endothelial cell

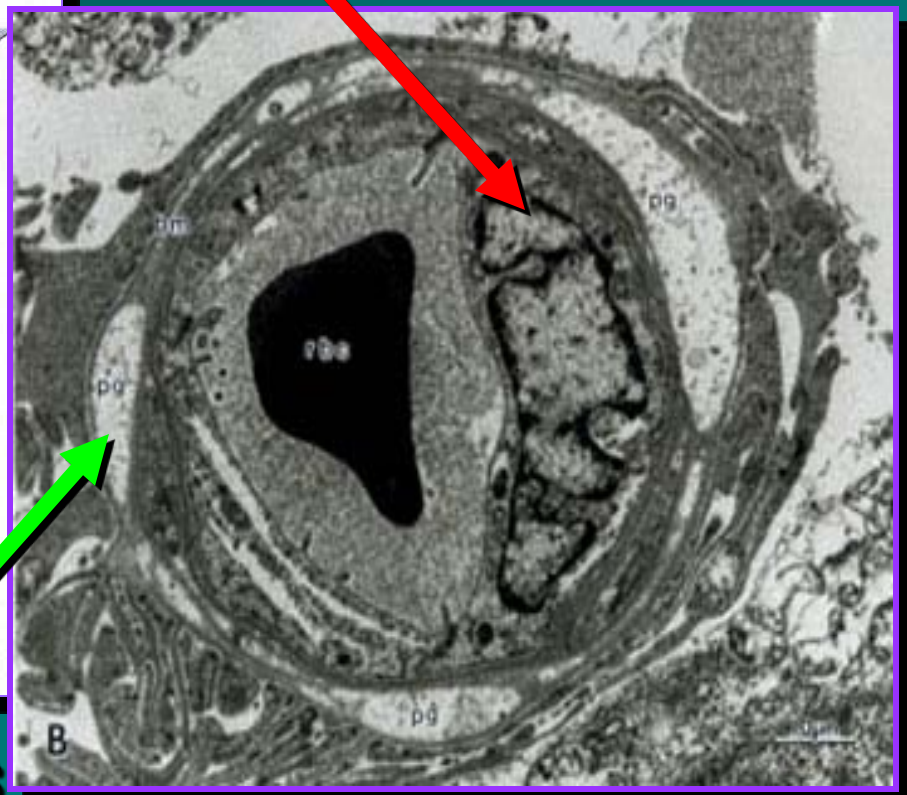


pericyte

CAPILLARY ALTERATIONS
IN DIABETIC RETINOPATHY

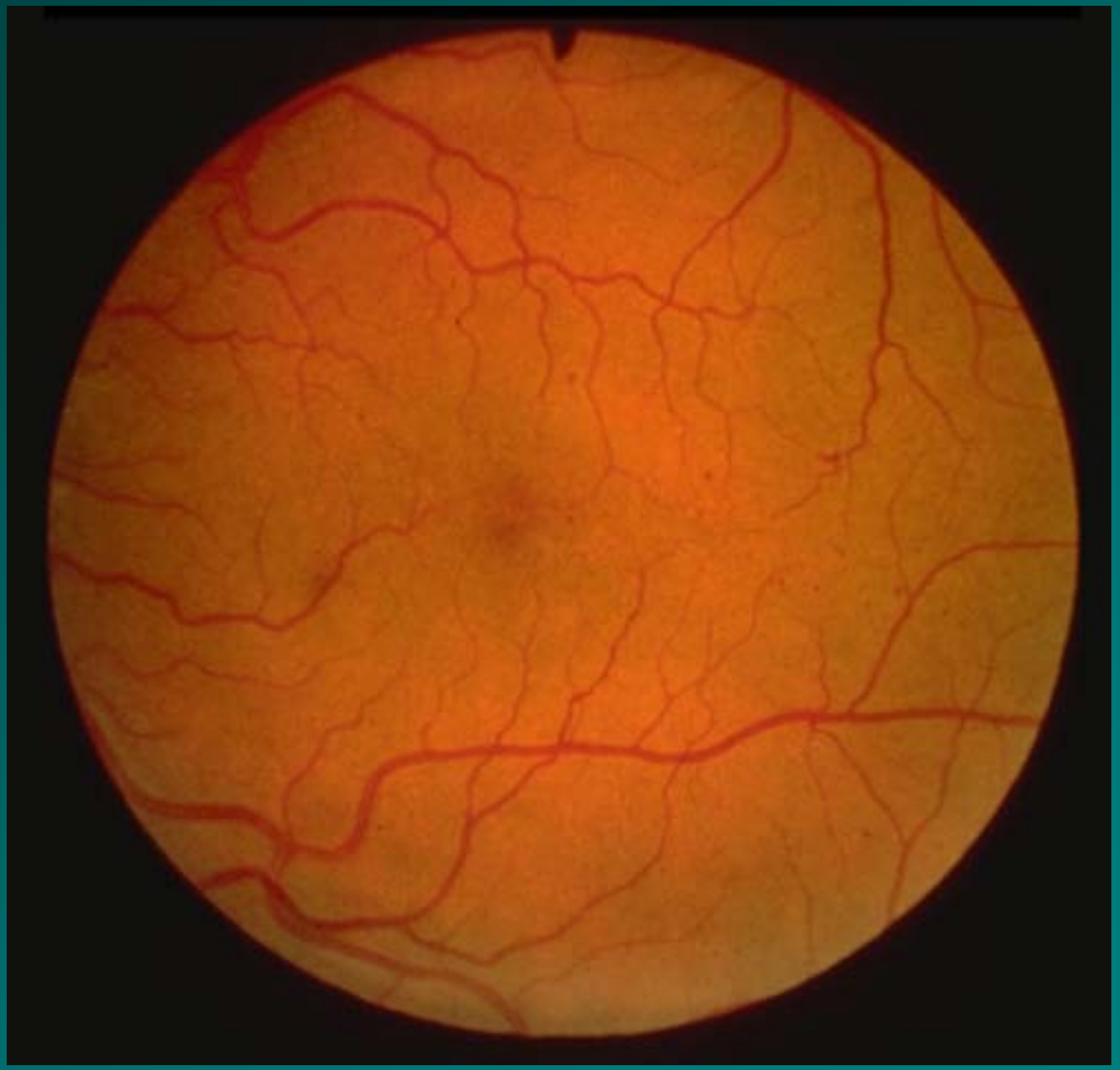


endothelial cells

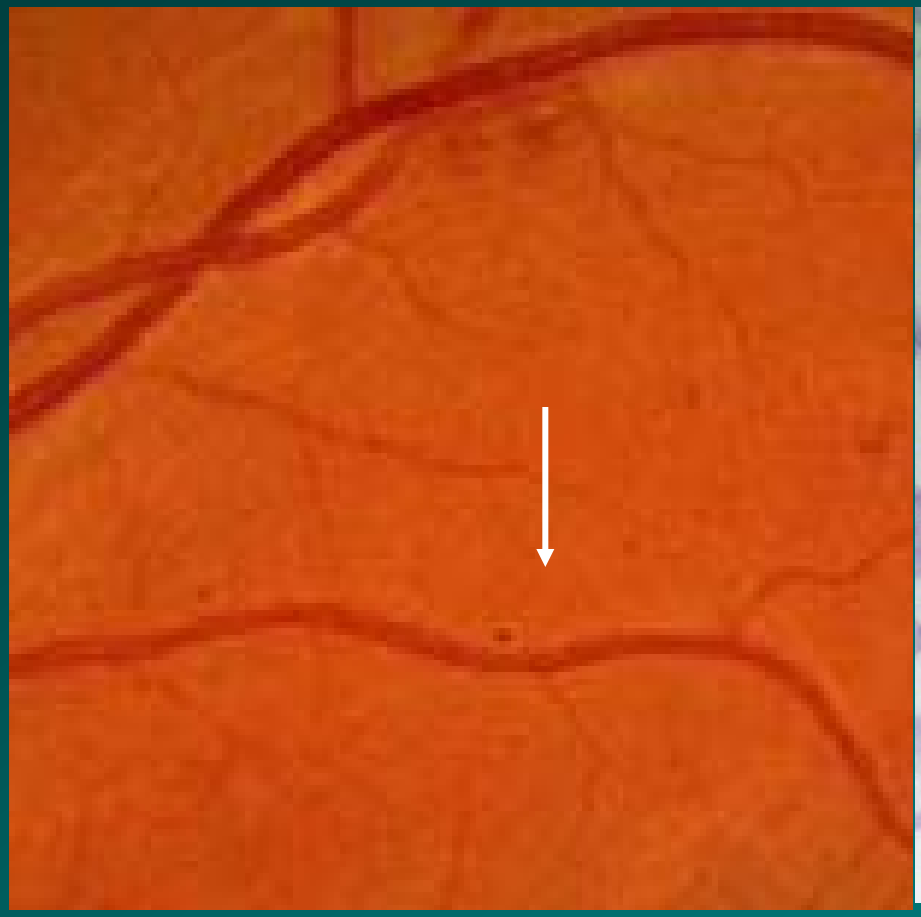


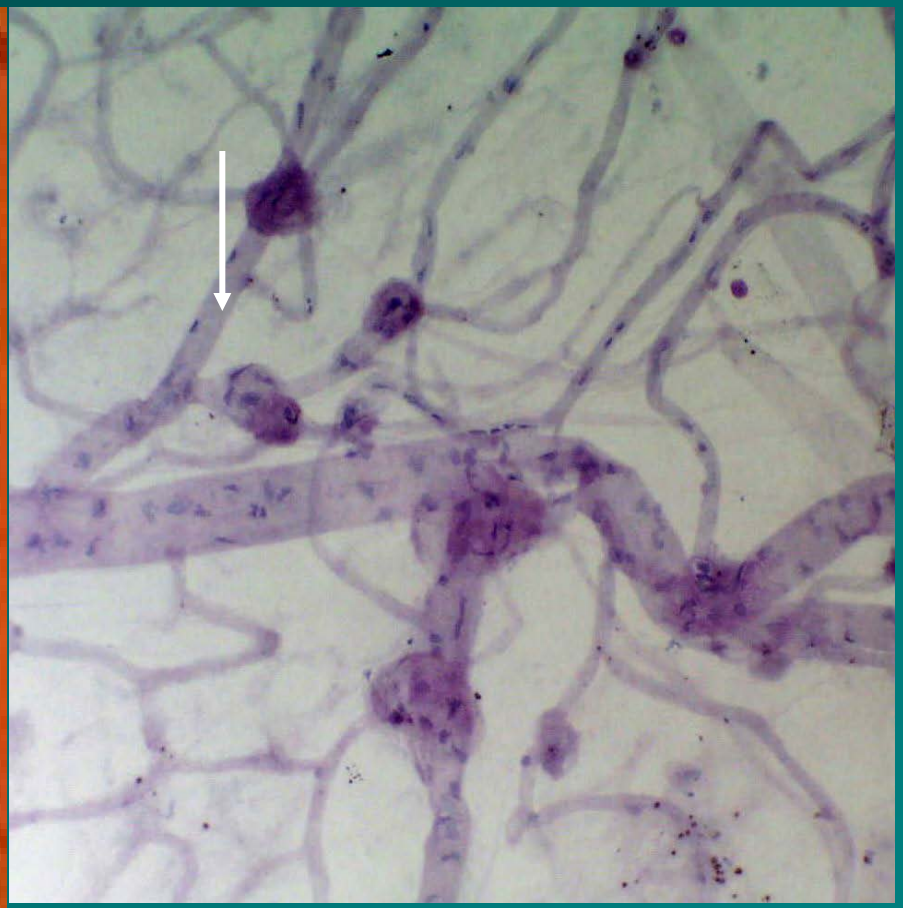
ghost pericytes

Mild NPDR: red dots and blots



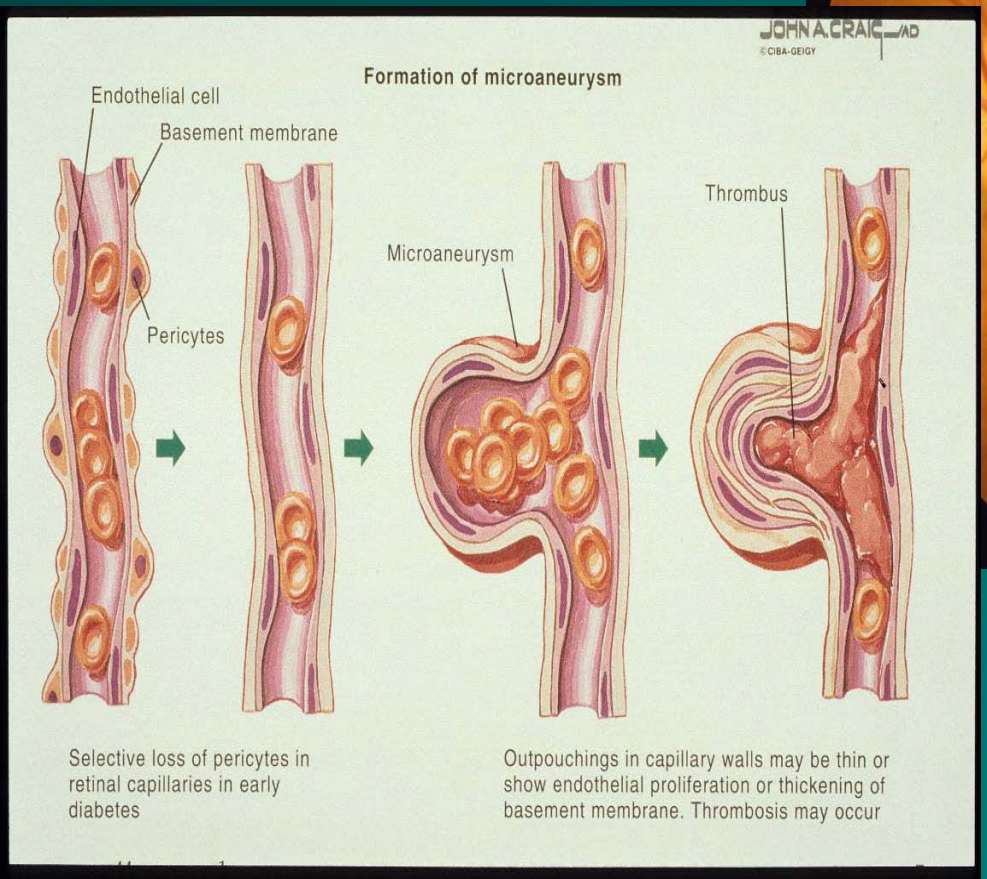
Mild non-proliferative DR

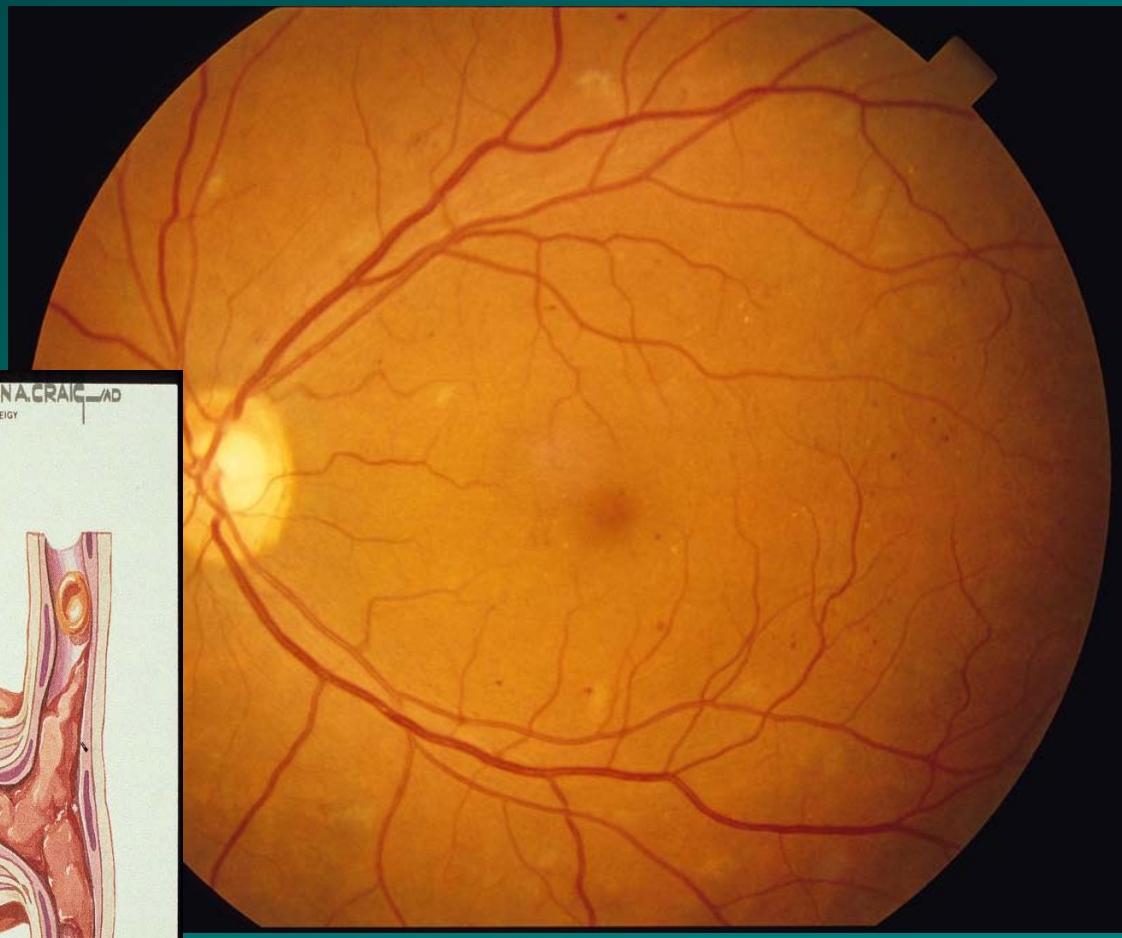




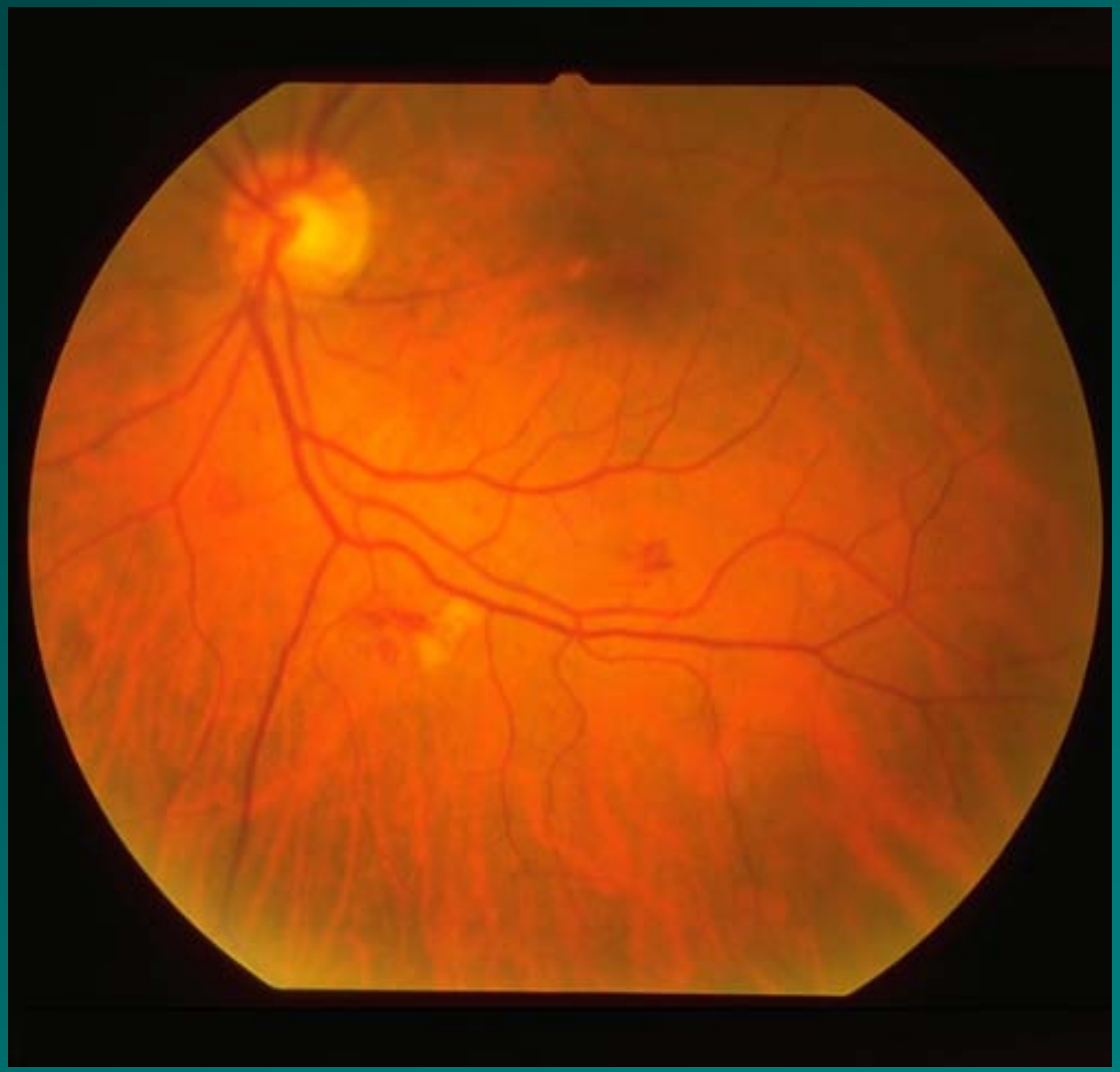
Microaneurysms

Mild non-proliferative diabetic retinopathy

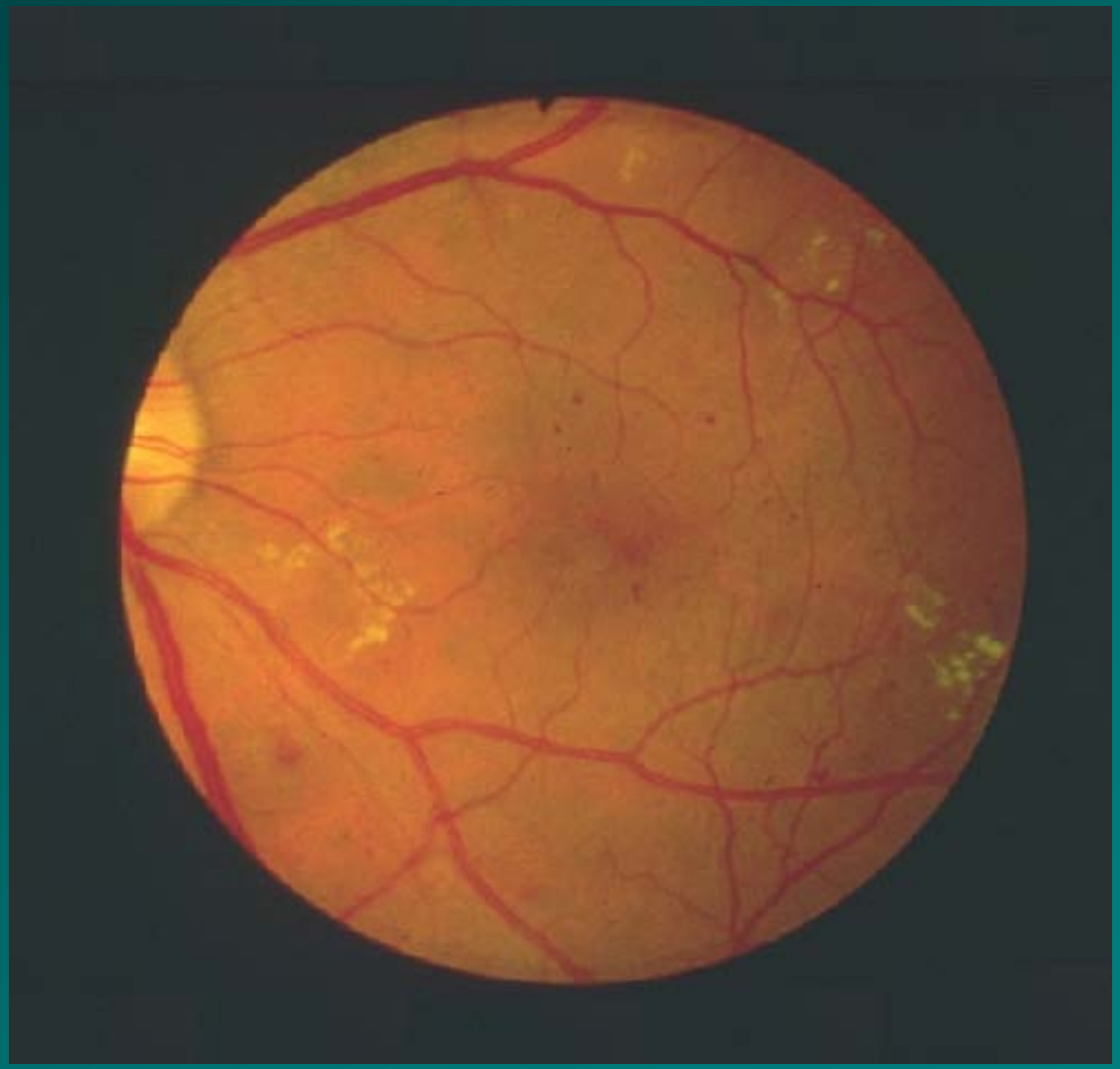




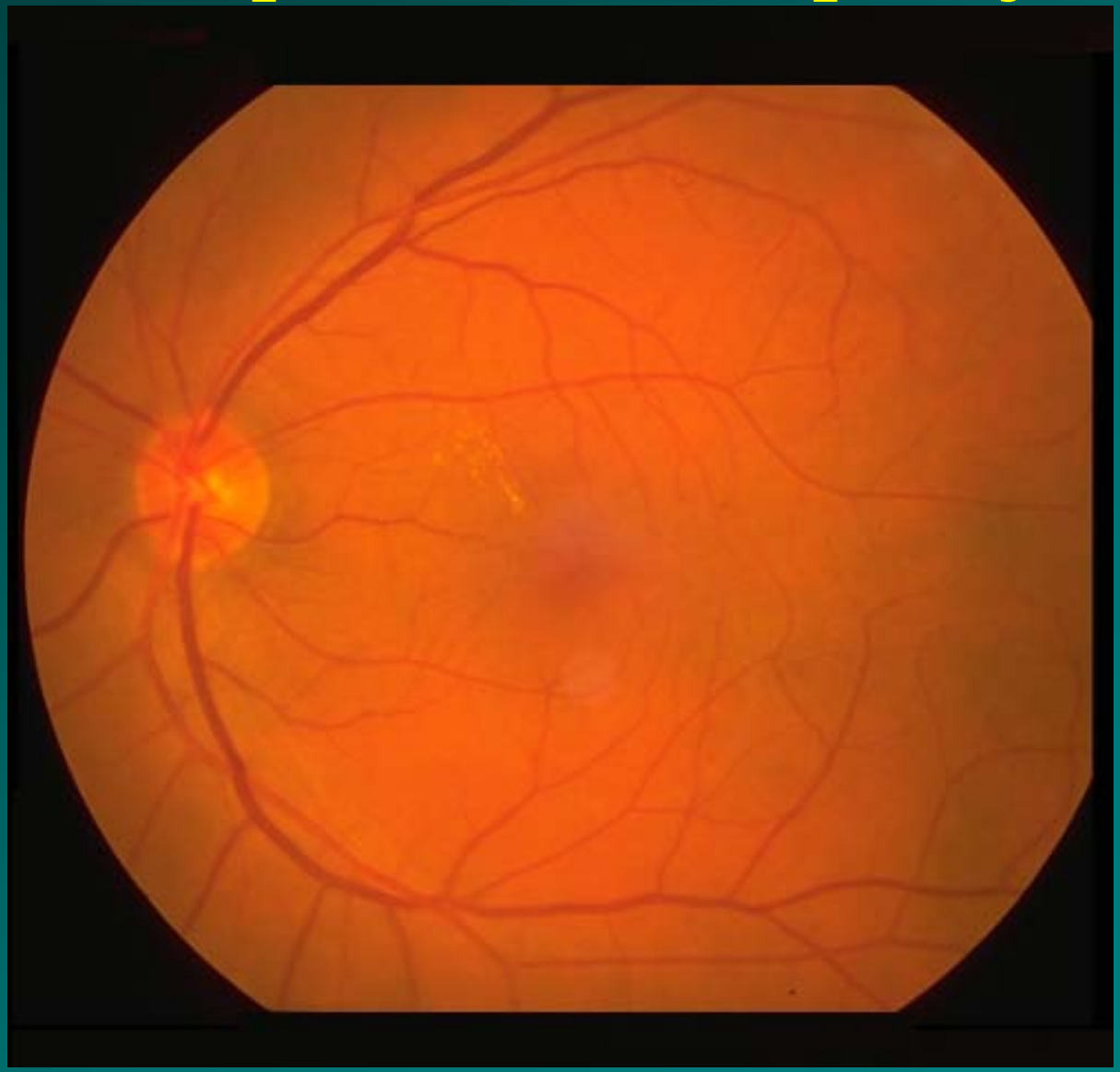
Moderate NPDR: red lesions, haemorrhages and cotton-wool spots



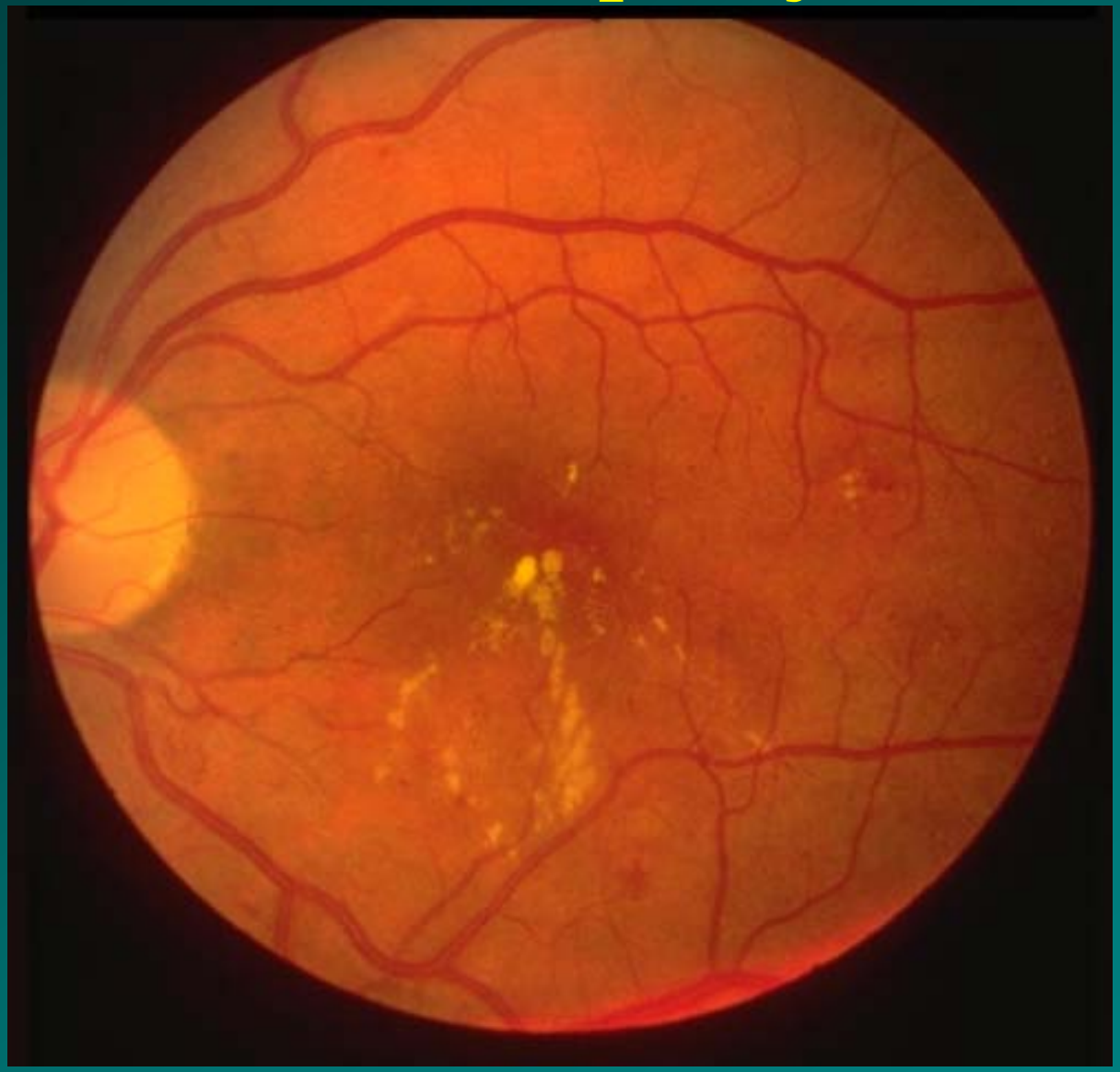
Moderate NPDR:
red lesions and hard exudates



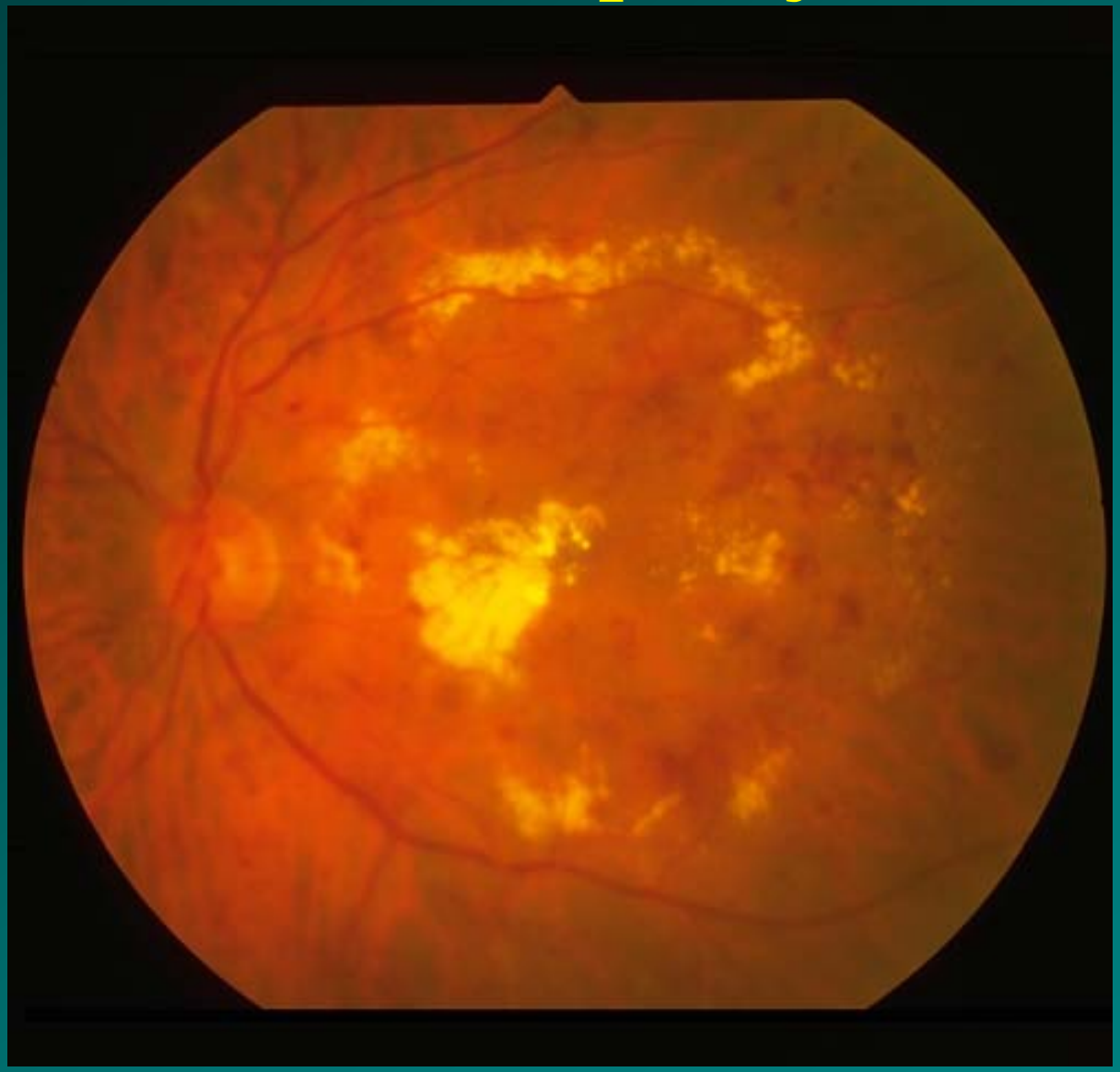
Incipient maculopathy



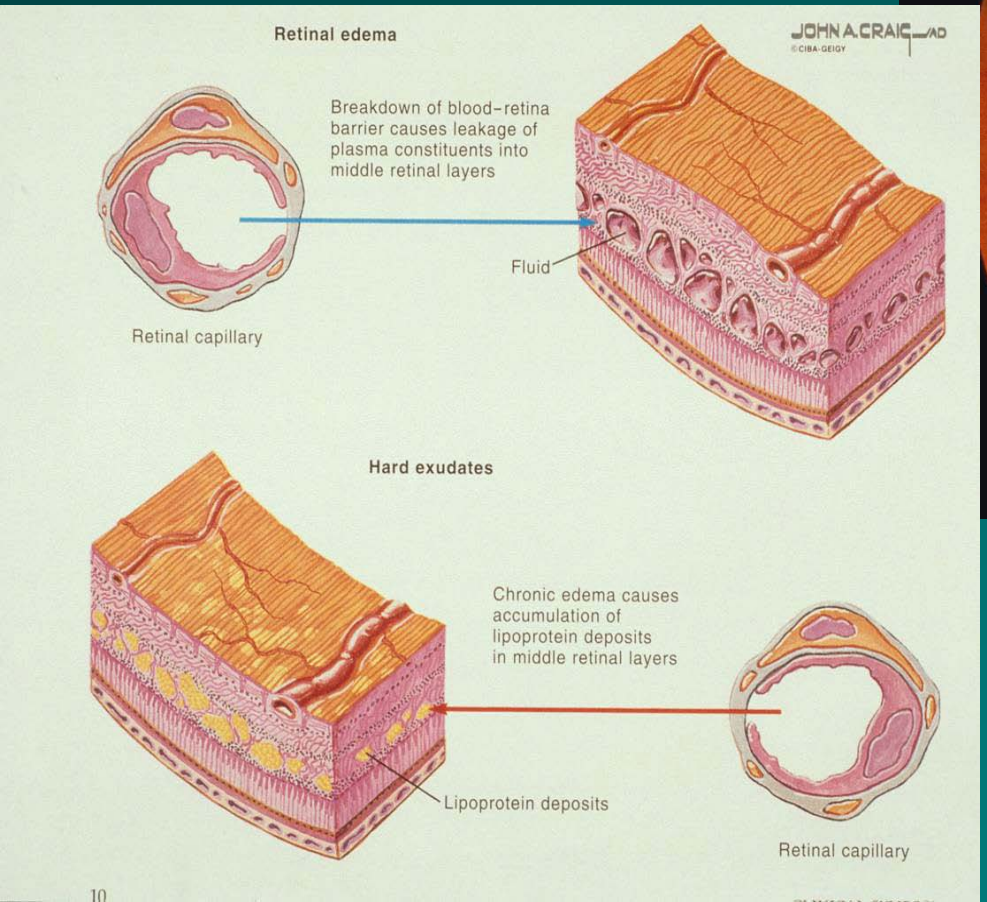
Maculopathy

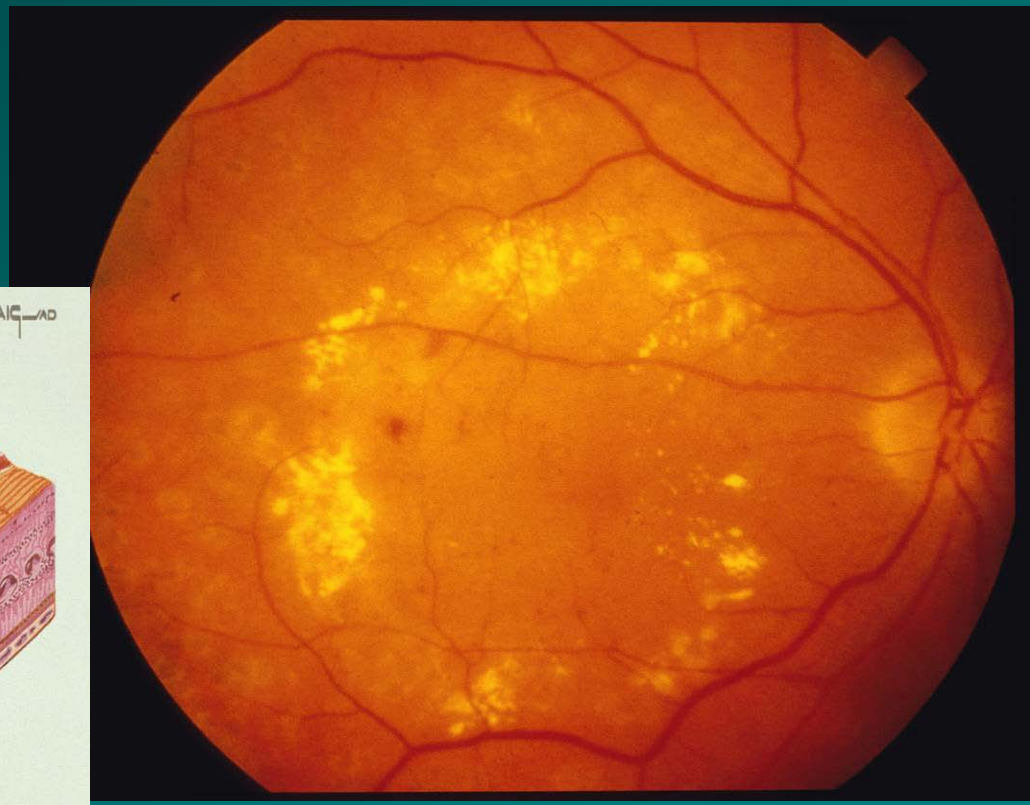


Maculopathy

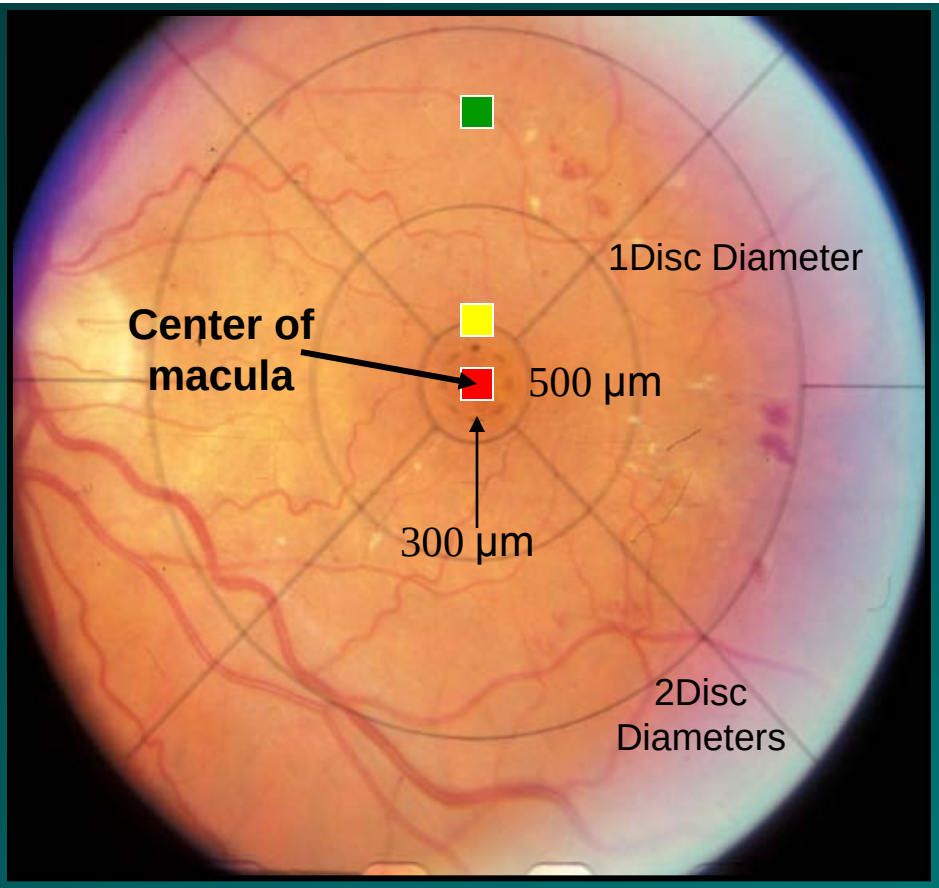


Diabetic macular oedema

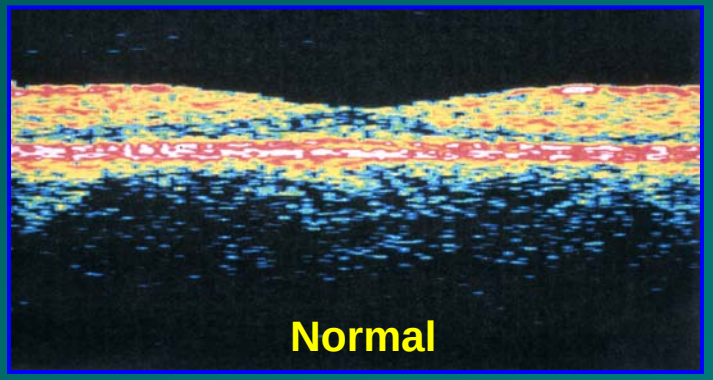


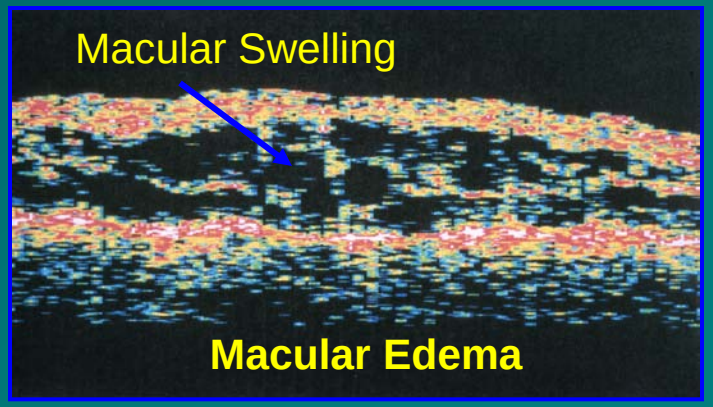


The DME Severity Scale



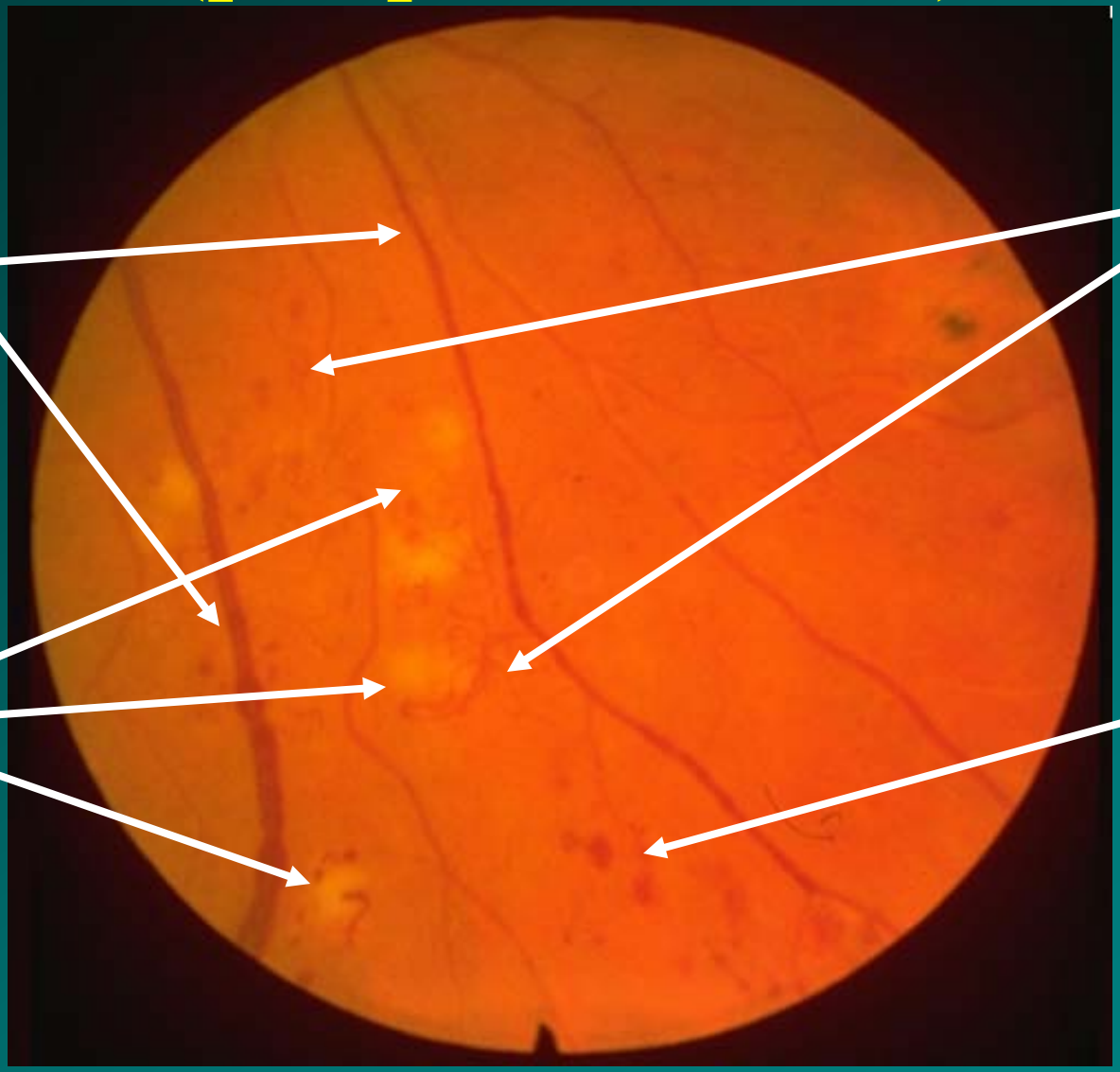
Optical Coherence Tomography (OCT)
Cross Sectional Image of the Macula





Pickup J, Williams G, *Textbook of Diabetes.* 2nd ed. Oxford, England. Blackwell Science Ltd; 1997. Chapter 58.

Severe (pre-proliferative) NPDR



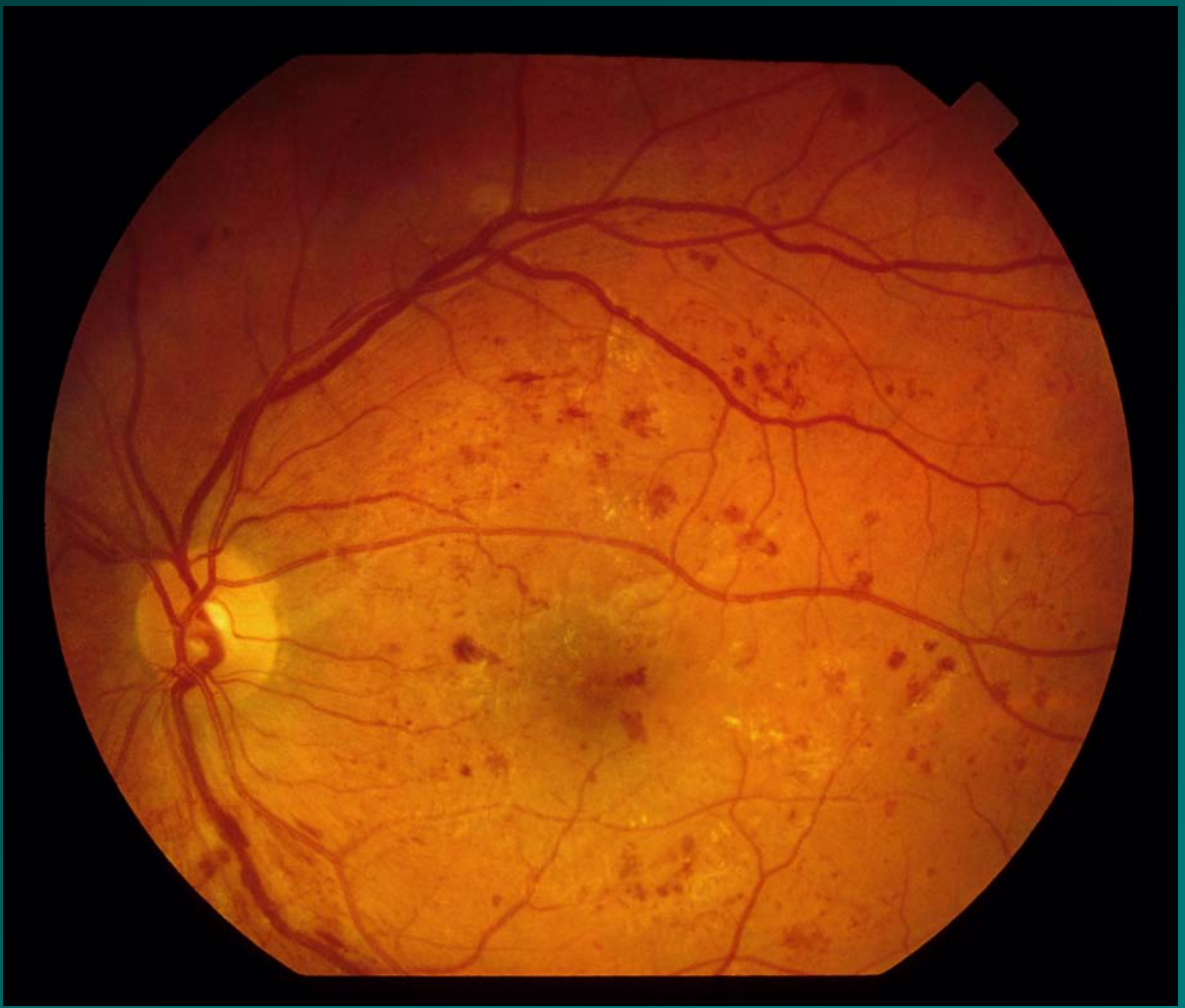
Venous beading

IRMAs

Cotton wool spots

Haemo rrhages

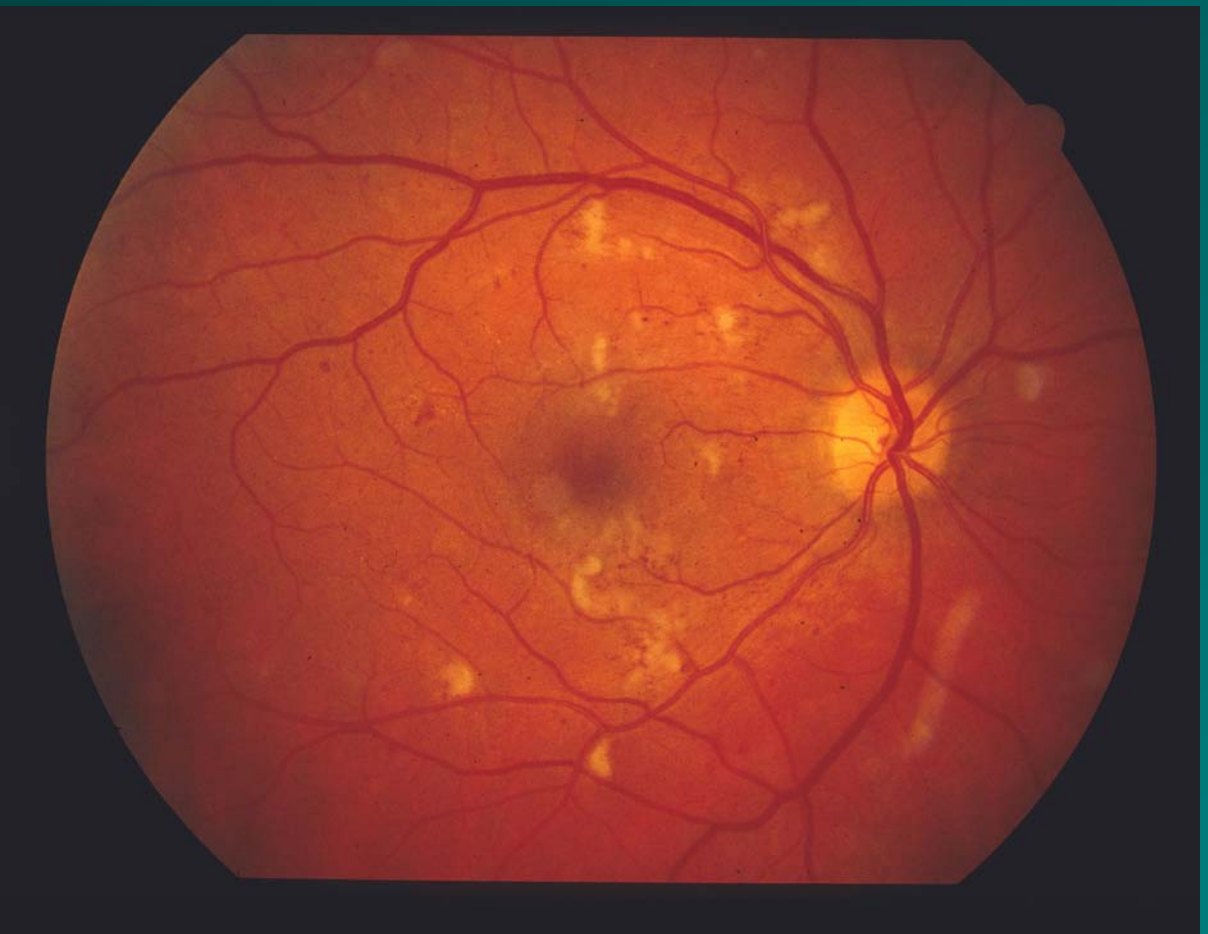
Intraretinal haemorrhages



Many in 4 quadrants:

PDR in >50% within 1 year

”Cotton wool spots”

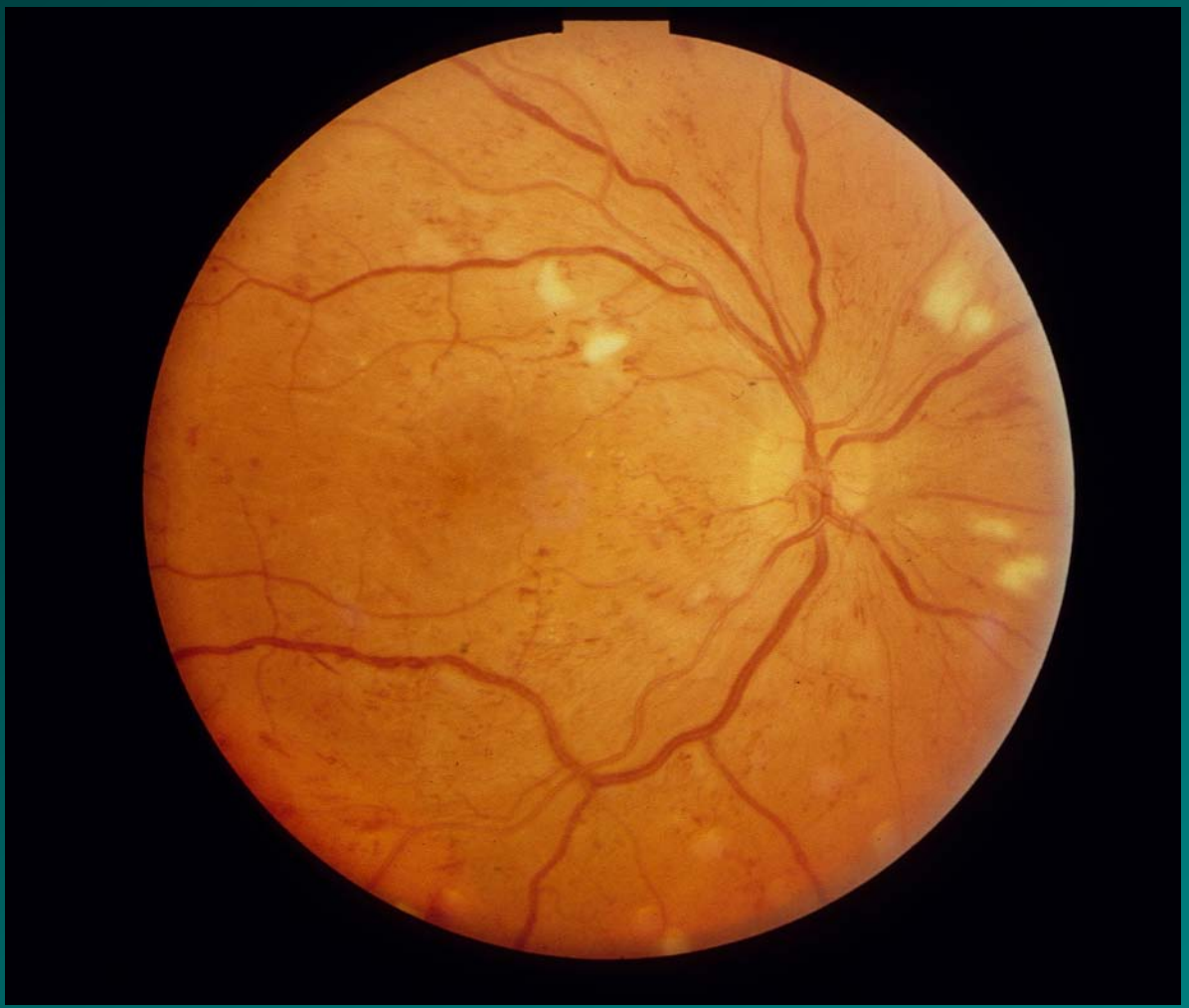


Few: No predictive value

Many in 3-4 quadrants:

PDR >50 % within 1 year

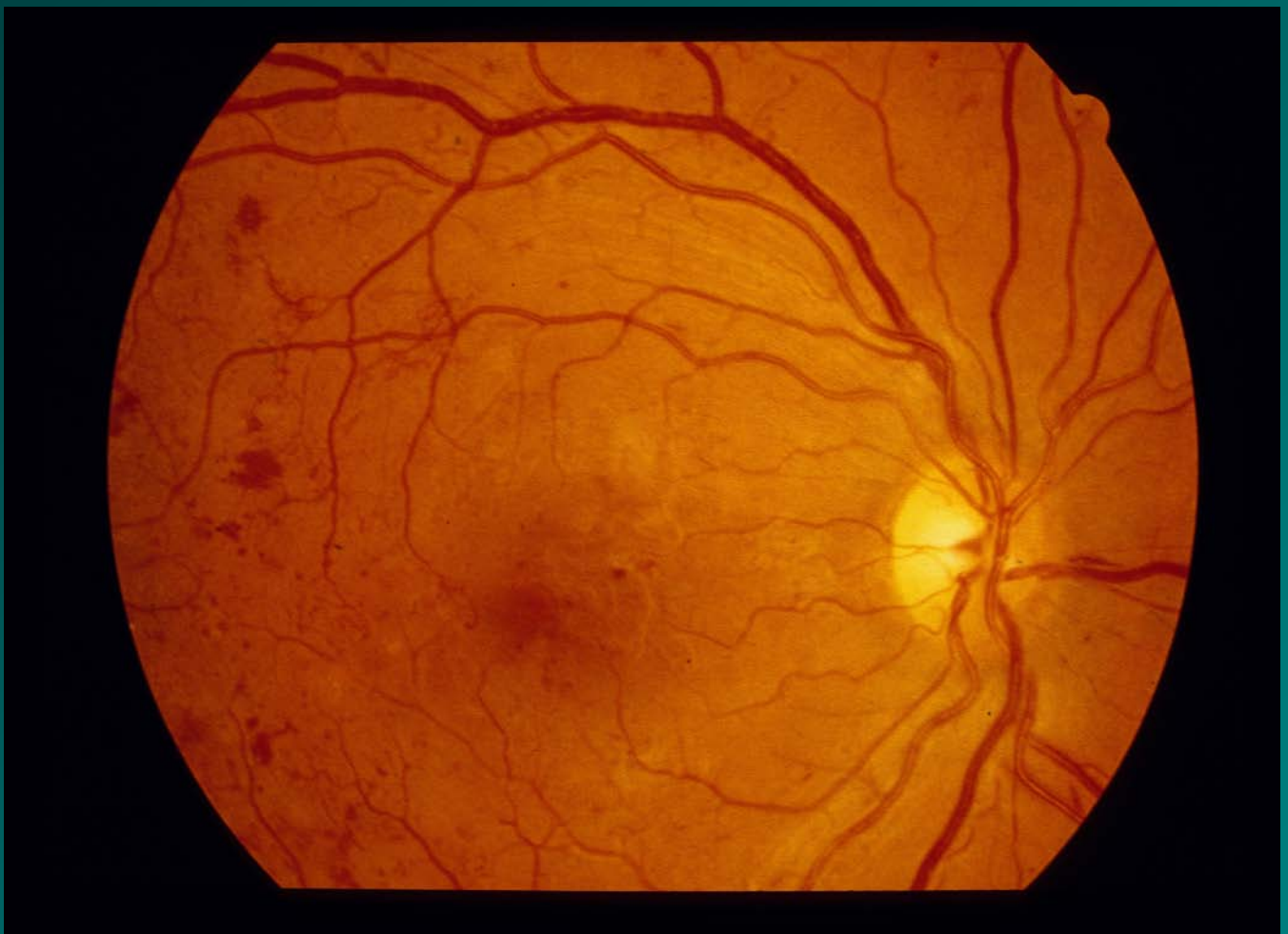
Venous beading



”venous beading” in at least 2 quadrants:

PDR > 60% within 1 year

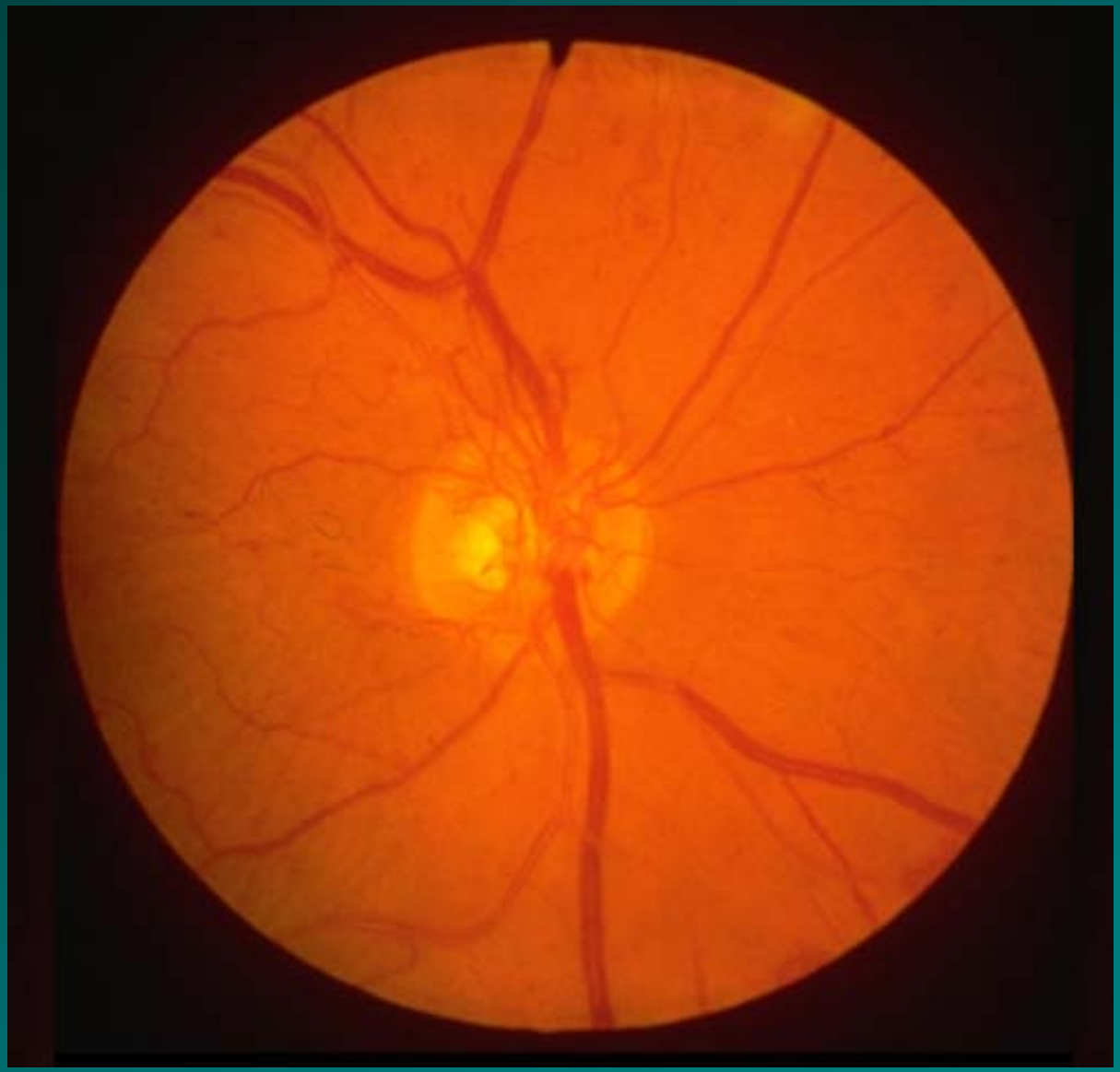
IRMA



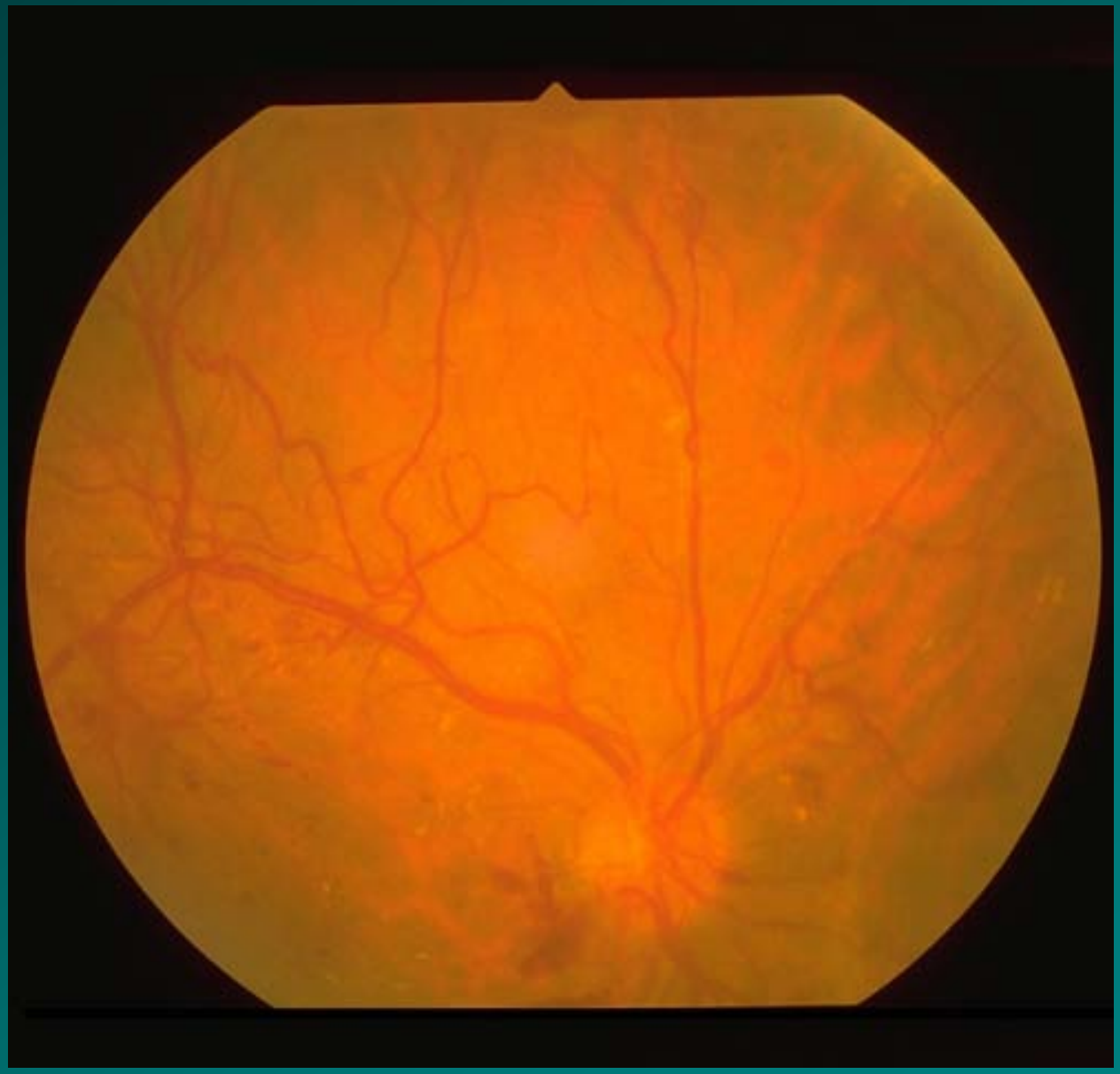
IRMA in 1 or 2 quadrants:

PDR >60% within 1 year

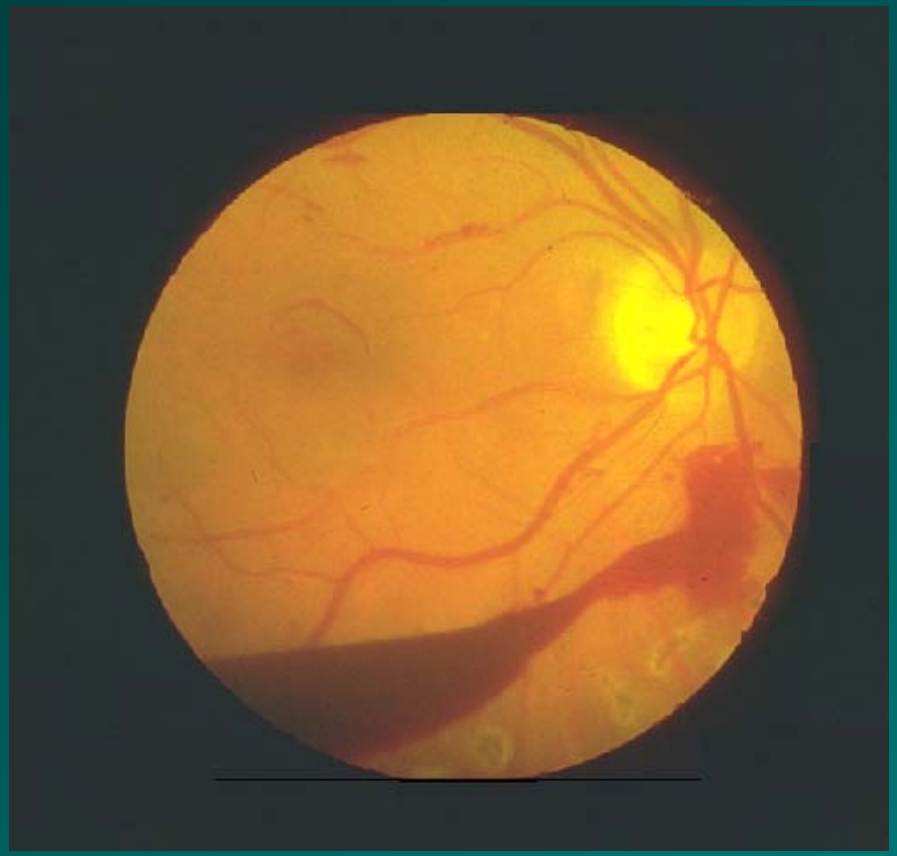
PDR: new vessels on disc

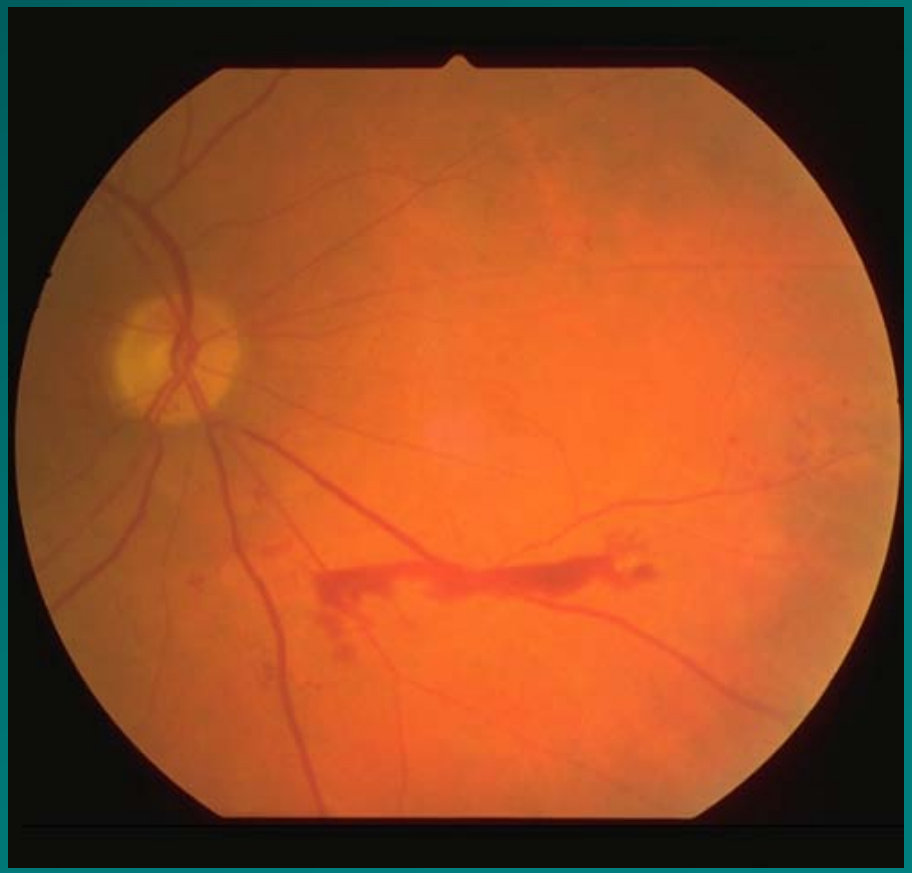


PDR: new vessels elsewhere

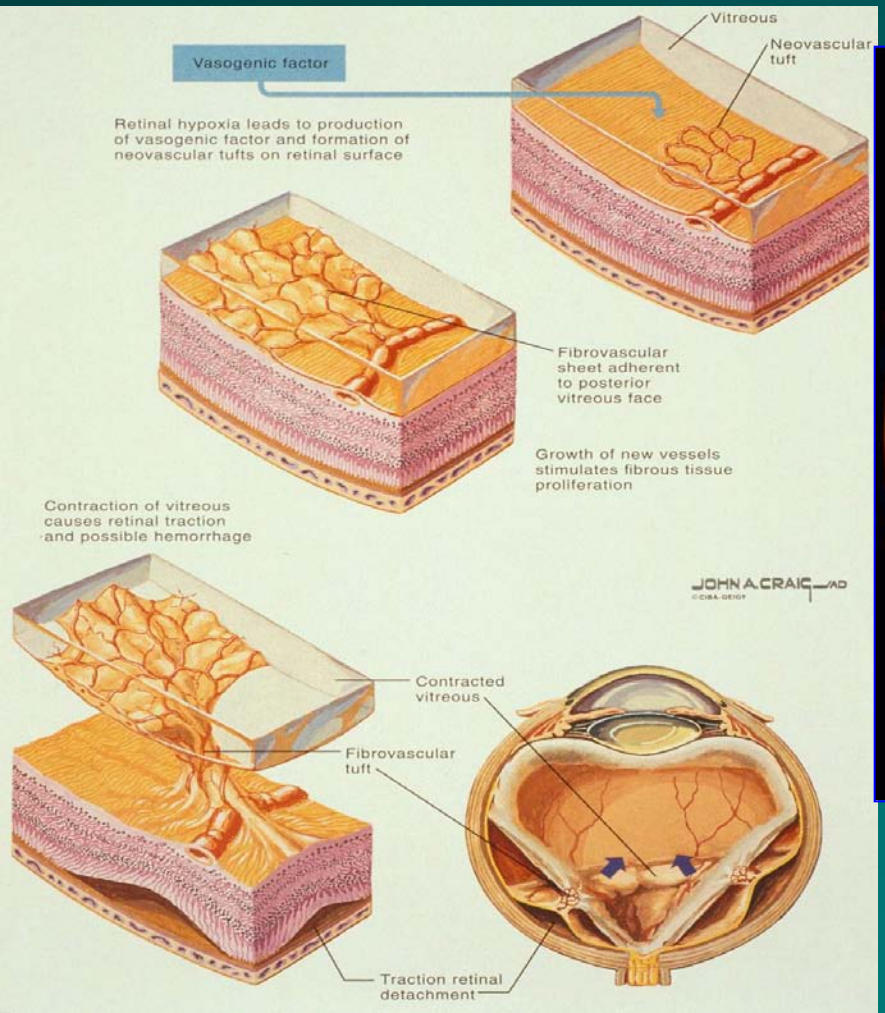


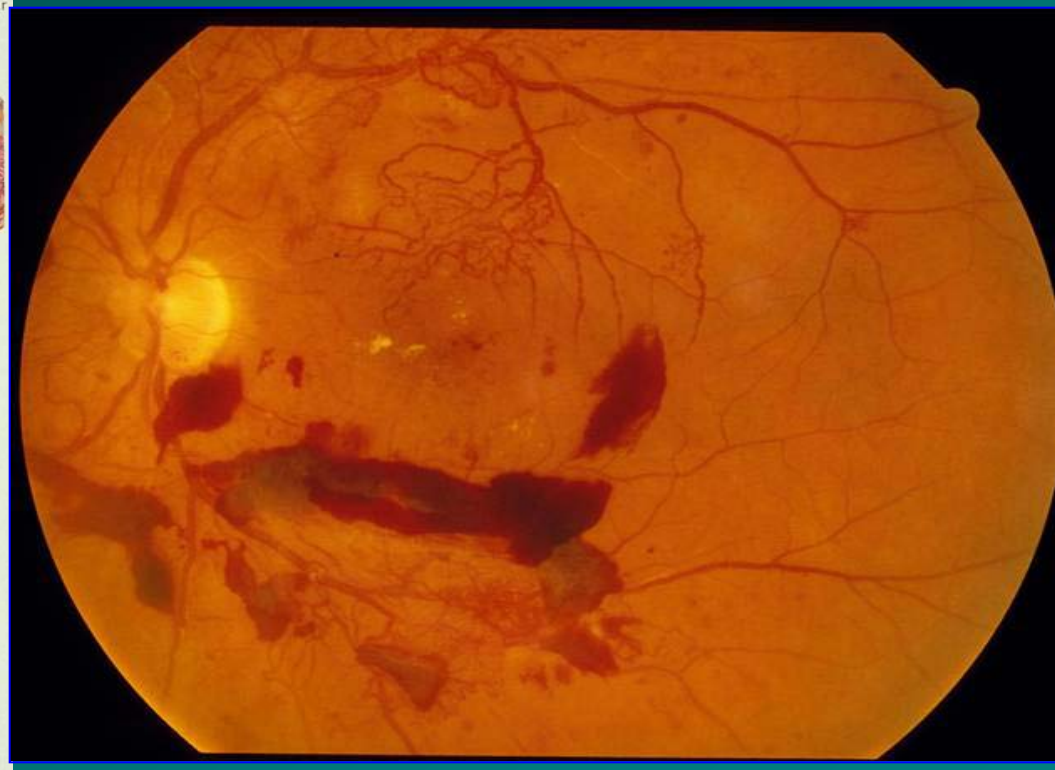
PDR: pre-retinal haemorrhages



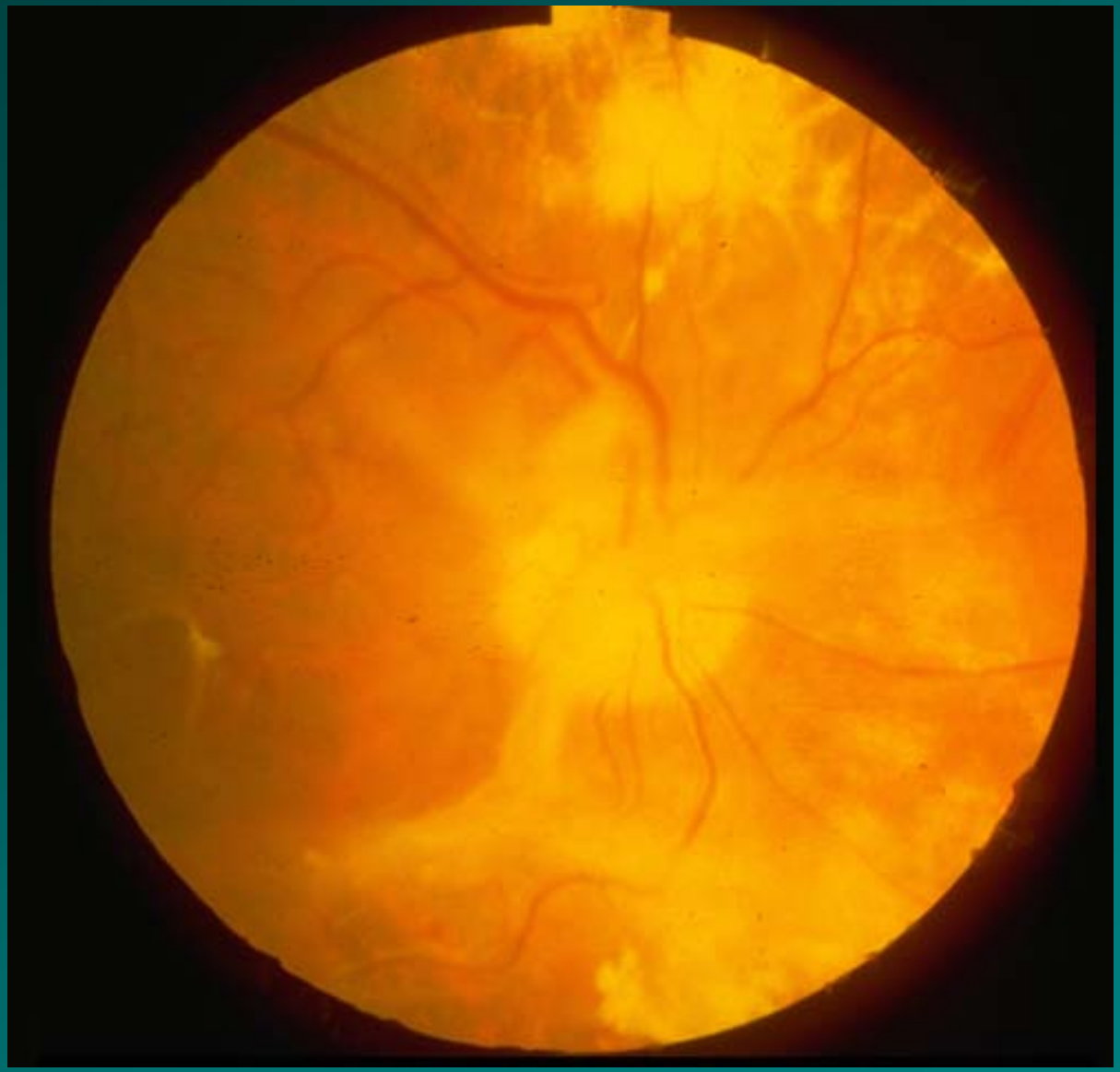


Proliferative diabetic retinopathy

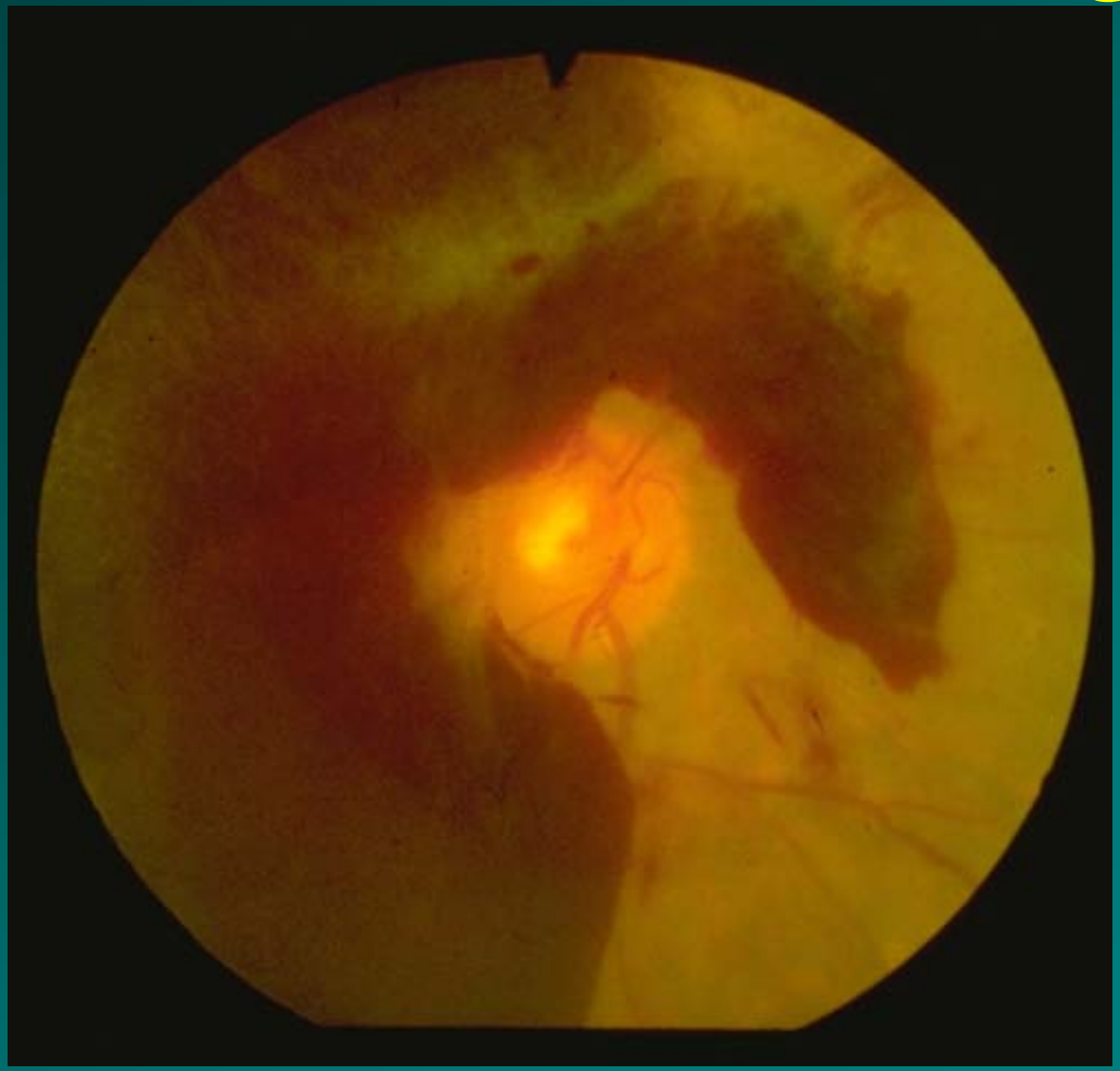




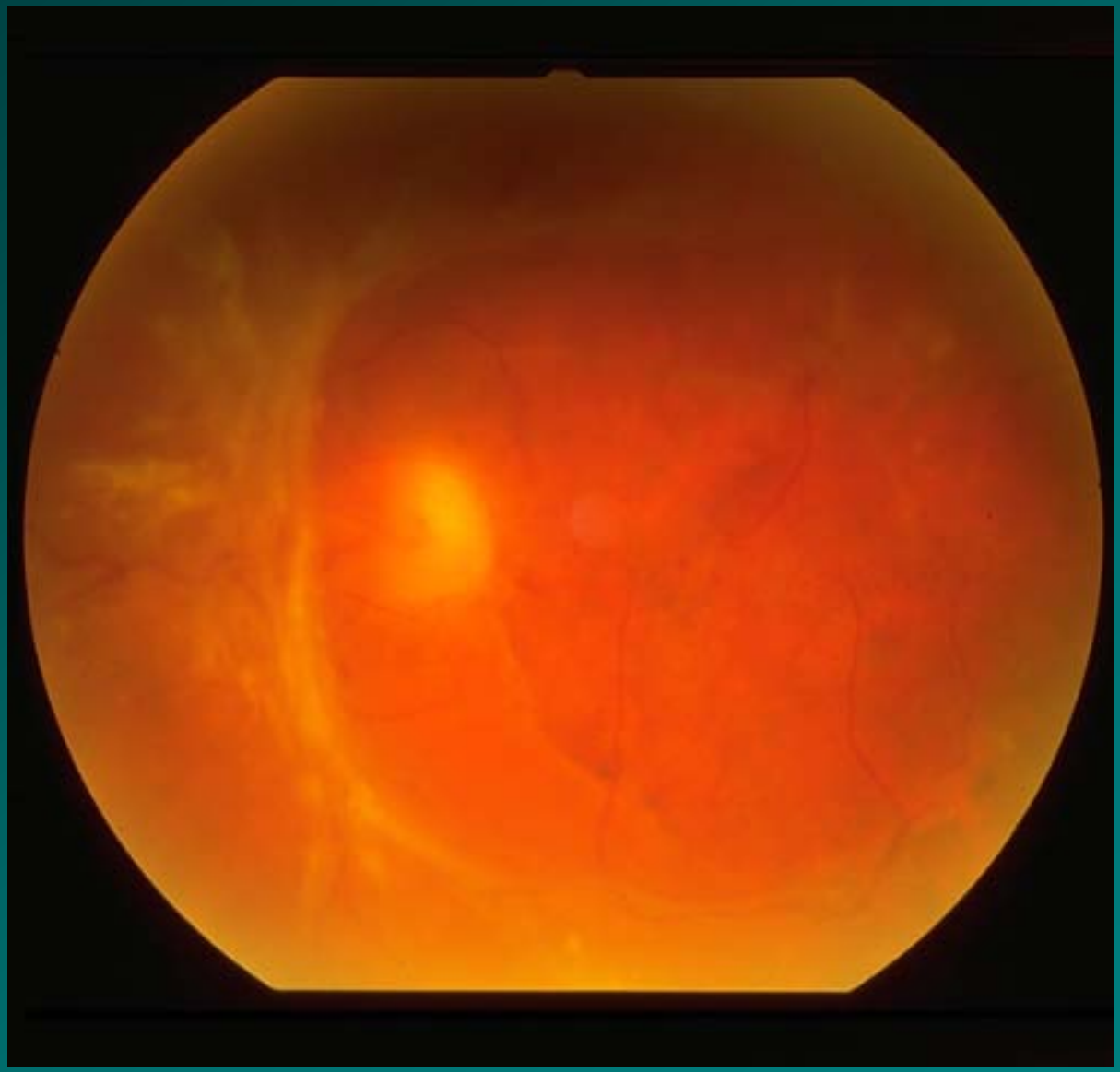
PDR: fibrous tissue



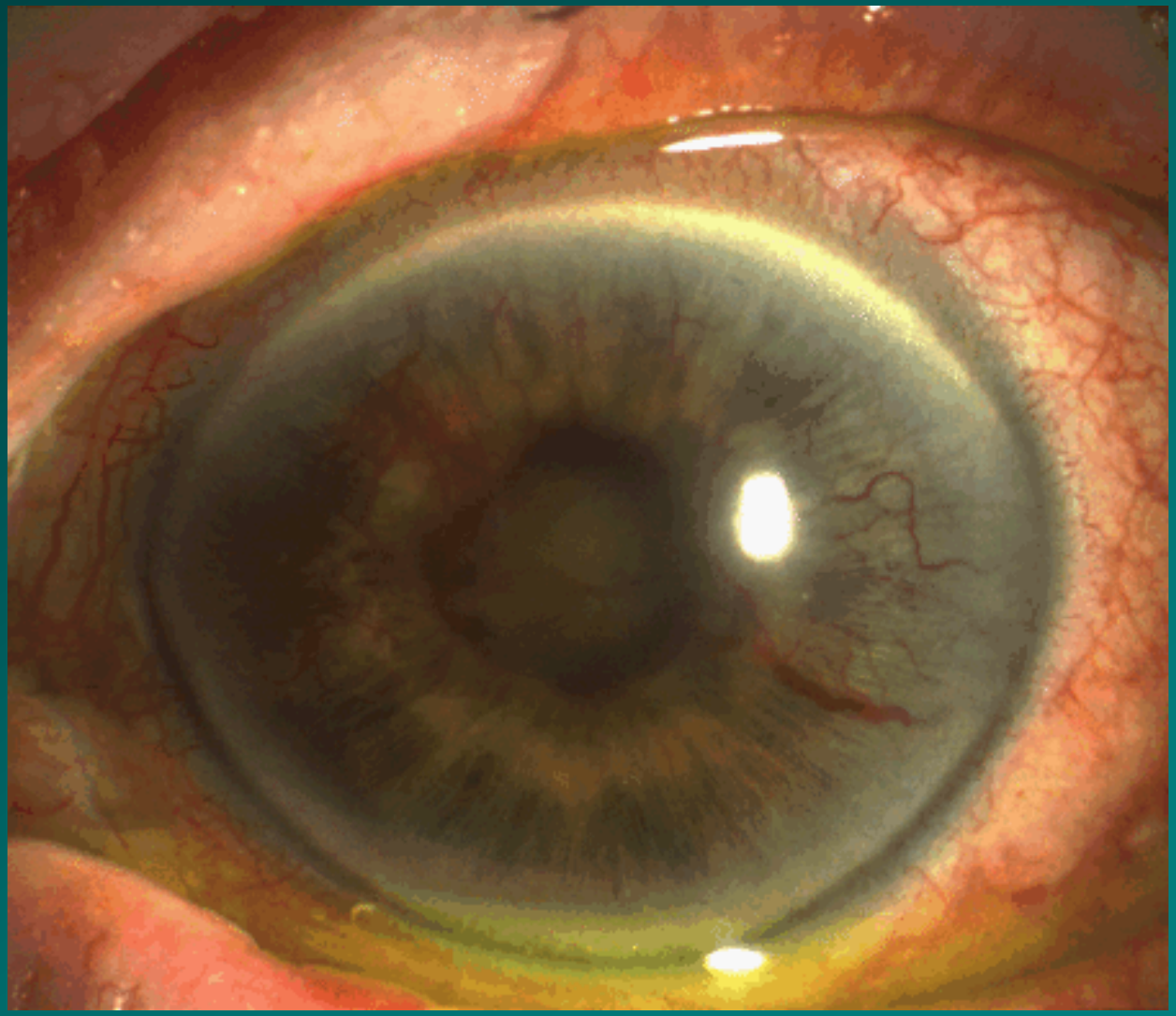
PDR: vitreous haemorrhage

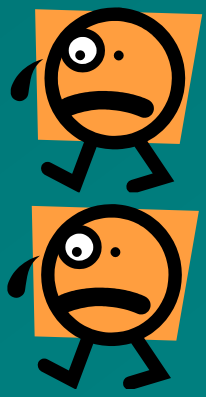


ADED: retinal detachment

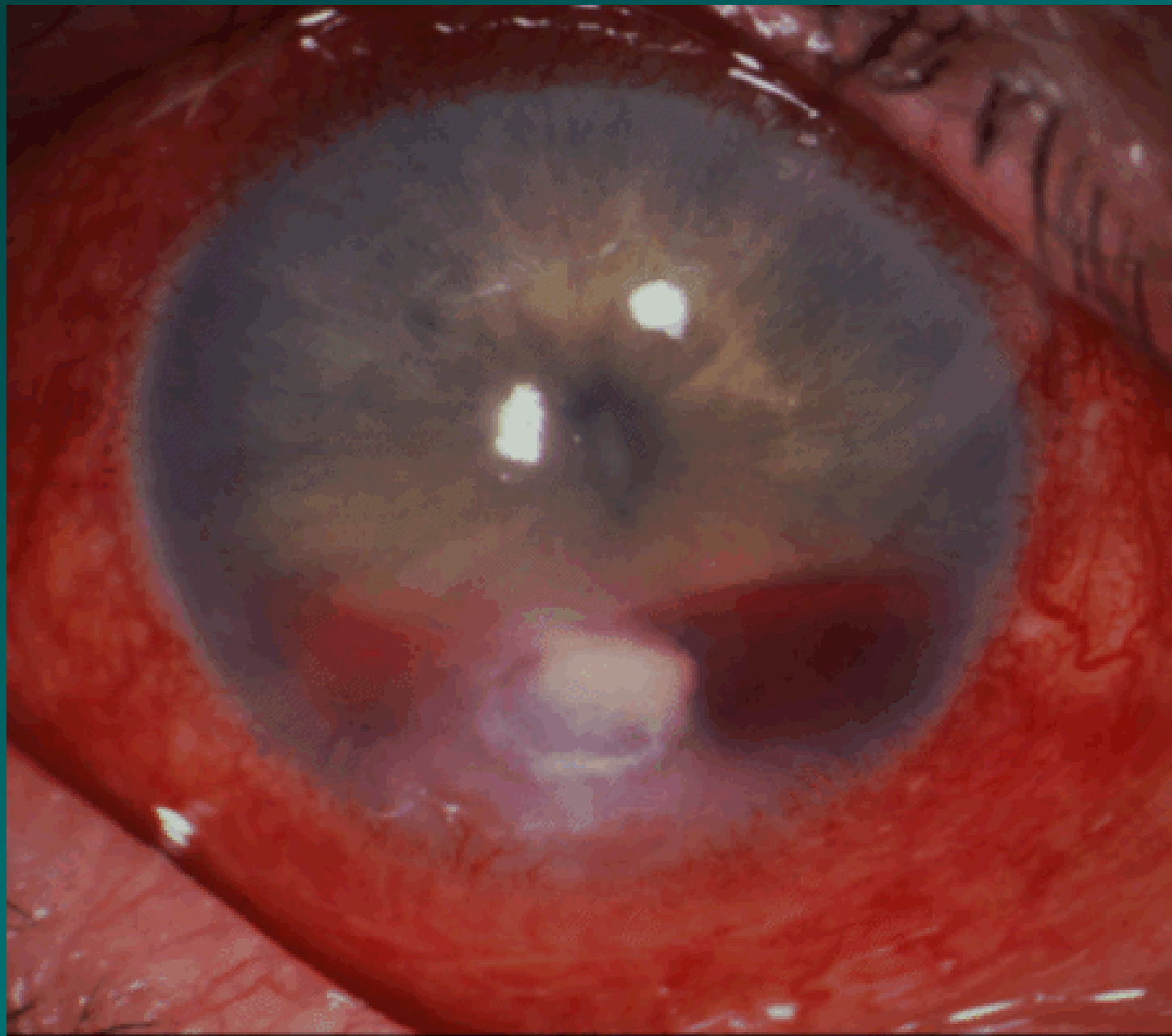


ADED: rubeosis iridis





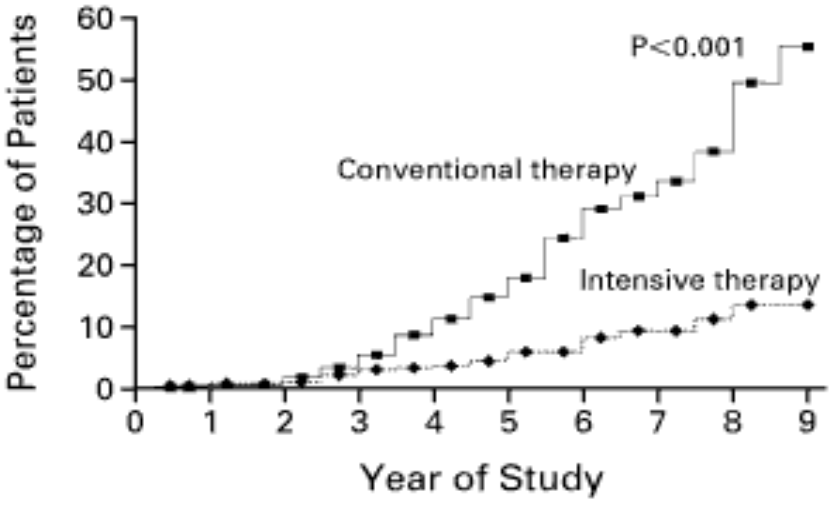
Hyphaema



Medical treatment of DR:

- **Metabolic control**
- Blood pressure control

Intensive insulin treatment *(DCCT)*:



No. of Patients					
Conventional therapy	378	375	220	79	52
Intensive therapy	348	342	202	78	49

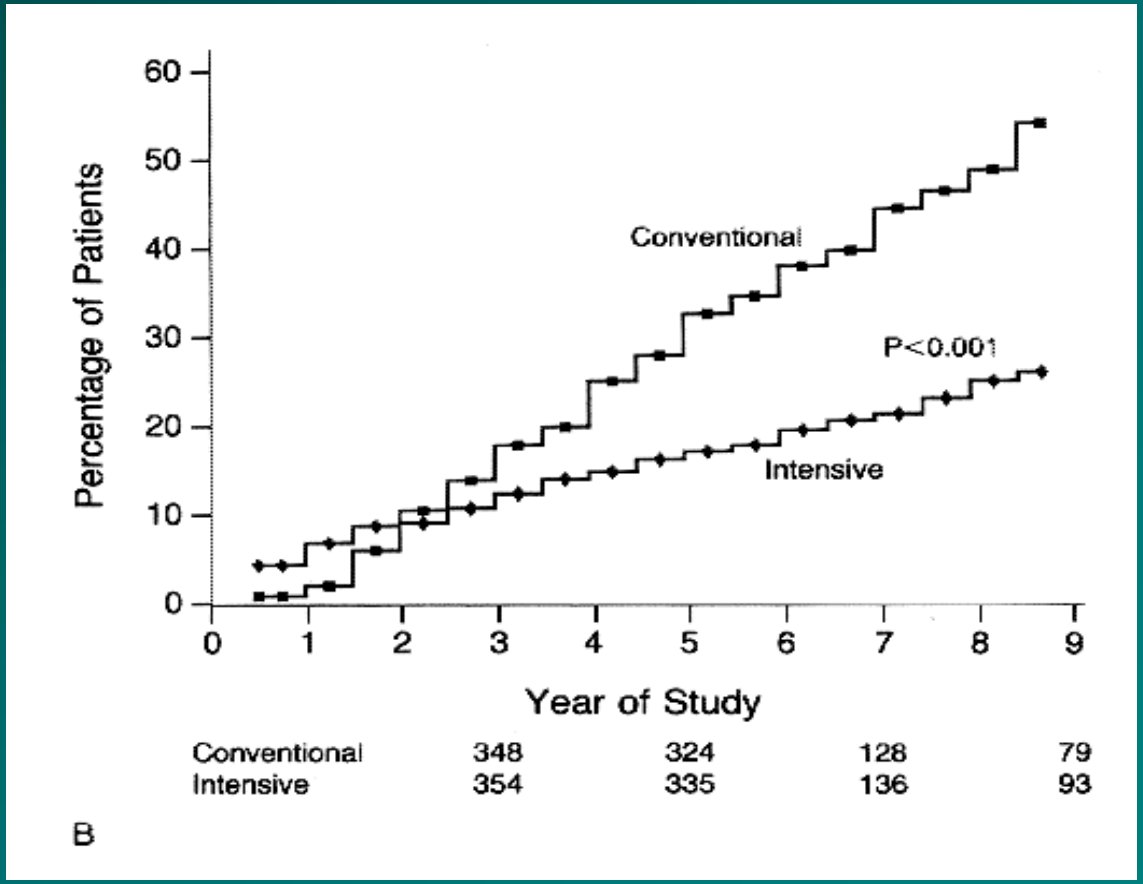
Reduces by 76% the risk of developing new retinopathy

(primary prevention)

Intensive insulin treatment *(DCCT)*:

- Reduces by 54% the risk of progression of mild retinopathy;
- Reduces by 47% the risk of developing severe NPDR or PDR;
- Reduces by 56% the necessity of laser treatment.

(secondary prevention)



Glucose Control Study Summary

The intensive glucose control policy maintained a lower HbA_{1c} by mean 0.9 % over a median follow up of 10 years from diagnosis of type 2 diabetes with reduction in risk of:

12%	for any diabetes related endpoint	p=0.029
25%	for microvascular endpoints	p=0.0099
16%	for myocardial infarction	p=0.052
24%	for cataract extraction	p=0.046
21%	for retinopathy at twelve years	p=0.015
33%	for albuminuria at twelve years	p=0.000054

ukpds

UKPDS: 25% reduction in microvascular events

- NNT to prevent 1 event/10 years = 19.6 patients
- Complication-free interval for any DM-related microvascular event: 14.0 vs. 12.7 years

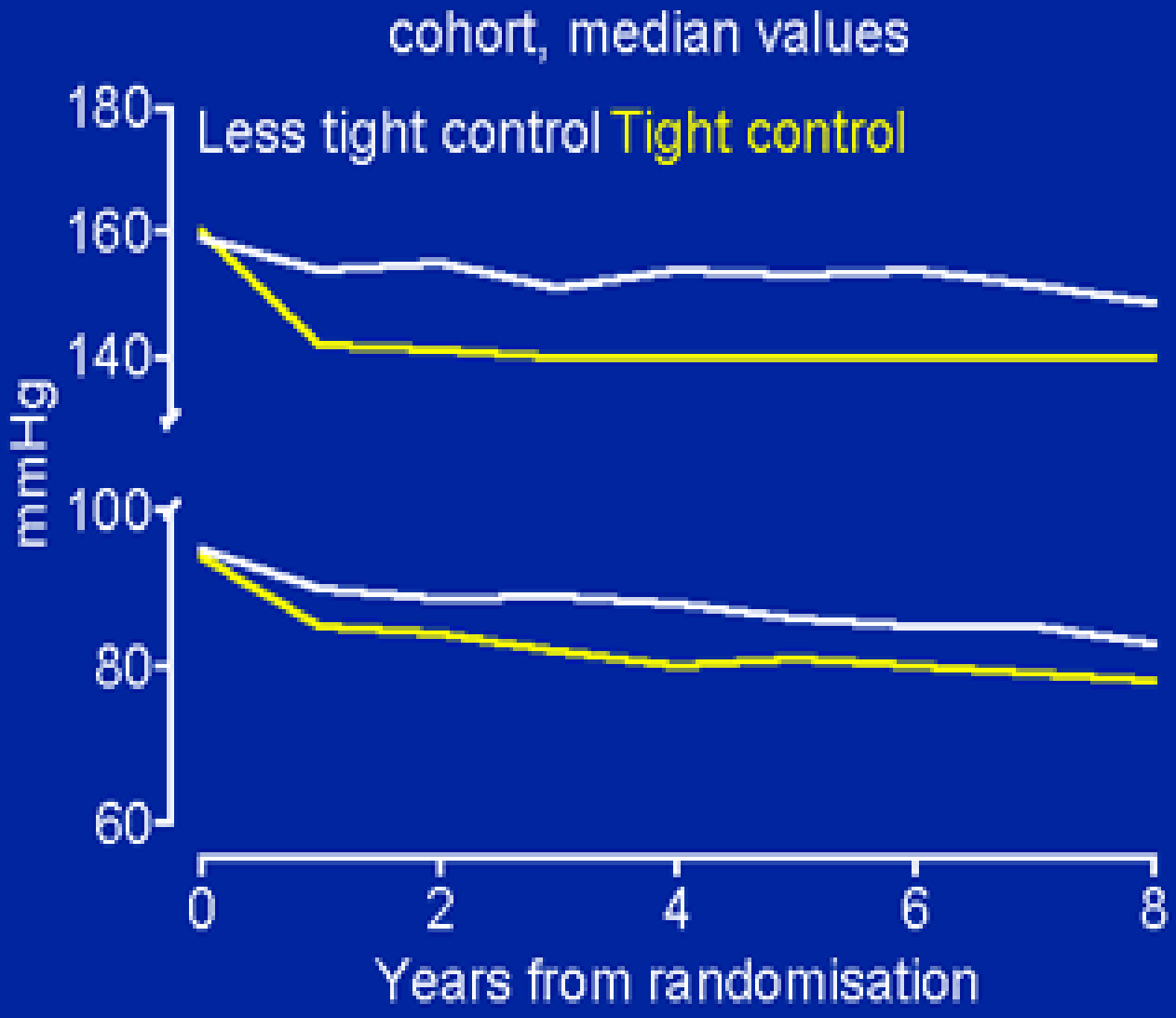
Optimised metabolic control:

- Prevents diabetic retinopathy (to a point…)
- Does not induce regression of existing retinopathy.

Medical treatment of DR:

- Metabolic control
- **Blood pressure control**

Blood Pressure : Tight vs Less Tight Control



ukpds

More tight control of blood pressure *(UKPDS)*:

- Reduces by 34% the risk of worsening of **diabetic retinopathy** (99% CI = 11-50%; p=0.0004)
- Reduces by 47% the risk of worsening of **visual acuity** (99% CI = 7-70%; p=0.004)

(For a reduction from 154/87 to 144/82 mmHg)

Standards of care for diabetic patients

- American Diabetes Association (ADA)[1]
  - Recommended glycaemic goals:
    - HbA_{1c} goal is <7%
  - Recommended blood pressure (BP) goals:
    - Systolic/diastolic BP <130 mm Hg/<80 mm Hg
- International Diabetes Federation (IDF)[2]
  - Recommended glycaemic goals:
    - HbA_{1c} goal is ≤6.5%
- WHO/ISH[3]
  - Recommended BP goals:
    - Systolic BP/diastolic BP <130 mm Hg/<80 mm Hg

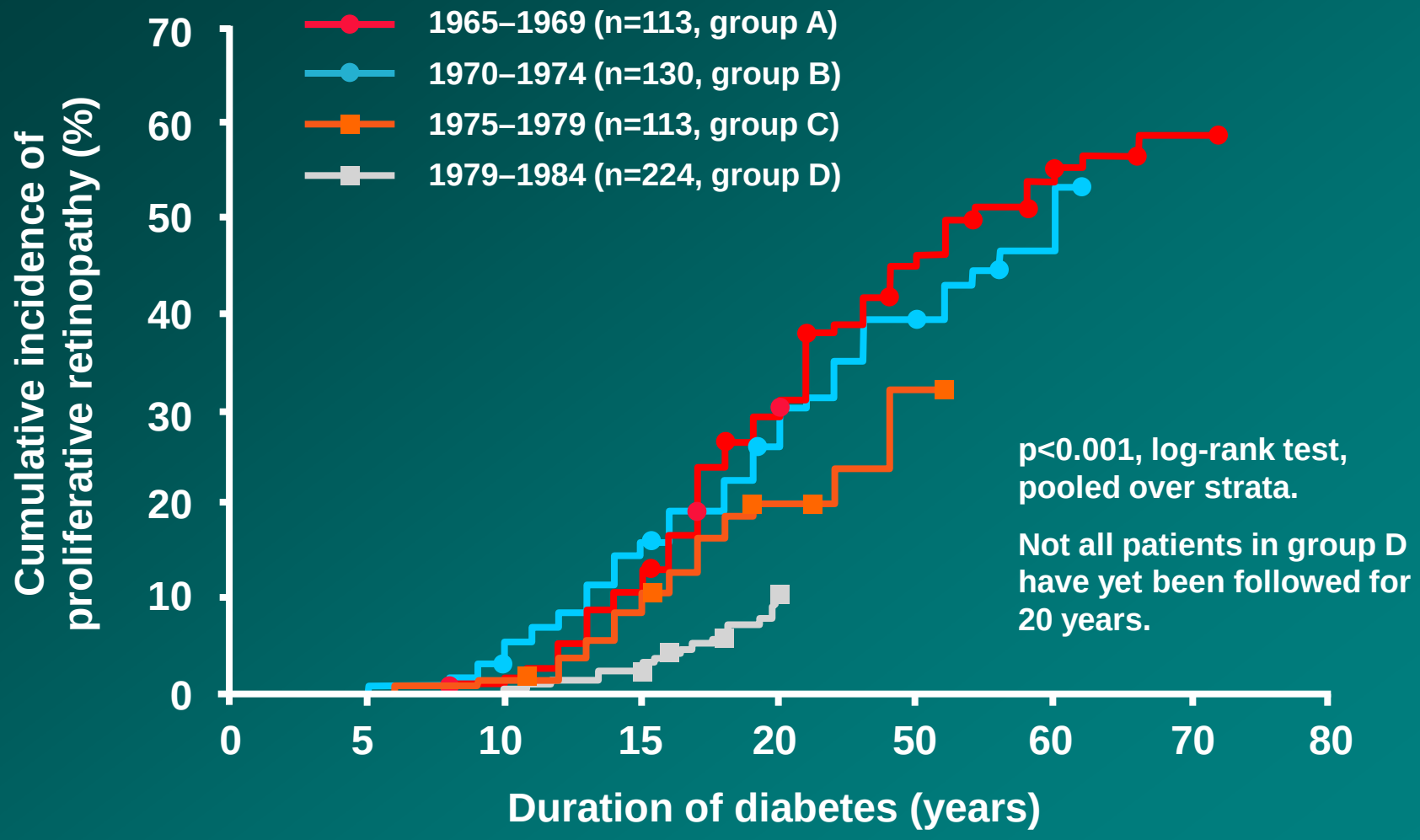
1. American Diabetes Association. *Diabetes Care* 2010; 33(Suppl 1): S11–S61.
2. IDF. Type 2 diabetes: practical targets and treatment. 2005.
3. World Health Organization. *J Hypertens* 2003; **21**(11): 1983–1992.

Years free from complications.

(Modified from: DCCT, JAMA 276:1409;1996)

Condition	Conv. IT	Int. IT	Diff.
Proliferative DR	39.1	53.9	**14.7**
Macular edema	44.7	52.9	**8.2**
Blindness	49.1	56.8	**7.7**
Microalbuminuria	34.5	43.7	**9.2**
Albuminuria	49.7	59.5	**9.7**
ESRD	55.6	61.3	**5.8**
L. extr. amputation	55.2	60.9	**5.6**

Incidence of proliferative diabetic retinopathy according to onset of Type 1 diabetes



Hovind P, *et al*. *Diabetes Care* 2003; **26**: 1258–1264.

The Wisconsin Epidemiologic Study of Diabetic Retinopathy XXII

The Twenty-Five-Year Progression of Retinopathy in Persons with Type 1 Diabetes

Ronald Klein, MD, MPH,[1] Michael D. Knudtson, MS,[1] Kristine E. Lee, MS,[1] Ronald Gangnon, PhD,[2] Barbara E. K. Klein, MD, MPH[1]

Ophthalmology 2008;115:1859–1868

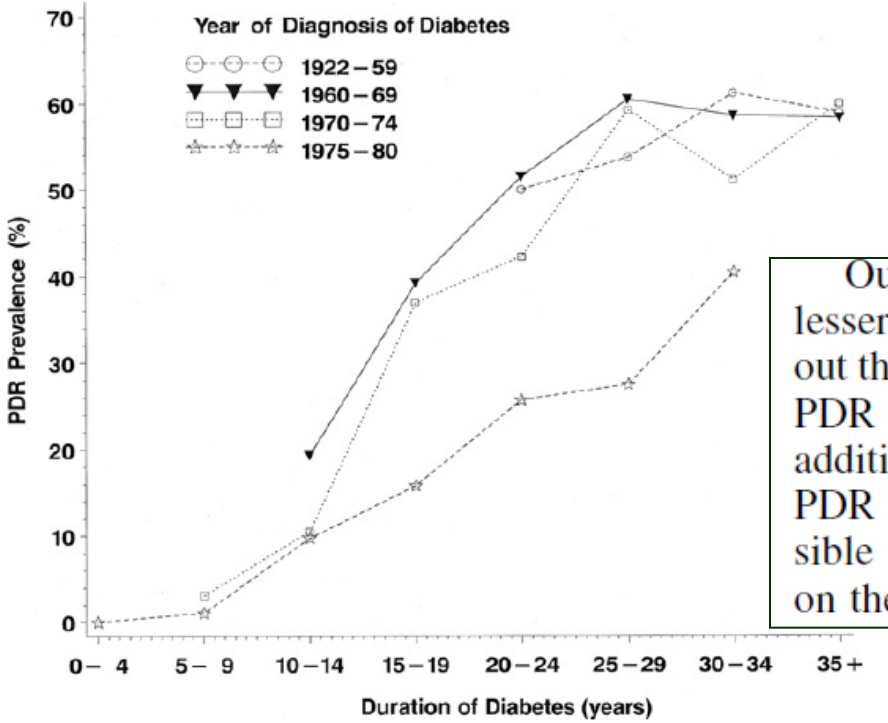


Figure 3. Relationship of prevalence of PDR to duration of diabetes by period of diabetes diagnosis in the WESDR. PDR = proliferative diabetic retinopathy.

Our data suggest that better glycemic control, and to a lesser extent blood pressure control at baseline and throughout the study, may be beneficial in reducing the incidence of PDR and increasing the odds of improvement of DR. In addition, our data show a reduction in the prevalence of PDR in more recently diagnosed cohorts, suggesting a possible benefit of recent changes in management of diabetes on the prevalence of PDR.

Projection of Diabetic Retinopathy and Other Major Eye Diseases Among People With Diabetes Mellitus

United States, 2005-2050

Jinan B. Saaddine, MD, MPH; Amanda A. Honeycutt, PhD; K. M. Venkat Narayan, MD, MBA; Xinzhi Zhang, MD, PhD; Ron Klein, MD, MPH; James P. Boyle, PhD

Arch Ophthalmol. 2008;126(12):1740-1747

Results: The number of Americans 40 years or older with DR and VTDR will triple in 2050, from 5.5 million in 2005 to 16.0 million for DR and from 1.2 million in 2005 to 3.4 million for VTDR. Increases among those 65 years or older will be more pronounced (2.5 million to 9.9 million for DR and 0.5 million to 1.9 million for VTDR). The

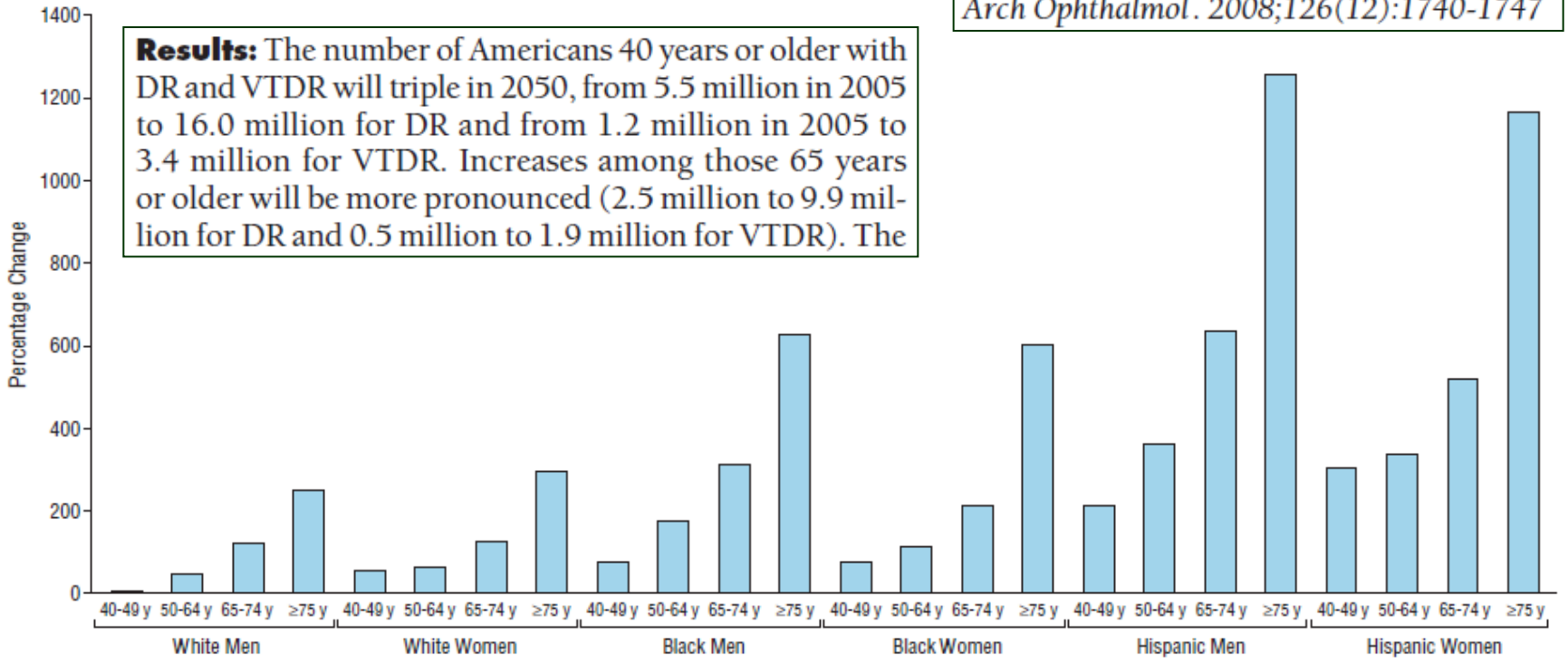
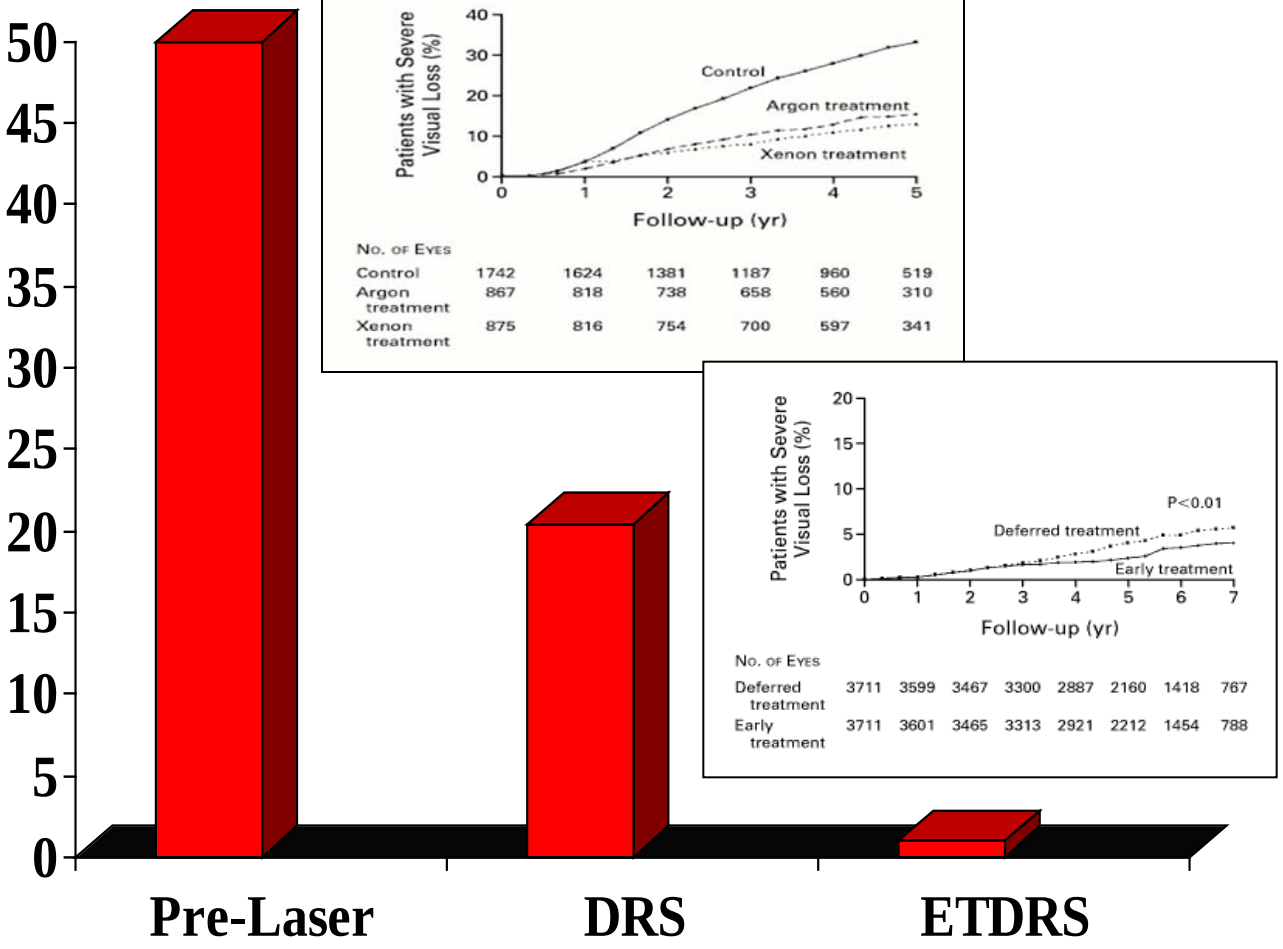


Figure 1. Percentage change in the number of people in the United States with diabetic retinopathy, 2005-2050.

Improving prognosis of proliferative DR from the pre-laser era to the ETDRS

5-yr incidence of severe visual loss (VA < 5/200) since onset of new vessels



New treatments under trial

- Intra-vitreal agents
- PKC inhibitors
- RAS blockers
- Lipid lowering drugs

New treatments under trial

- **Intra-vitreal agents**
- PKC inhibitors
- RAS blockers
- Lipid lowering drugs

Agents for intra-vitreal use

Agent	Action	Indication
Pegaptanib sodium	Intravitreal aptamer VEGF inhibitor	DME
Ranibizumab	Intravitreal humanized anti-VEGF antibody fragment	DME
Bevacizumab	Anti-VEGF antibody	DME
Triamcinolone acetonide	Intravitreal steroid injection	DME

New treatments under trial

- Intra-vitreal agents
- **PKC inhibitors**
- RAS blockers
- Lipid lowering drugs

New treatments under trial

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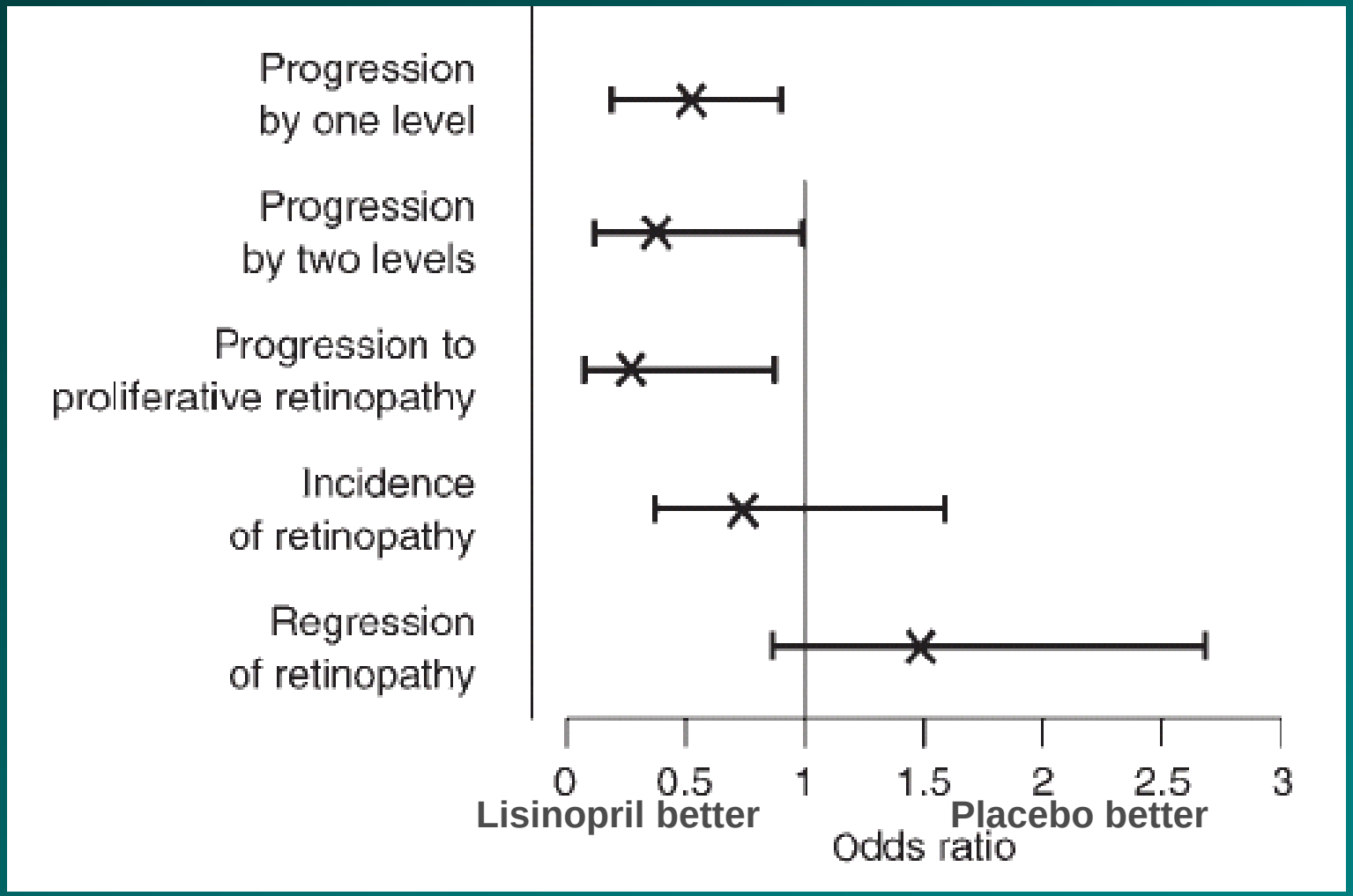
EUCLID

Incidence, progression and regression of diabetic retinopathy in patients with type 1 diabetes



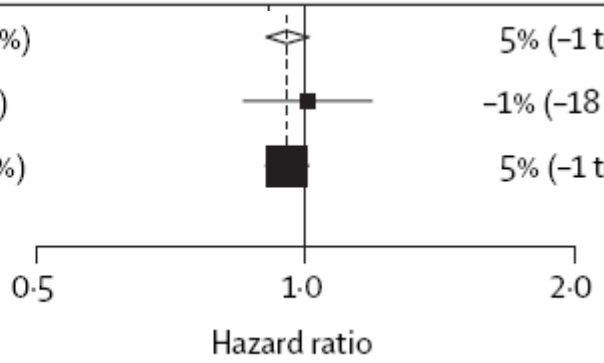
Chaturvedi et al. *Lancet* 351:28–31, 1998

Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial

*ADVANCE Collaborative Group**

www.thelancet.com Published online September 2, 2007 DOI:10.1016/S0140-6736(07)61303-8

	Number (%) of patients with event		Favours perindopril–indapamide	Favours placebo	Relative risk reduction (95% CI)
	Perindopril–indapamide (n=5569)	Placebo (n=5571)			
Total eye events	2531 (45·4%)	2611 (46·9%)			5% (–1 to 10)
New or worsening retinopathy	289 (5·2%)	286 (5·1%)			–1% (–18 to 15)
Visual deterioration	2446 (43·9%)	2514 (45·1%)			5% (–1 to 10)



Effect of candesartan on prevention (DIRECT-Prevent 1) and progression (DIRECT-Protect 1) of retinopathy in type 1 diabetes: randomised, placebo-controlled trials

*Nish Chaturvedi, Massimo Porta, Ronald Klein, Trevor Orchard, John Fuller, Hans Henrik Parving, Rudy Bilous, Anne Katrin Sjølie, for the DIRECT Programme Study Group**

Summary

Background Results of previous studies suggest that renin-angiotensin system blockers might reduce the burden of diabetic retinopathy. We therefore designed the DIabetic REtinopathy Candesartan Trials (DIRECT) Programme to assess whether candesartan could reduce the incidence and progression of retinopathy in type 1 diabetes.

Published Online September 26, 2008 DOI:10.1016/S0140-6736(08)61412-9

Effect of candesartan on progression and regression of retinopathy in type 2 diabetes (DIRECT-Protect 2): a randomised placebo-controlled trial

*Anne Katrin Sjølie, Ronald Klein, Massimo Porta, Trevor Orchard, John Fuller, Hans Henrik Parving, Rudy Bilous, Nish Chaturvedi, for the DIRECT Programme Study Group**

Summary

Background Diabetic retinopathy remains a leading cause of visual loss in people of working age. We examined whether candesartan treatment could slow the progression and, secondly, induce regression of retinopathy in people with type 2 diabetes.

Published Online September 26, 2008 DOI:10.1016/S0140-6736(08)61411-7

DIRECT

- Candesartan reduced incidence of retinopathy in normoalbuminuric normotensive type 1 diabetes by 18% (p=0.0508) 2-step change, primary endpoint 35% (p=0.003) 3-step change (NNT=18), post hoc analysis
- No effect on progression of retinopathy
- Candesartan enhanced regression of retinopathy by 34% (p=0.009) (NNT=21) in type 2 diabetes
- Level of retinopathy was more favourably affected on candesartan at the end of all three studies compared to placebo

N Engl J Med 2009;361:40-51.

ORIGINAL ARTICLE

Renal and Retinal Effects of Enalapril and Losartan in Type 1 Diabetes

Michael Mauer, M.D., Bernard Zinman, M.D., Robert Gardiner, M.D., Samy Suissa, Ph.D., Alan Sinaiko, M.D., Trudy Strand, R.N., Keith Drummond, M.D., Sandra Donnelly, M.D., Paul Goodyer, M.D., Marie Claire Gubler, M.D., and Ronald Klein, M.D., M.P.H.

Table 3. Effects of Enalapril and Losartan on Retinopathy, as Measured by the Odds Ratio of Progression, during the Five-Year Follow-up Period.

Progression	No. of Events	Adjusted Odds Ratio (95% CI)*	P Value
	no./total no. (%)		
By two steps or more			
Placebo	28/74 (38)	Reference	Reference
Enalapril	19/77 (25)	0.35 (0.14–0.85)	0.02
Losartan	15/72 (21)	0.30 (0.12–0.73)	0.008
By three steps or more			
Placebo	21/74 (28)	Reference	Reference
Enalapril	15/77 (19)	0.41 (0.16–1.05)	0.06
Losartan	9/72 (12)	0.21 (0.07–0.62)	0.005

* The odds ratio was adjusted for baseline characteristics, center, and baseline grade on the 15-point diabetic retinopathy severity scale.

New treatments under trial

- Intra-vitreal agents
- PKC inhibitors
- RAS blockers
- **Lipid lowering drugs**

Retinopathy in the FIELD Trial

In diabetic patients, 5 years of treatment with fenofibrate:

- Reduced the need for laser treatment for diabetic retinopathy
- Reduced 2-step progression of retinopathy grade in patients with but not without pre-existing retinopathy
- Did not reduce fasting glucose, A1c or blood pressure

Keech et al. Lancet 2007; DOI:10.1016/S0140-6736(07)61607-9

Statins and retinopathy

Study	Treatment	No	Follow-up (years)	Results
HPS	Simvastatin 40 mg	5.963	5	+8% laser treatment **(p=NS)**
CARDS	Atorvastatin 10 mg	2.832	4-4,5	-6% progression of retinopathy **(p=NS)** -13% photocoagulation **(p=NS)**
ASCOT-LLA	Atorvastatina 10 mg (+amlodipine)	2.532	3,3	+3% retinal thrombosis **(p=NS)**

Heart Protection Study Lancet 2003;361:2005-2016
Colhoun HM et al., Lancet. 2004;364:685-696
Sever PS et al., Diabetes Care 2005;28:1151-1157

Grazie per l'attenzione !