Treatment of Diabetic Retinopathy

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Financial Disclosure

Speaker, Joseph Wilhelm, M.D. has a financial interest/agreement or affiliation with Lansing Ophthalmology, where he is a shareholder and employed as a retina specialist.

Diabetes Mellitus

- 14 million Americans are affected
- 8000 become blind from retinopathy annually

Laser surgery for Retinopathy is most effective before visual loss occurs.

Visual loss is a late symptom of Diabetic Retinopathy.

Currently, much disease is detected too late for effective laser surgery.

Diabetic Retinopathy: Effective Screening

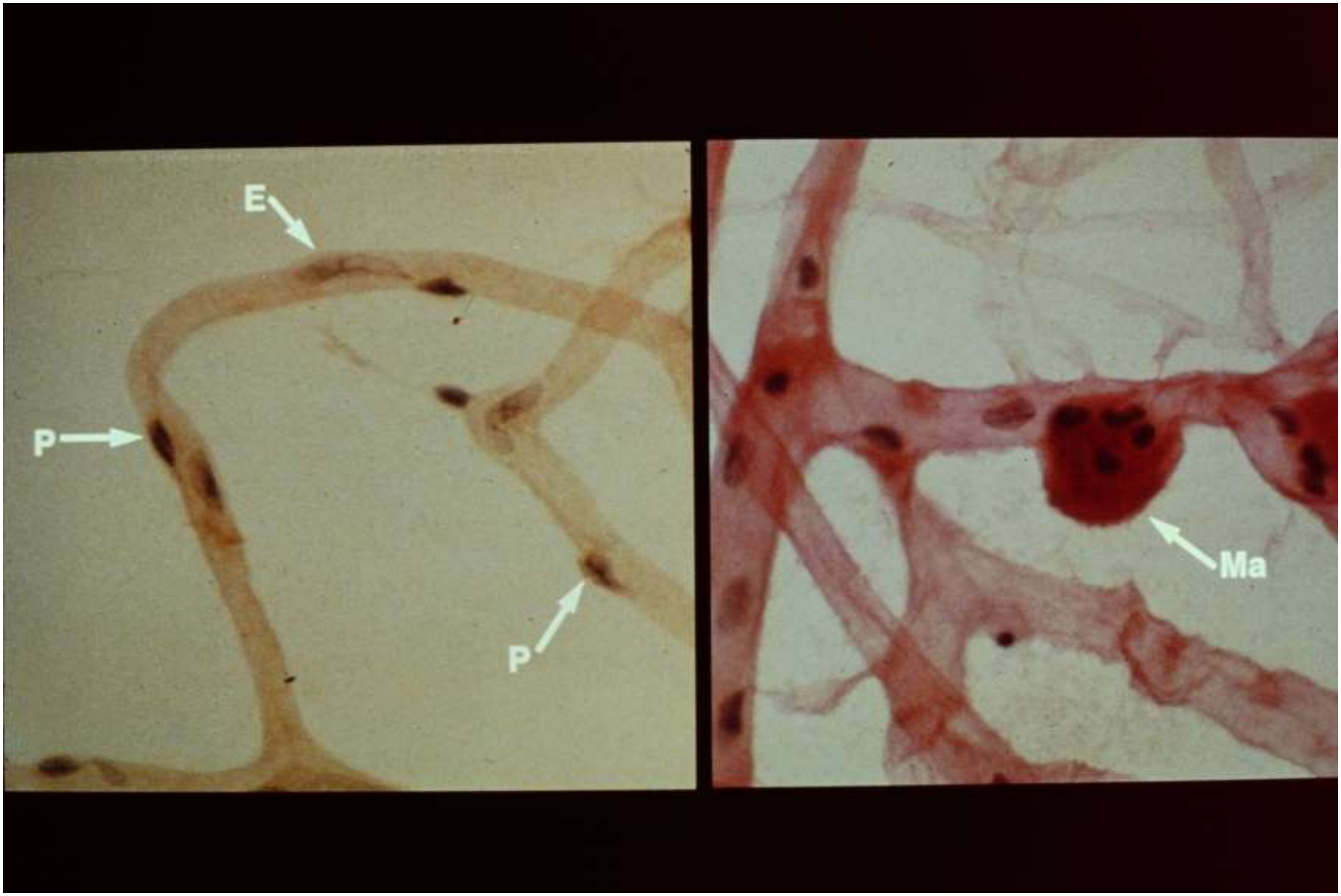
- Depends on retinal examination
- $62 million potential saving annual

Diabetic Retinopathy: A Public Health Issue

- Prevalence may rise as % of aged in population rises
- Screening is a cost-effective way to reduce the incidence of blindness

Pathogenesis

- High blood sugar levels may affect retinal capillaries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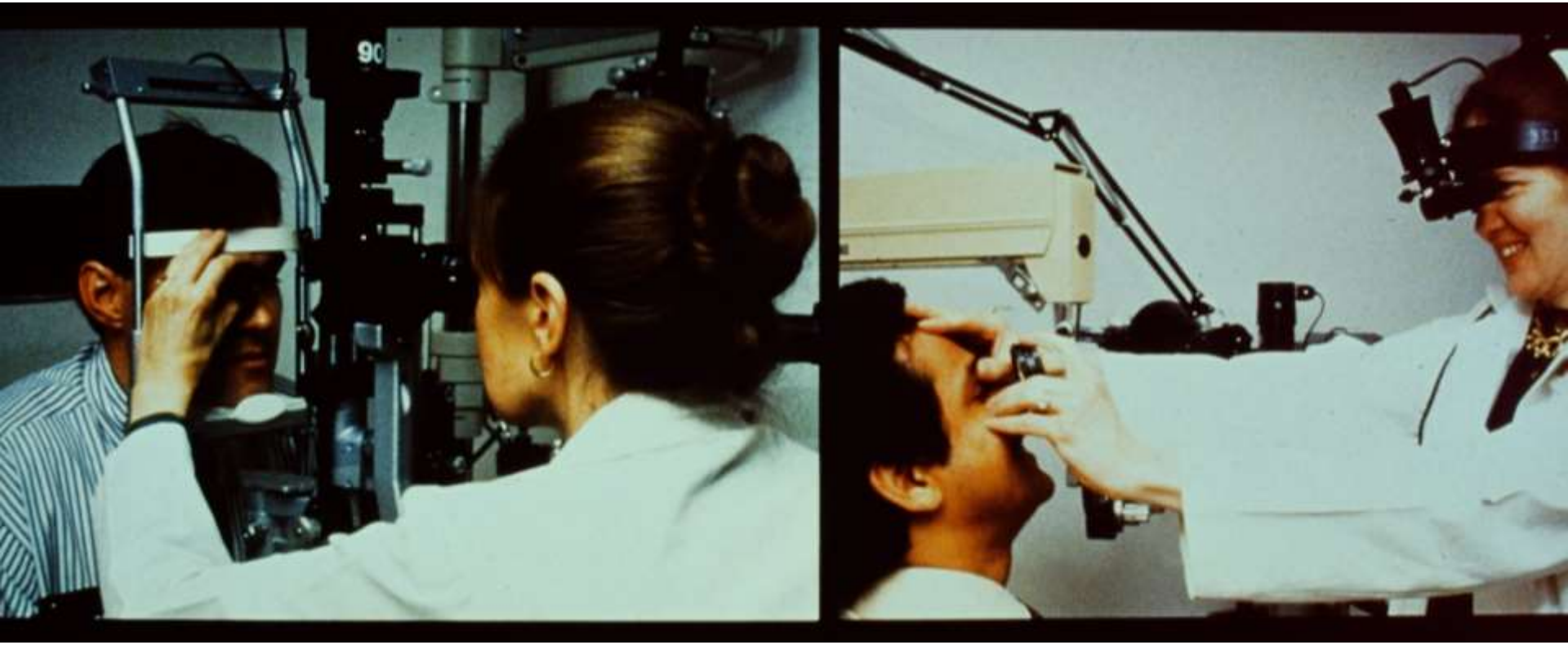


Nonproliferative Retinopathy (NPDR)

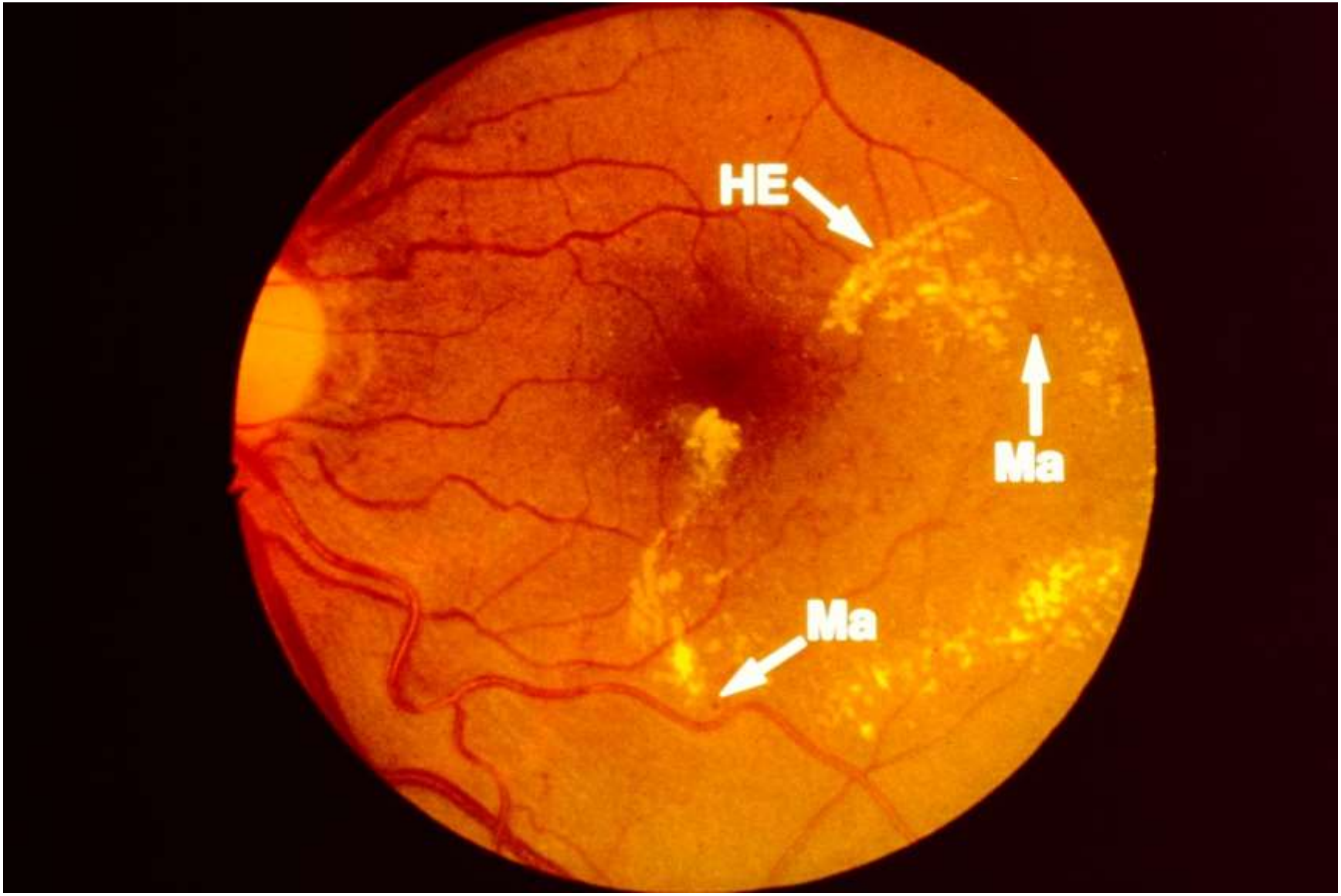
- Retinal blood vessels leak
- Leakage into macula may reduce vision

Proliferative Retinopathy (PDR)

- Neovascularization
- Fibrous proliferation
- Bleeding and traction
- Retinal detachment and blindness

Early NPDR: Ophthalmoscopic Signs

- Microaneurysms
- Hard exudates
- Intraretinal hemorrhages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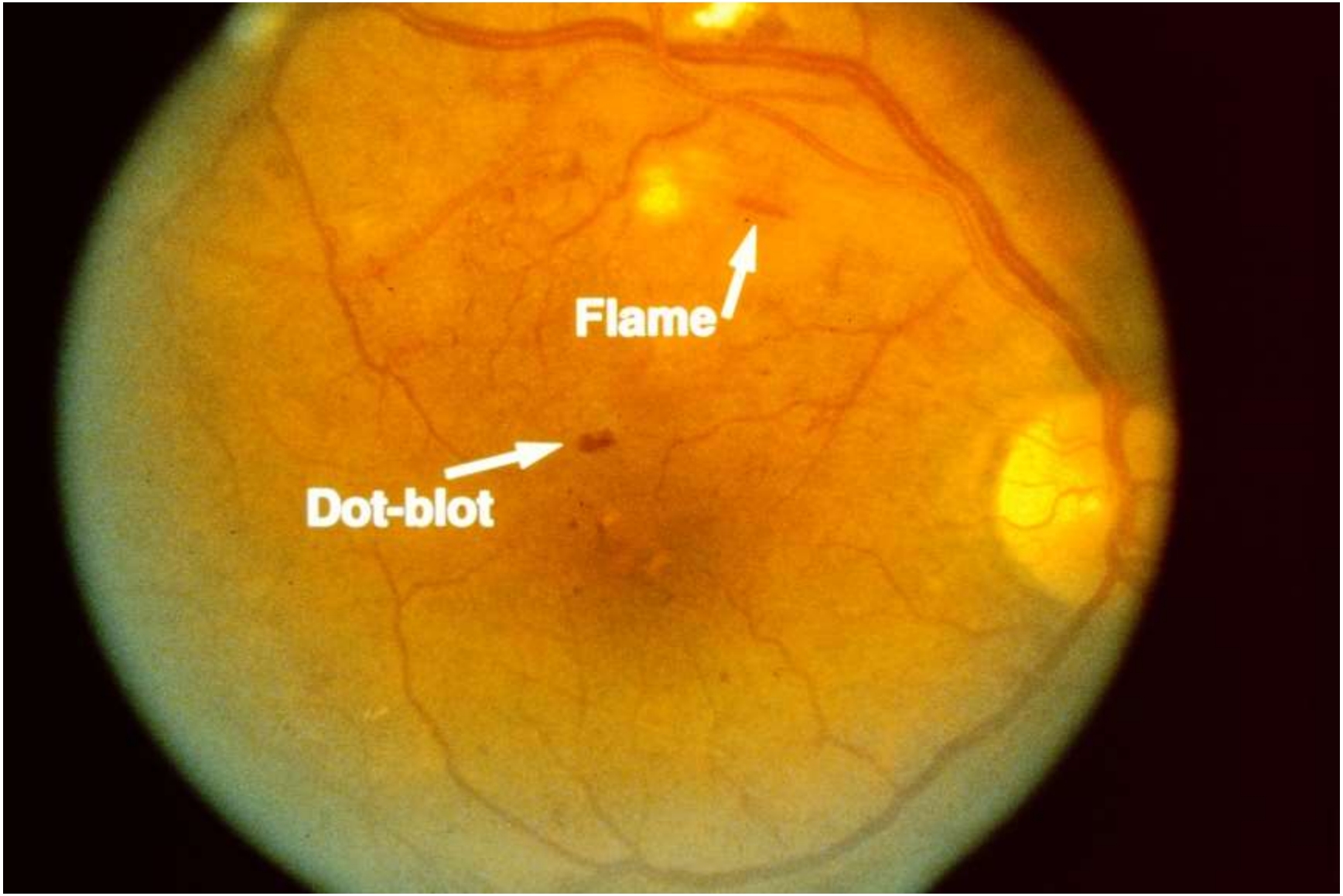
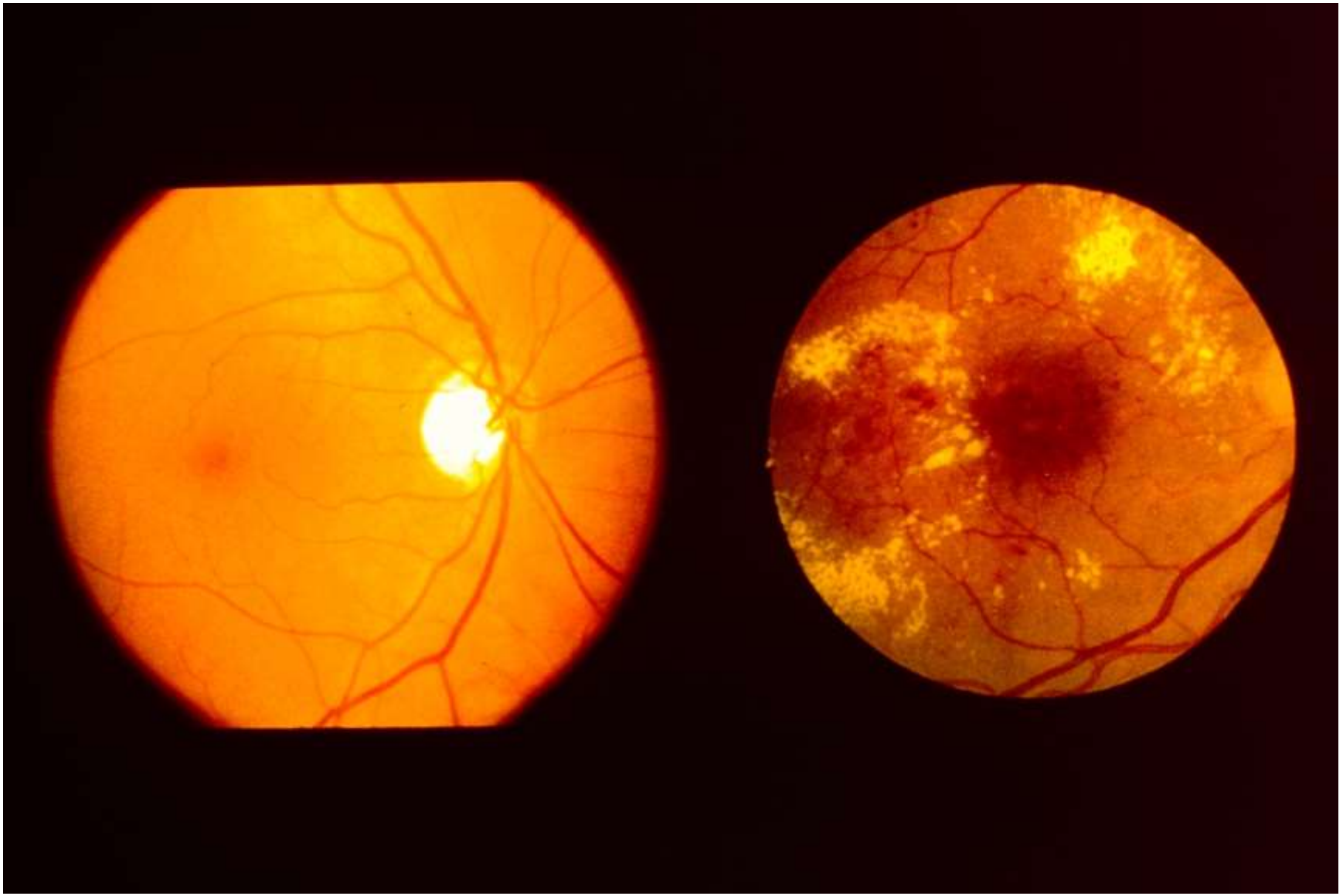

Flame
Dot-blot

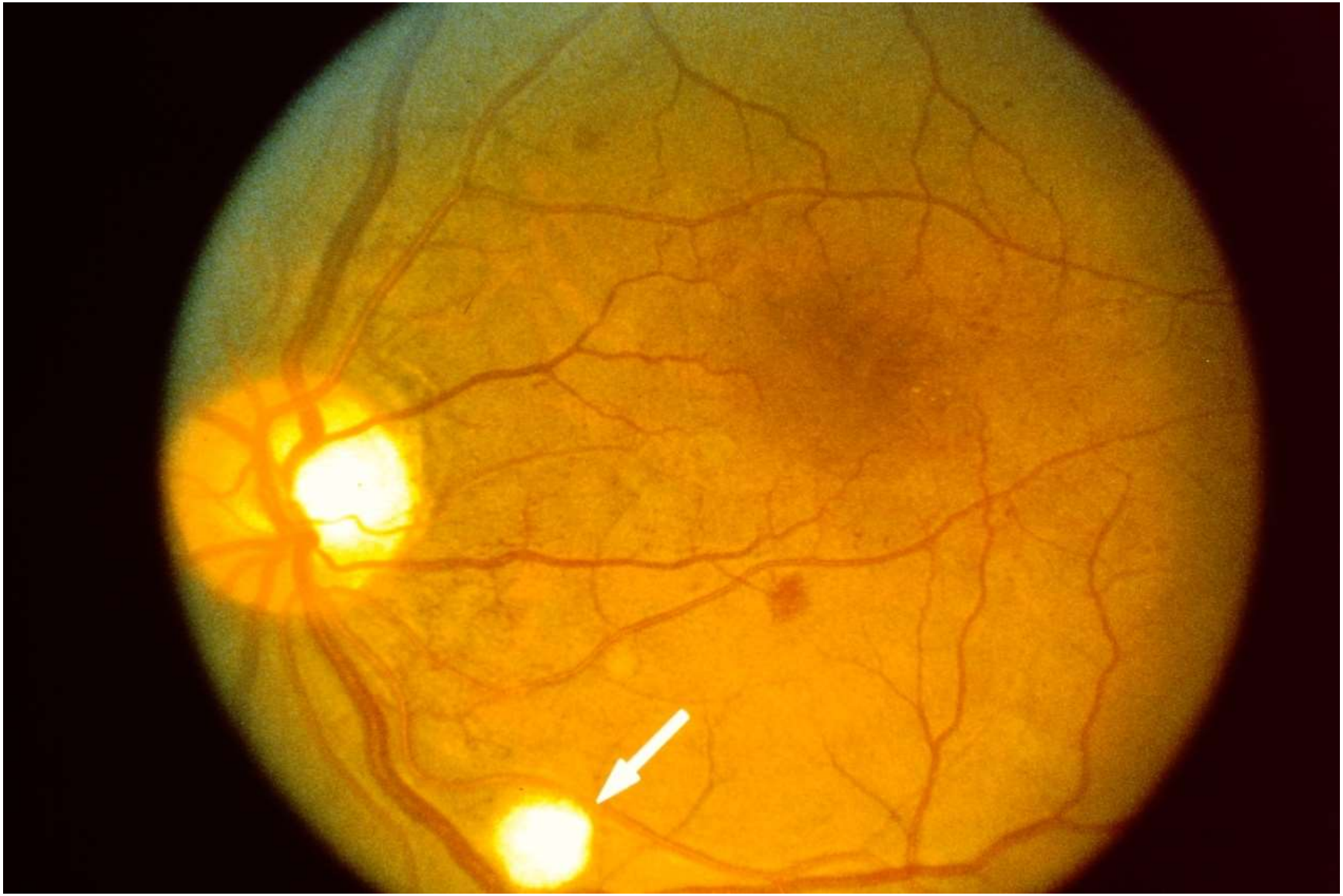


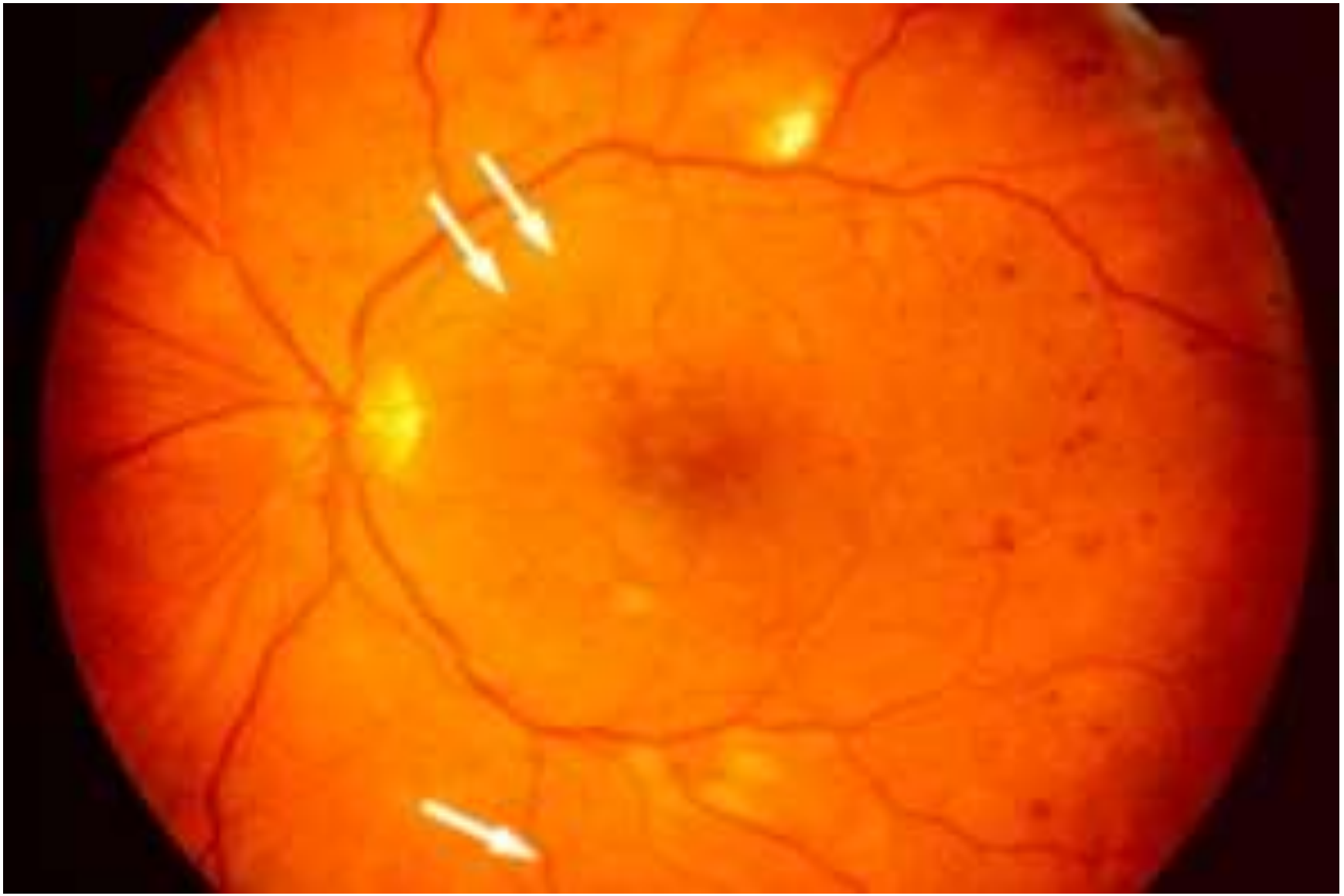
Diabetic Macular Edema: Prevalence

- Diabetes Dx ≤ 5 yrs = 5%
- Diabetes Dx ≥ 15 yrs = 15%

Advanced NPDR

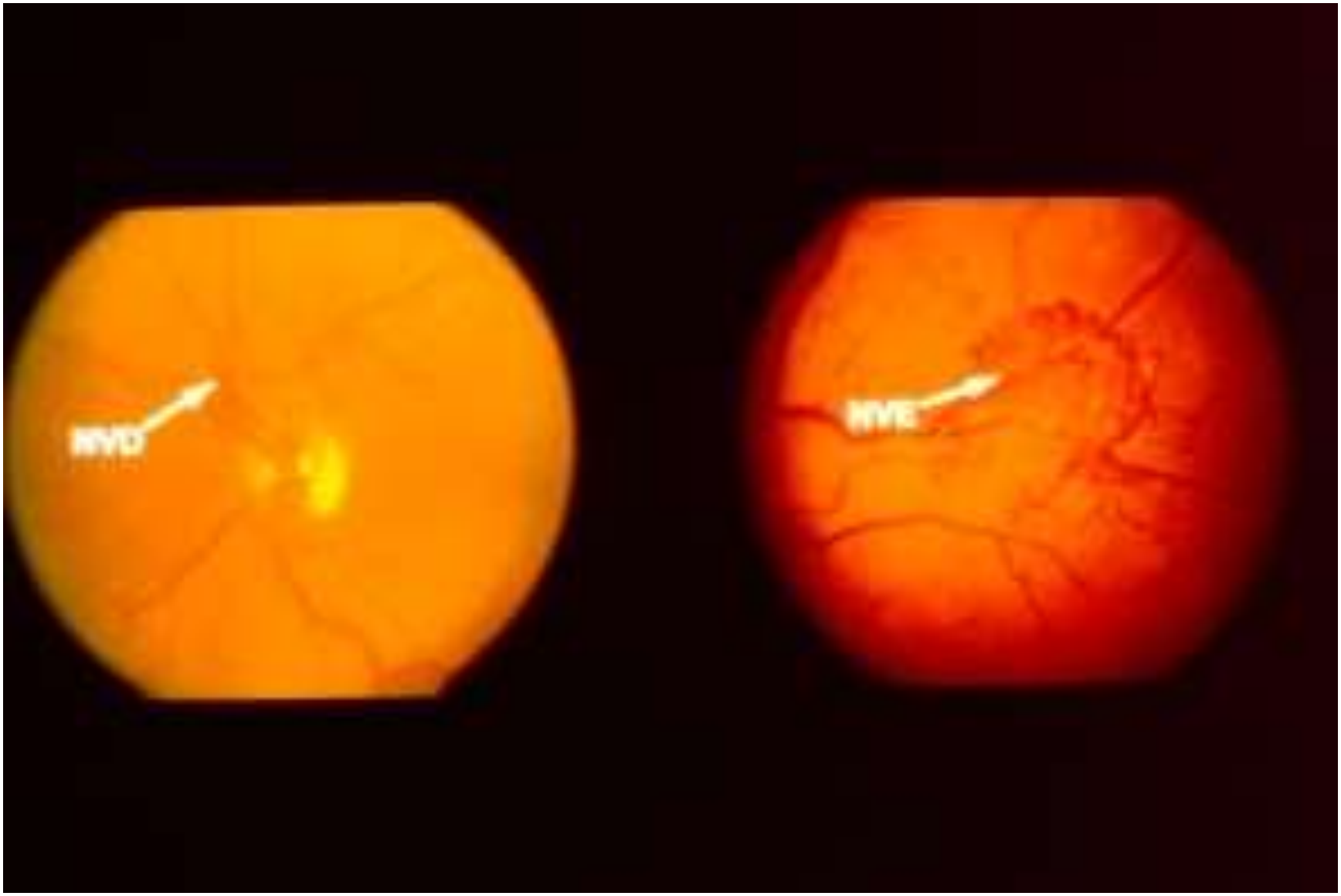
- High risk of imminent PDR
- No immediate treatment
- Patient needs re-evaluation in 2 to 4 months





PDR: Ophthalmoscopic Signs

- Neovascularization
- Vitreous hemorrhage
- Fibrous proliferation
- Can have all NPDR findings, including macular edema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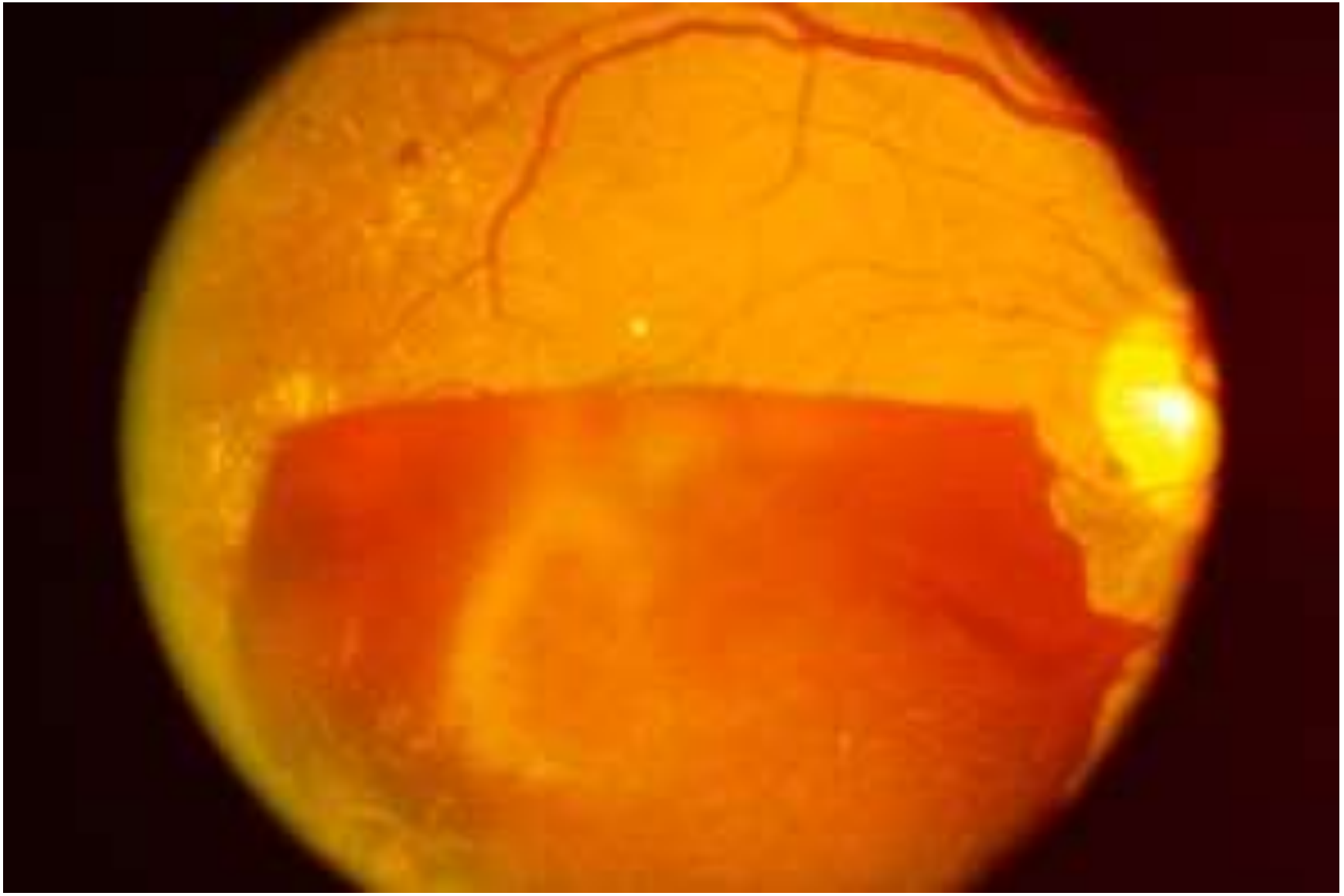
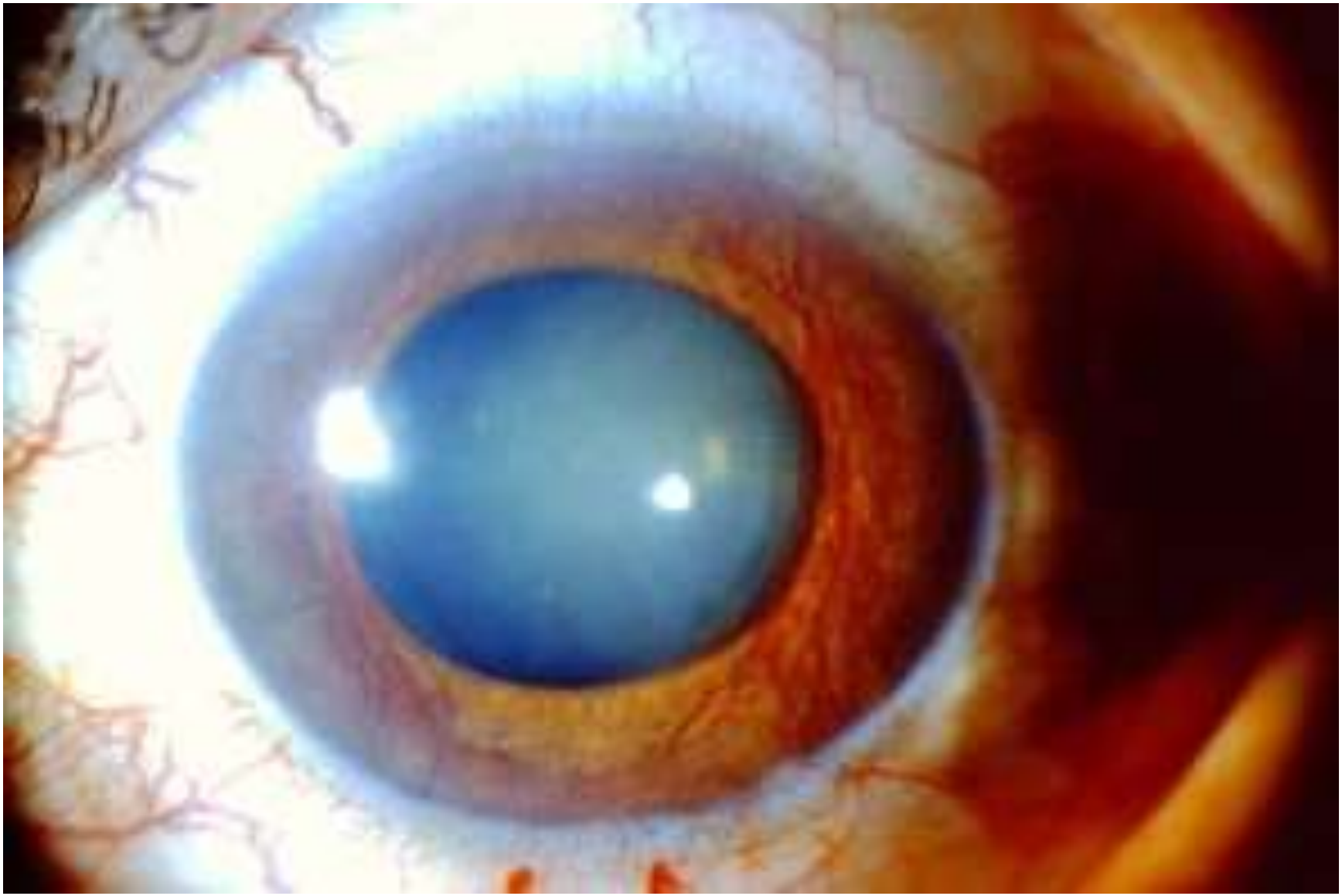
NVE

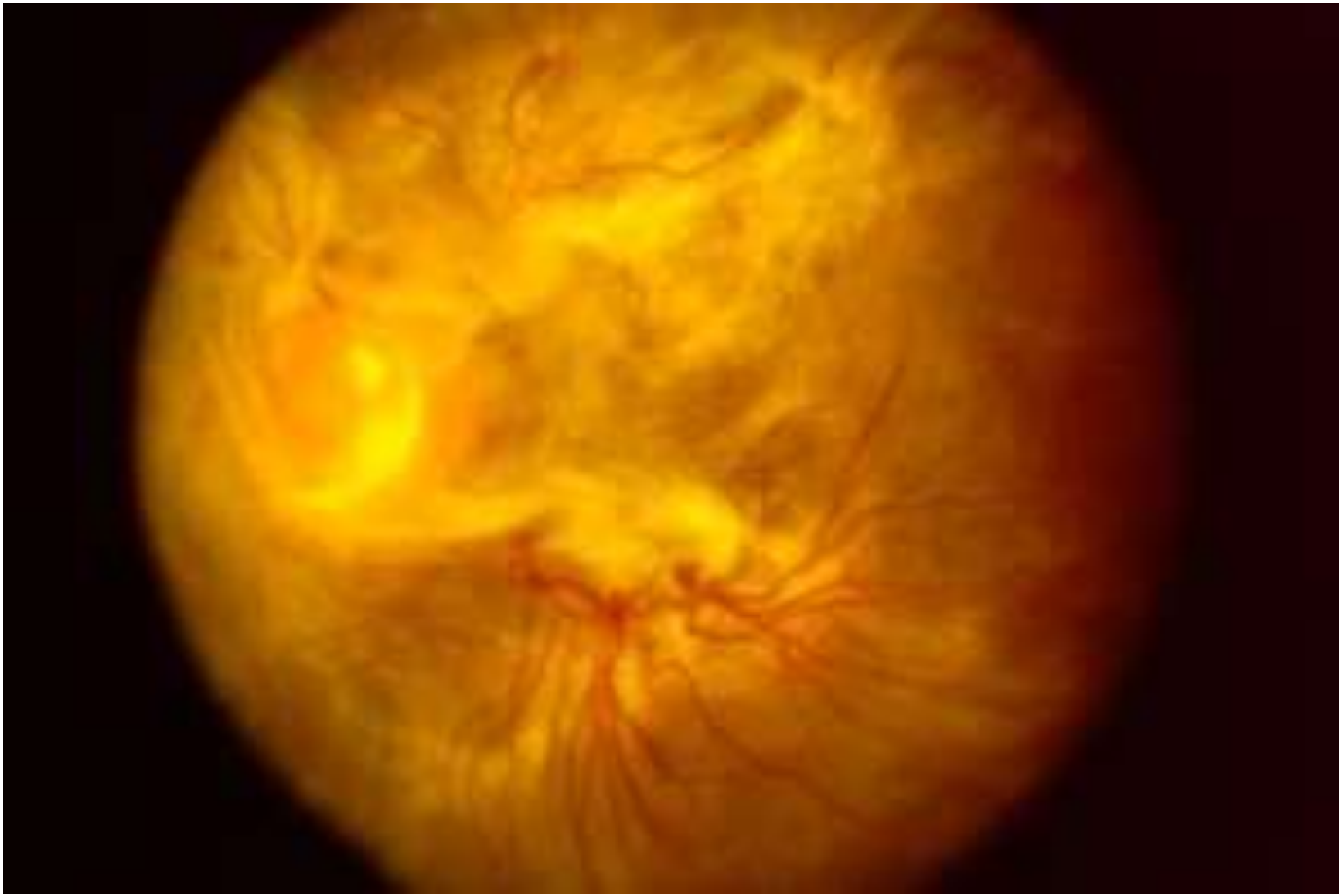


Vitreous Hemorrhage: Symptoms

- Shower of dots or floaters
- Vision may decrease to light perception only

Refer for urgent ophthalmologic examination.





PDR: Prevalence

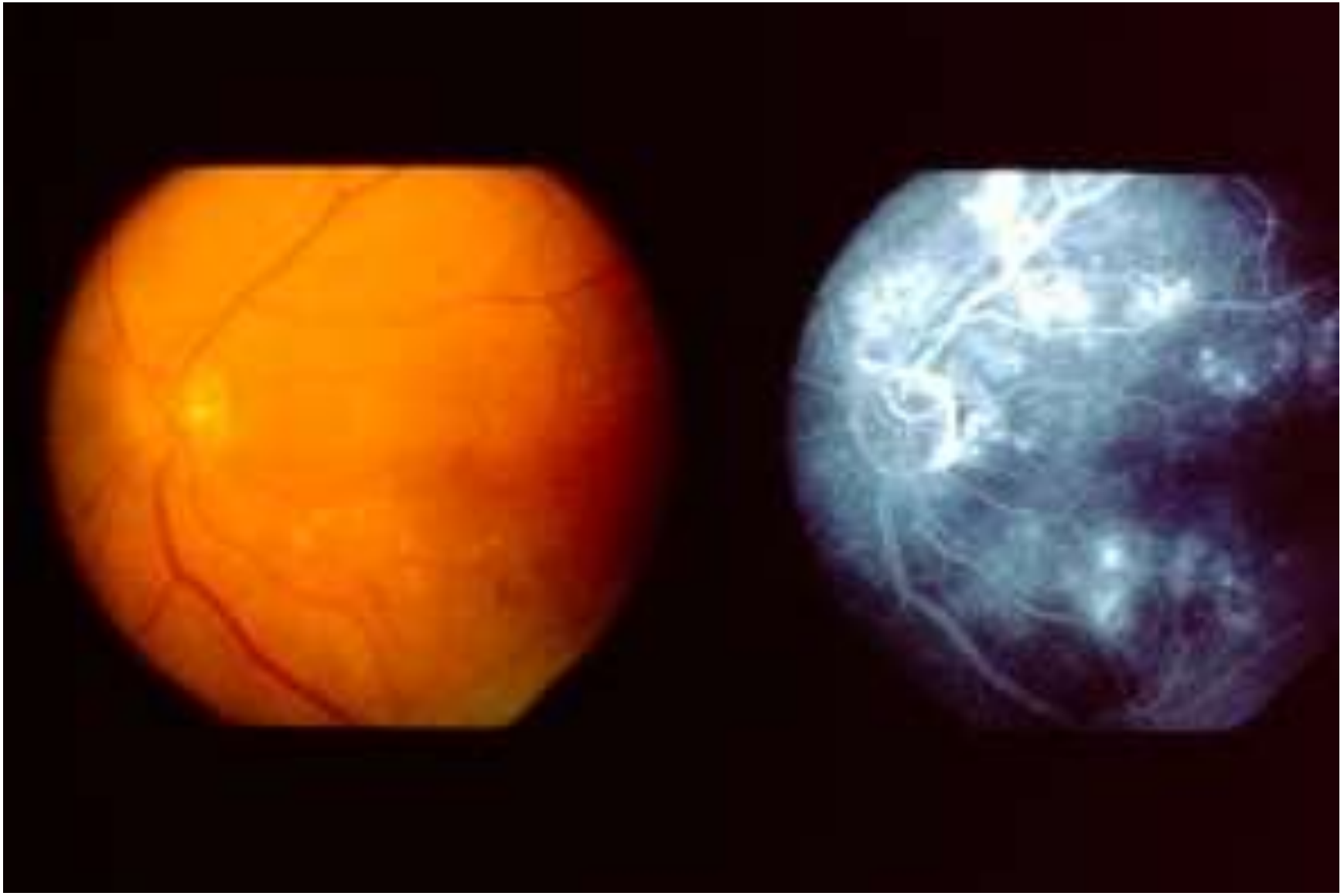
- Related to
  - Duration of diabetes
  - Patient's age at Dx

% Patients With PDR: Insulin Users Dx < Age 30

Yrs After Dx	%
5	Nil
15	25%
20	55%

% Patients With PDR: Insulin Users Dx > Age 30

Yrs After Dx	%
20	20%



Focal Laser Photocoagulation Can Reduce Visual Loss From Macular Edema By 50% or More.


Macular edema
Before
After

Laser Surgery Most Benefits Patients With NVD Or NVE With Vitreous Hemorrhage.


PDR
Before
After

Panretinal Photocoagulation

- Outpatient procedure
- 1000 to 2000 burns
- 1 to 3 sessions

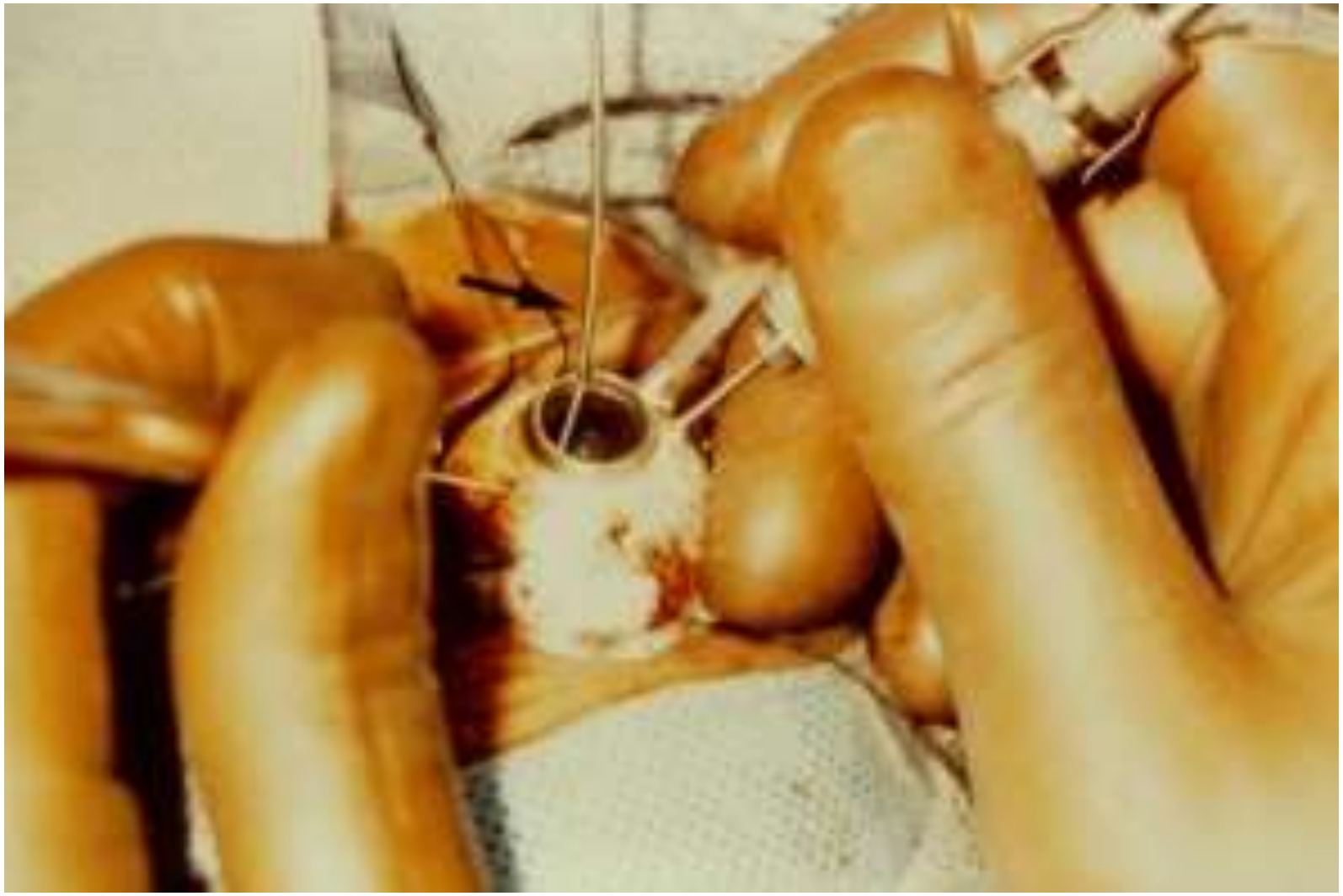
Panretinal Laser Surgery Can Decrease Risk Of Severe Visual Loss By About 50% For Patients With High-Risk PDR.

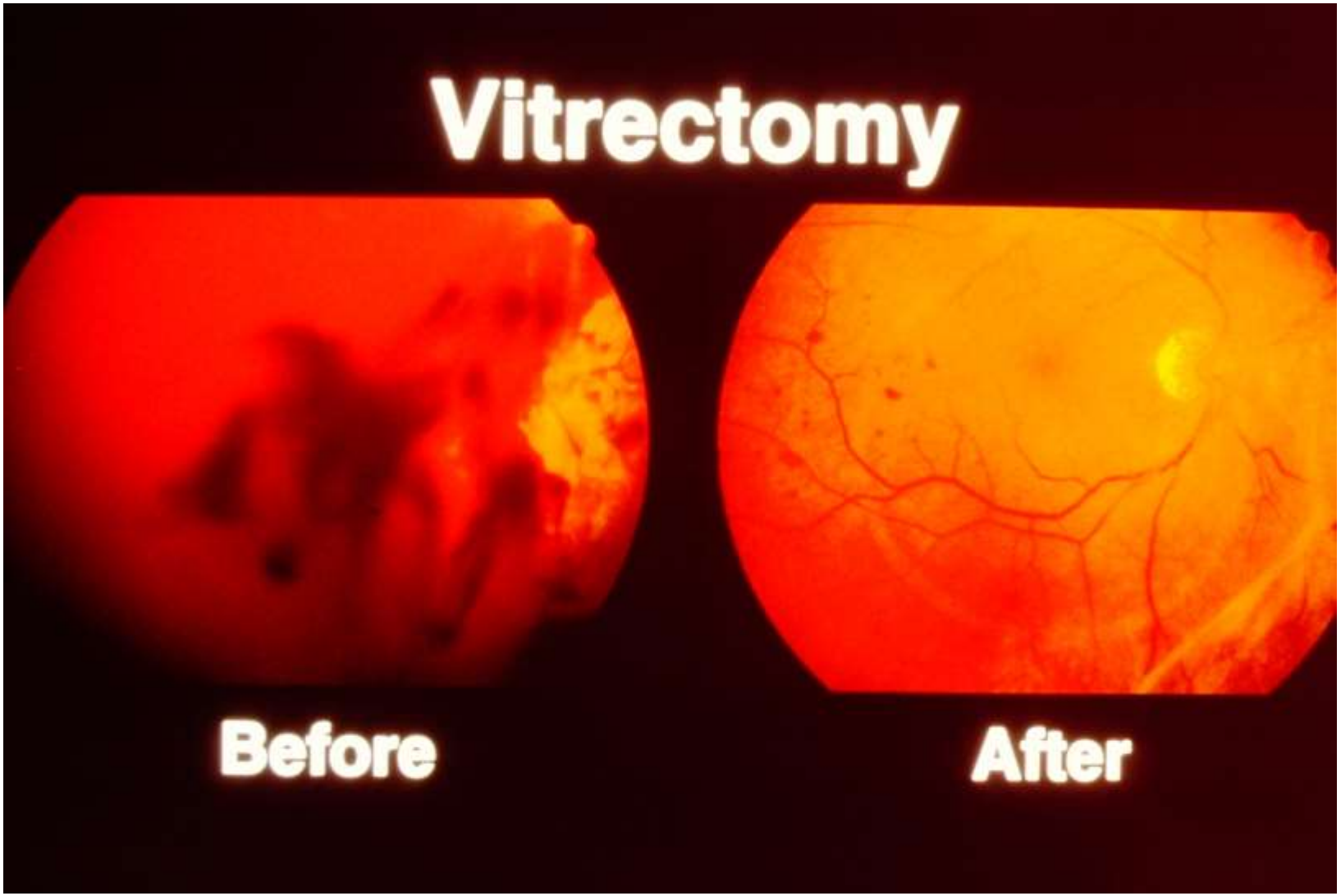
Panretinal Photocoagulation: Side Effects

- Some loss of night vision
- Some loss of side vision
- Occasional slight decrease of central vision

Vitrectomy

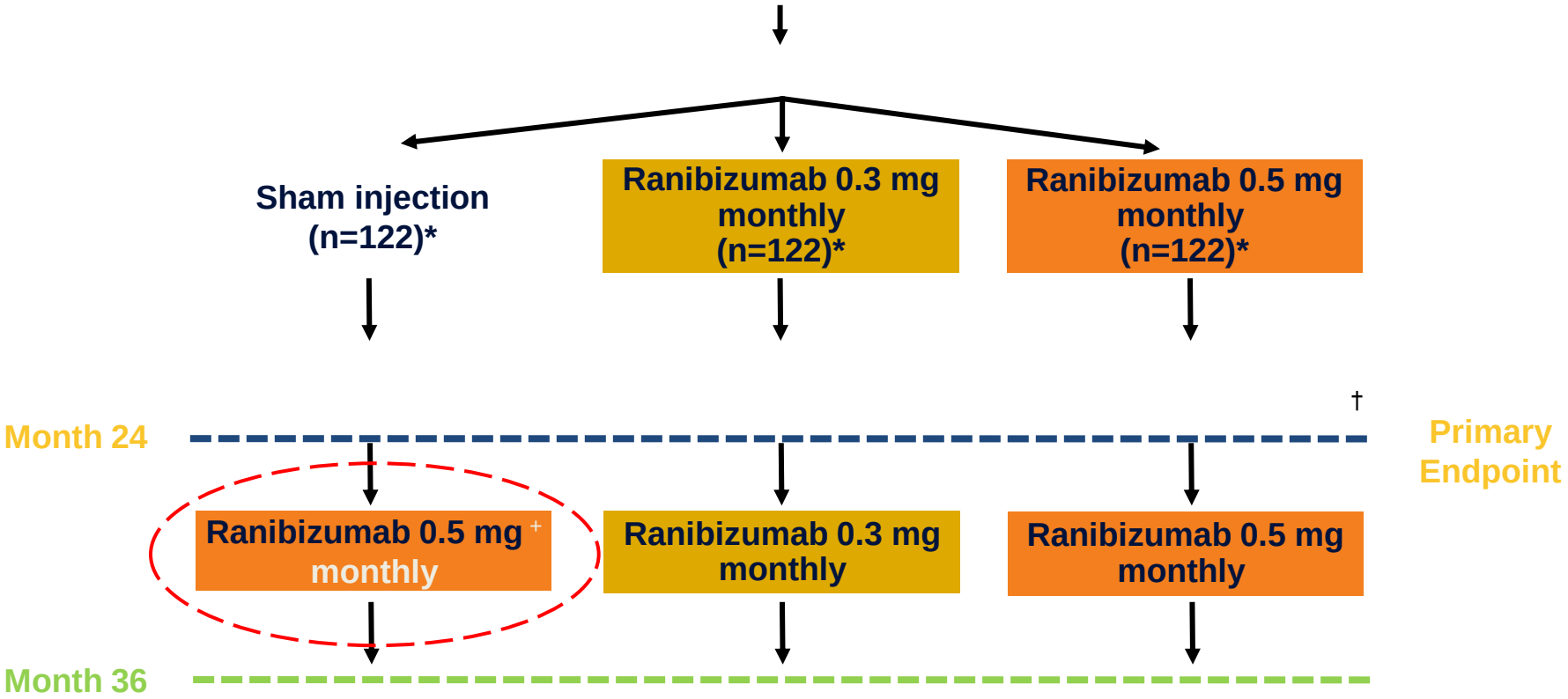
- To remove vitreous hemorrhage
- To treat or prevent retinal detachment




Vitrectomy
Before
After

RIDE and RISE Study Design

Sham subjects eligible for crossover to ranibizumab 0.5 mg monthly

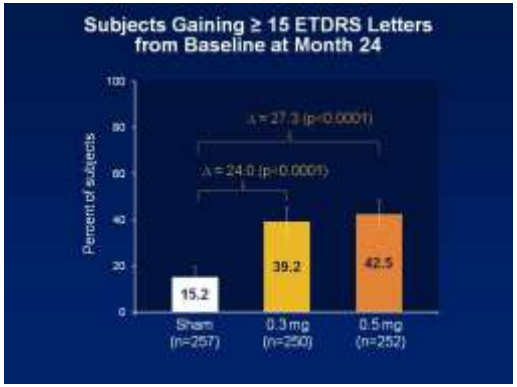


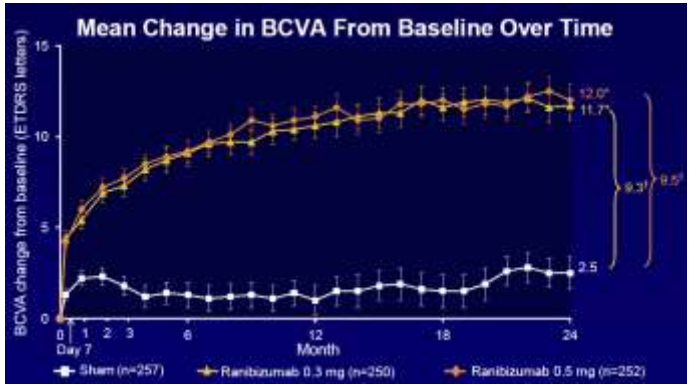
† Macular laser criteria: OCT ≥ 250μm with < 50 μm change from prior month, no laser in prior 3 months, and evaluating physician deems laser therapy to be beneficial.

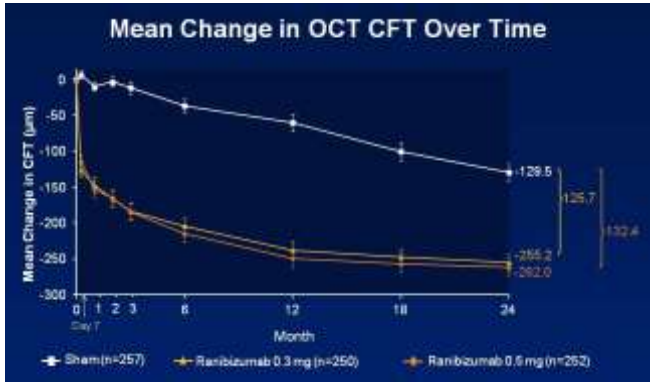
+ Sham subjects were eligible for crossover to monthly ranibizumab 0.5 mg after Month 24 . Subjects who met predefined criteria became eligible for early

Month 24 Outcomes

- DME patients treated with ranibizumab experienced rapid, sustained, and statistically significant improvements in vision and retinal anatomy
- Results validated crucial role of VEGF in DR pathophysiology







- Incidence of ocular AEs consistent with prior clinical trials of ranibizumab across multiple retinal diseases
- Overall rates of ATEs were similar to those reported in other Phase III studies of DME with ranibizumab, although a higher number of strokes and deaths were observed with 0.5 mg ranibizumab compared to 0.3 mg in RIDE/RISE

AE = adverse events; ATE = arterial thromboembolic events; DME = diabetic macula edema; DR = diabetic retinopathy; VEGF = vascular endothelial growth factor A.

Key Questions Addressed At 36 Months

- Are efficacy outcomes seen with ranibizumab at Month 24 maintained over longer periods of time?

- What is the consequence, if any, of delayed initiation of ranibizumab treatment for DME?
  - What happens to VA in sham/crossover patients, who received 2 years of sham (plus macular laser) prior to one year of monthly ranibizumab?

DME = diabetic macula edema.

RIDE and RISE

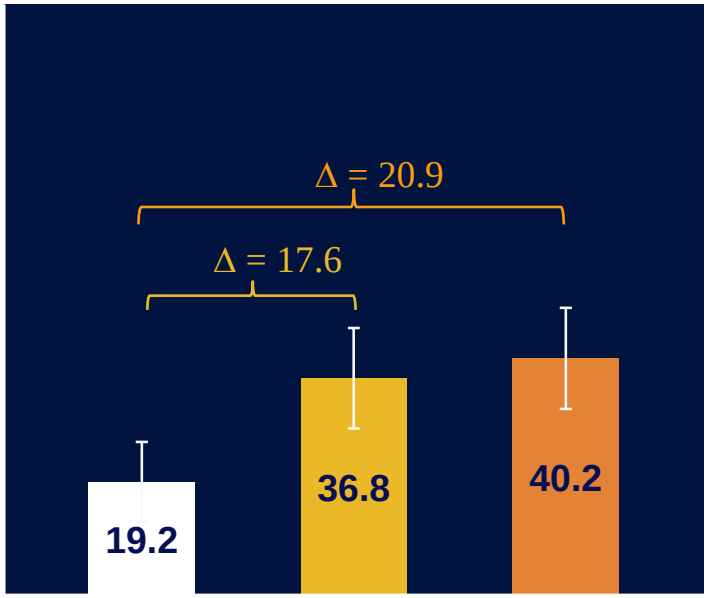
36 Month Efficacy

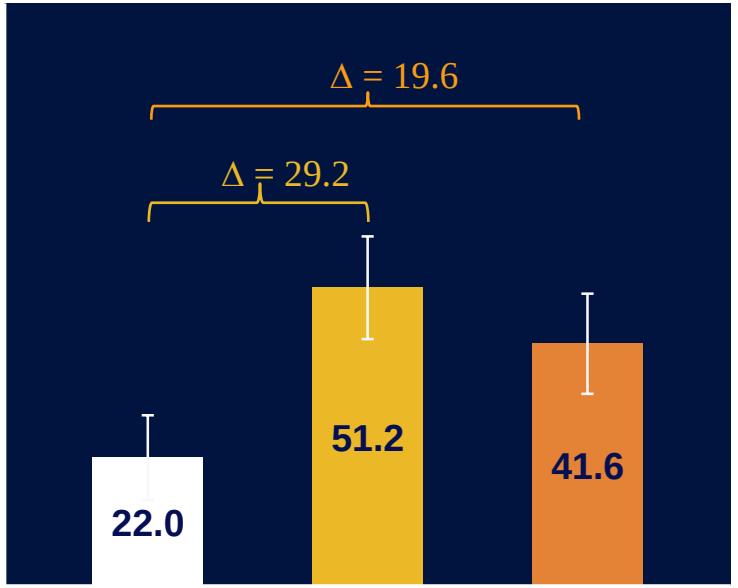
Subject Disposition and Study Eye Treatment

Category	RIDE and RISE		
		Ranibizumab	
	Sham/0.5 mg	0.3 mg	0.5 mg
Number of subjects randomized	257	250	252
On study at month 24, n (%)	210 (81.7)	210 (84.0)	216 (85.7)
On study at month 36, n (%)	188 (73.2)	196 (78.4)	198 (78.6)
Ranibizumab exposure			
Months	25-35*	0-35	0-35
Number of subjects who received ranibizumab	190†	250	249
Total number of injections	1896	7223	7327
Per patient			
Mean (SD)	10.0 (2.0)	28.9 (10.7)	29.4 (9.8)
Median	11	34	34

ets roughly 1 year of ranibizumab 0.5 mg exposure post crossover

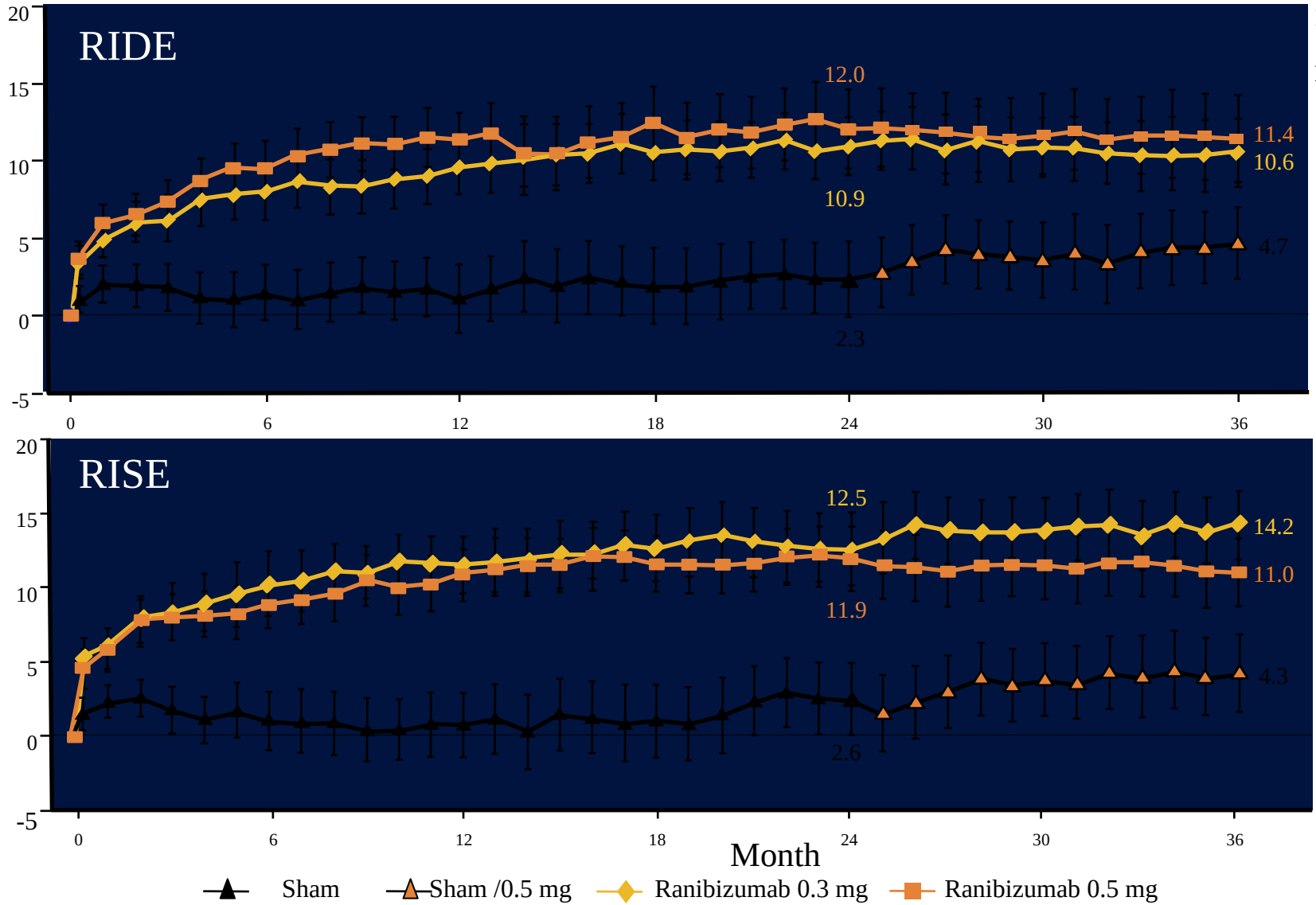
Subjects Gaining ≥ 15 ETDRS Letters from Baseline at Month 36





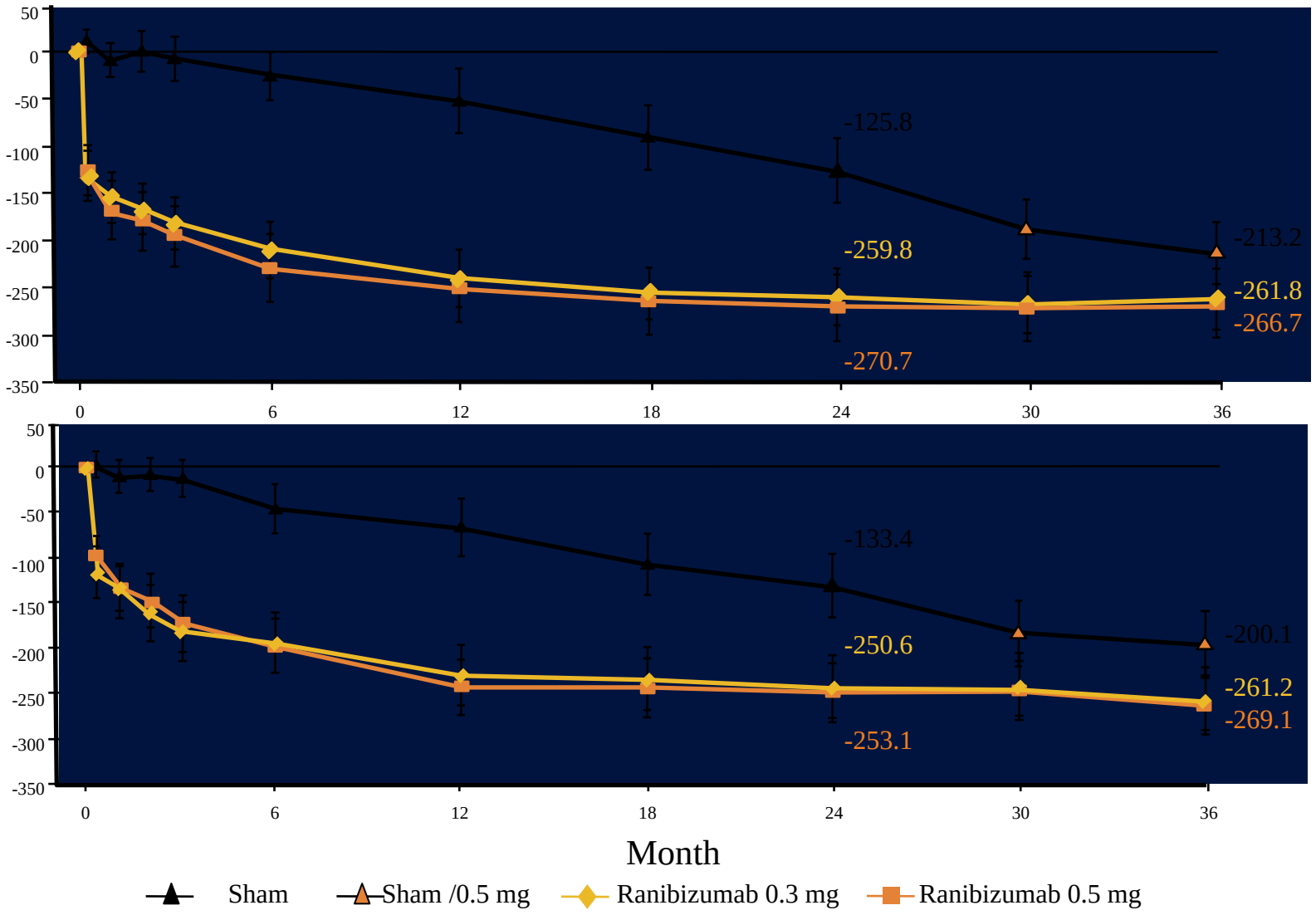
The last observation carried forward imputation method was used. Vertical bars are 95% confidence interval.
ETDRS = Early Treatment Diabetic Retinopathy Study; DME = diabetic macular edema.

Mean Change in BCVA Over Time (ITT Population)



Vertical bars are 95% confidence intervals. Missing data were imputed by LOCF (last observation carried forward).
BCVA = best corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study; ITT = intention-to-treat; Tx = ranibizumab treatment.

Mean Change in OCT CFT Over Time



OCT CFT at Month 36 Pts Txd After Month24

193.7 +/-99.2

207.8 +/-139.9

182.2 +/-94.2

OCT CFT at Month 36 in Pts Txd After Month24

194.7 +/- 135.8

198.2 +/- 117.3

171.7 +/- 90.1

Last observation carried forward imputation method was used.

OCT = optical coherence tomography.

Macular Laser Through 36 Months

Proportion of patients receiving macular laser, %	Pooled RISE and RIDE		
	Sham/0.5 mg (n=257)	Ranibizumab	
		0.3 mg (n=250)	0.5 mg (n=252)
From Months 1-24	72.0	37.6	27.4
From Months 1-36	73.2	38.8	29.4
Between Months 24 and 36	6.6	7.2	6.0

RIDE and RISE
Ocular and Systemic Safety Outcomes

Select Ocular SAEs, Study Eye through Month 36

Consistent with month 24 and prior ranibizumab studies

SOC/Preferred Term, n (%)	Pooled RIDE and RISE		Pooled RIDE and RISE	
	Originally randomized to ranibizumab		Originally randomized to sham	
	Months 0-36		Months 0-24	Months 0-36
	0.3 mg (n=250)	0.5 mg (n=249)	Sham (n=250)	Sham/0.5 mg* (n=251)
Any Ocular SAEs	12 (4.8)	26 (10.4)	16 (6.4)	22 (8.8)
Vitreous Hemorrhage	1 (0.4)	3 (1.2)	7 (2.8)	9 (3.6)
Cataract	1 (0.4)	3 (1.2)	0	1 (0.4)
Visual Acuity Reduced	0	3 (1.2)	4 (1.6)	3 (1.2)†
Retinal Detachment	0	1 (0.4)	1 (0.4)	2 (0.8)
Retinal Tear	0	1 (0.4)	0	0
Endophthalmitis+	4 (1.6)	2 (0.8)	0	0
IOP Increased	0	2 (0.8)	0	0

†

+

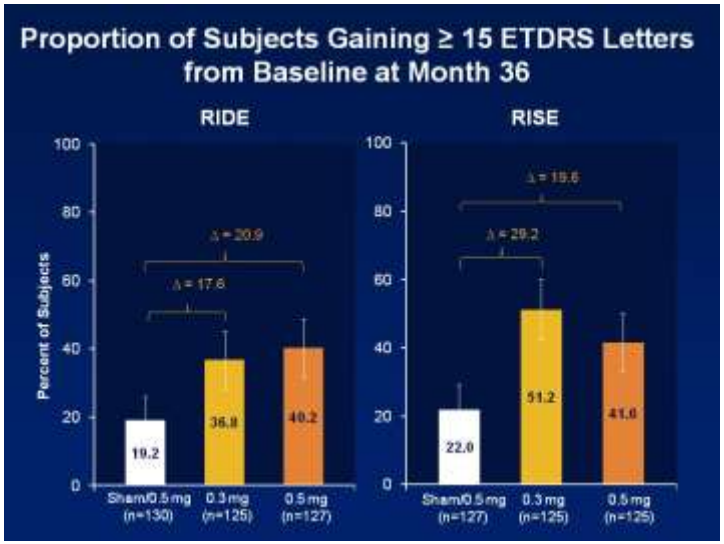
APTC Events through Month 36

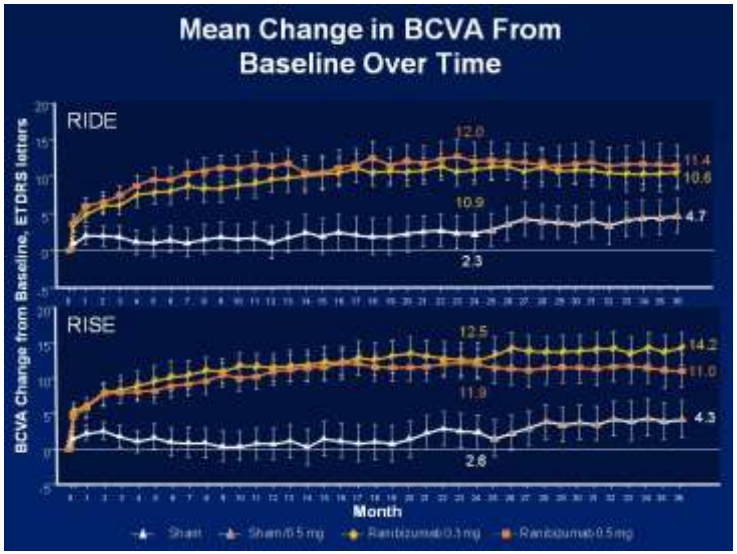
AE Group Term, n (%)	Pooled RISE and RIDE		Pooled RISE and RIDE	
	Originally randomized to ranibizumab		Originally randomized to sham	
	Months 0-36		Months 0-24	Months 0-36
	0.3 mg (n=250)	0.5 mg (n=249)	Sham (n=250)	Sham/0.5 mg * (n=251)
Deaths, overall	11 (4.4)	16 (6.4)	3 (1.2)	7 (2.8)
Vascular	8 (3.2)	8 (3.2)	3 (1.2)	5 (2.0)
Non-vascular	2 (0.8)	7 (2.8)	0	2 (0.8)
Unknown Cause	1 (0.4)	1 (0.4)	0	0
MI, overall	18 (7.2)	9 (3.6)	9 (3.6)	13 (5.2)
Fatal	3 (1.2)	1 (0.4)	2 (0.8)	4 (1.6)
Non-fatal	15 (6.0)	8 (3.2)	7 (2.8)	9 (3.6)
CVA, overall	5 (2.0)	12 (4.8)	4 (1.6)	6 (2.4)
Fatal	1 (0.4)	3 (1.2)	1 (0.4)	2 (0.8)
Non-fatal	4 (1.6)	9 (3.6)	3 (1.2)	4 (1.6)
APTC events†	27 (10.8)	26 (10.4)	13 (5.2)	18 (7.2)

There is no pure sham control group at Month 36 so it is not valid to compare the sham groups with the ranibizumab treatment groups.
* Includes Sham and Crossover to 0.5 mg and Sham and No Crossover to 0.5 mg.
† Includes vascular deaths, unknown cause deaths, non-fatal MIs, non-fatal CVAs.
APTC = Antiplatelet Trialists' Collaboration; CVA = cerebrovascular accident ; MI = myocardial infarction

Conclusions

- DME patients treated with ranibizumab experienced rapid, sustained improvements in visual acuity and retinal anatomy. Improvements seen at 24 months were sustained through 36 months.
- Delayed treatment with ranibizumab (after month 24) in patients originally randomized to sham did not result in the same extent of improvement seen in patients treated with ranibizumab from the outset.





- Ocular and systemic safety generally consistent with Month 24 results
- Potential for new standard of care for patients with DME

Screening Guidelines: Diabetes Dx < Age 30

- Annual ophthalmologic exams starting 5 years after DX
- Ophthalmosopy for signs by PCP at other intervals

Screening Guidelines: Diabetes Dx > Age 30

- Annual ophthalmologic exams starting at time of Dx
- Ophthalmoscopy for signs by PCP at other intervals

Screening Guidelines: Conception and Pregnancy

- Ophthalmologic exam before conception
- Ophthalmologic exams at 3-month intervals beginning in first trimester

Conclusion

- Early treatment my prevent blindness
- Improved screening can ensure early treatment