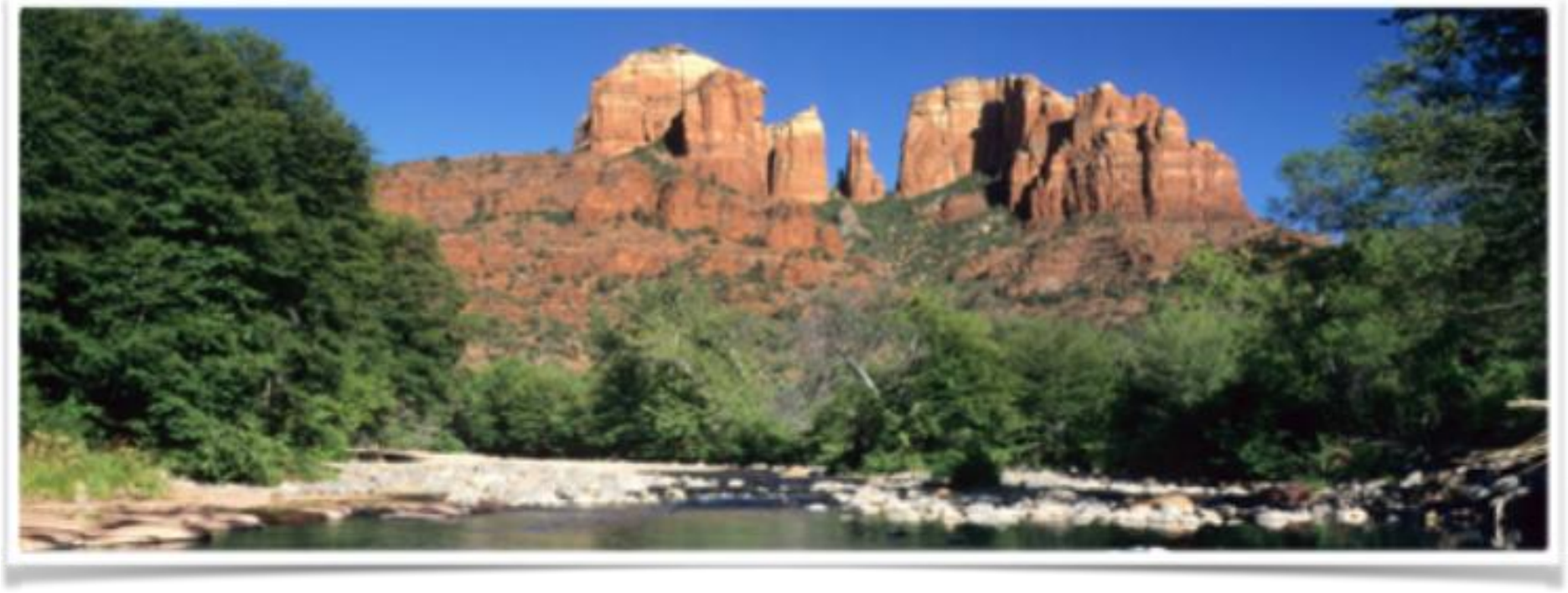
# Diabetic Eye Disease

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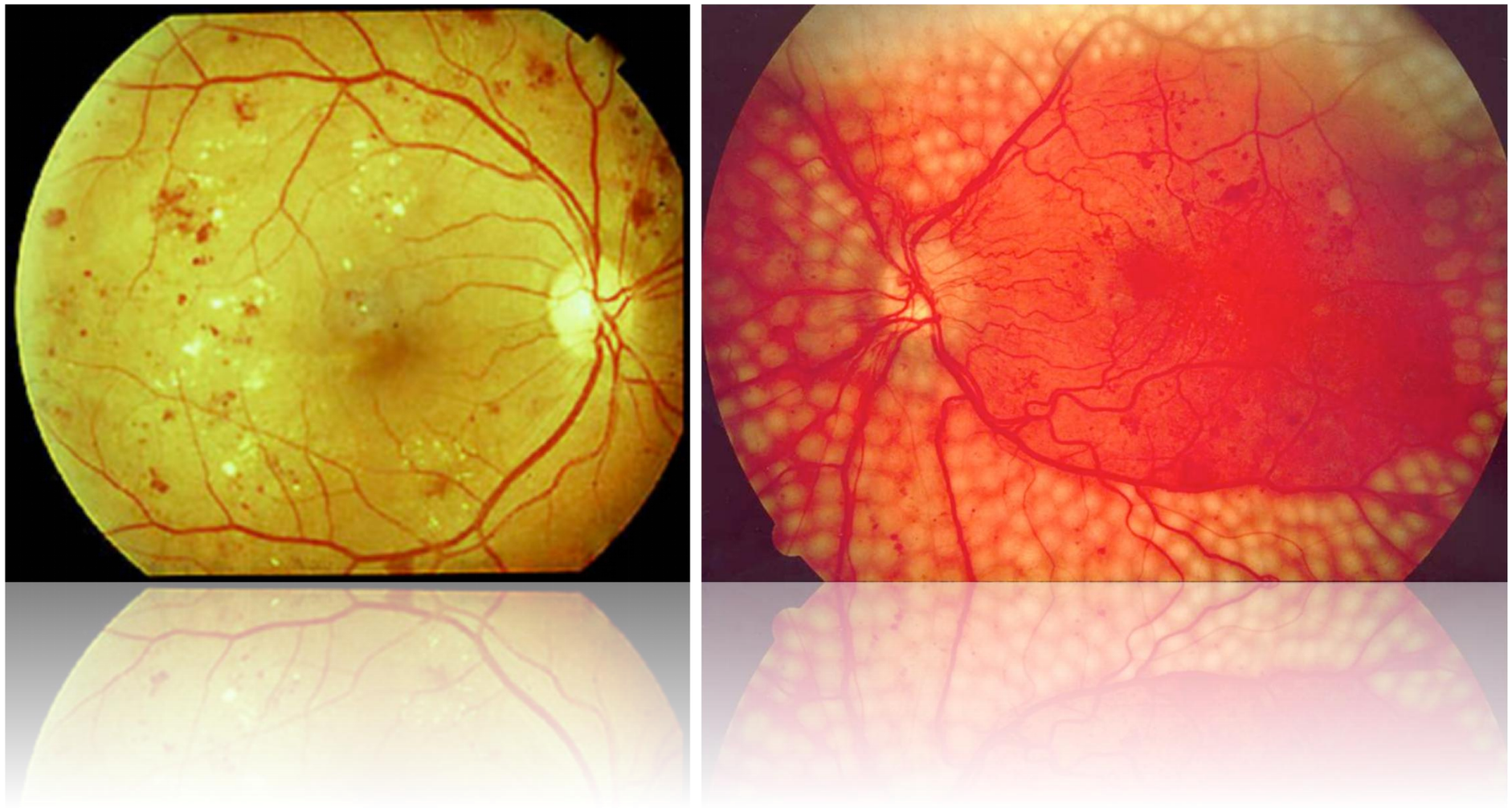
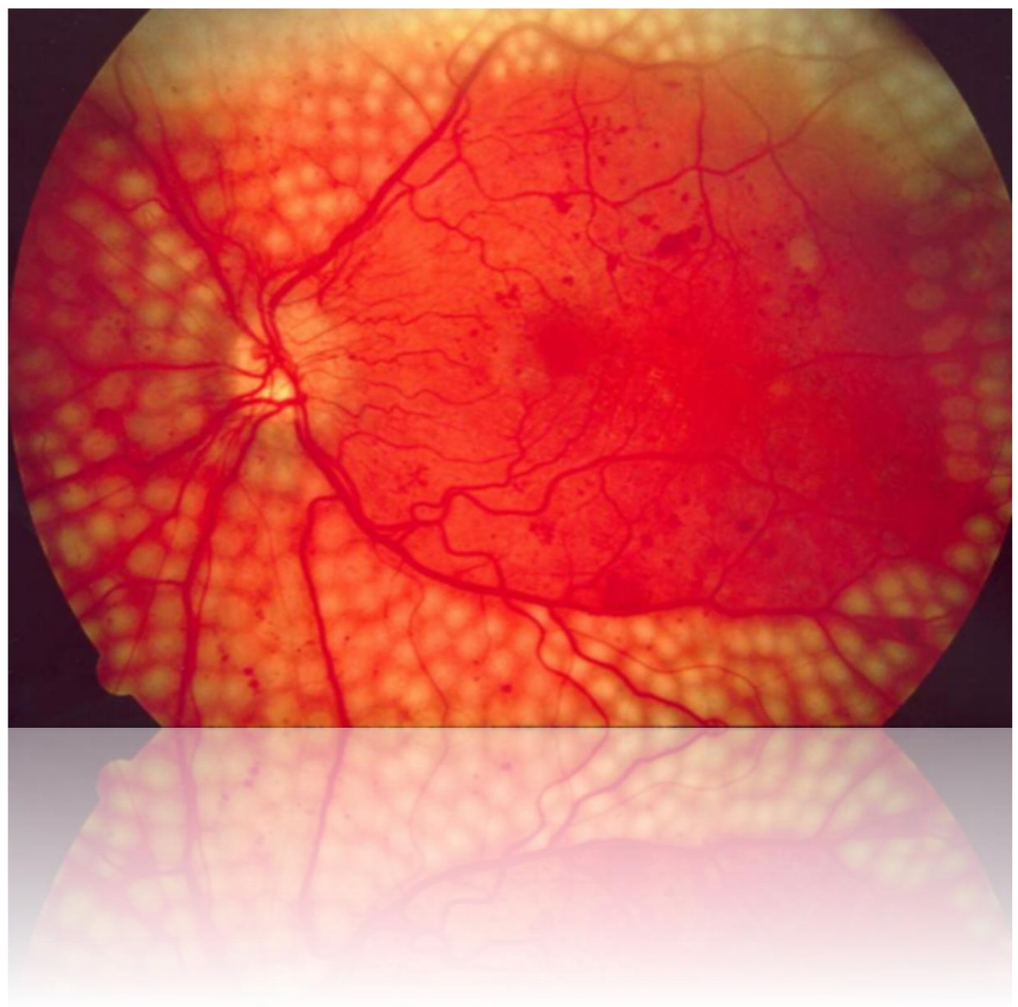
# Diabetic Retinopathy



# Overview

- Epidemiology
- Pathophysiology
- Clinical Definitions
- Treatment options
- Current Research



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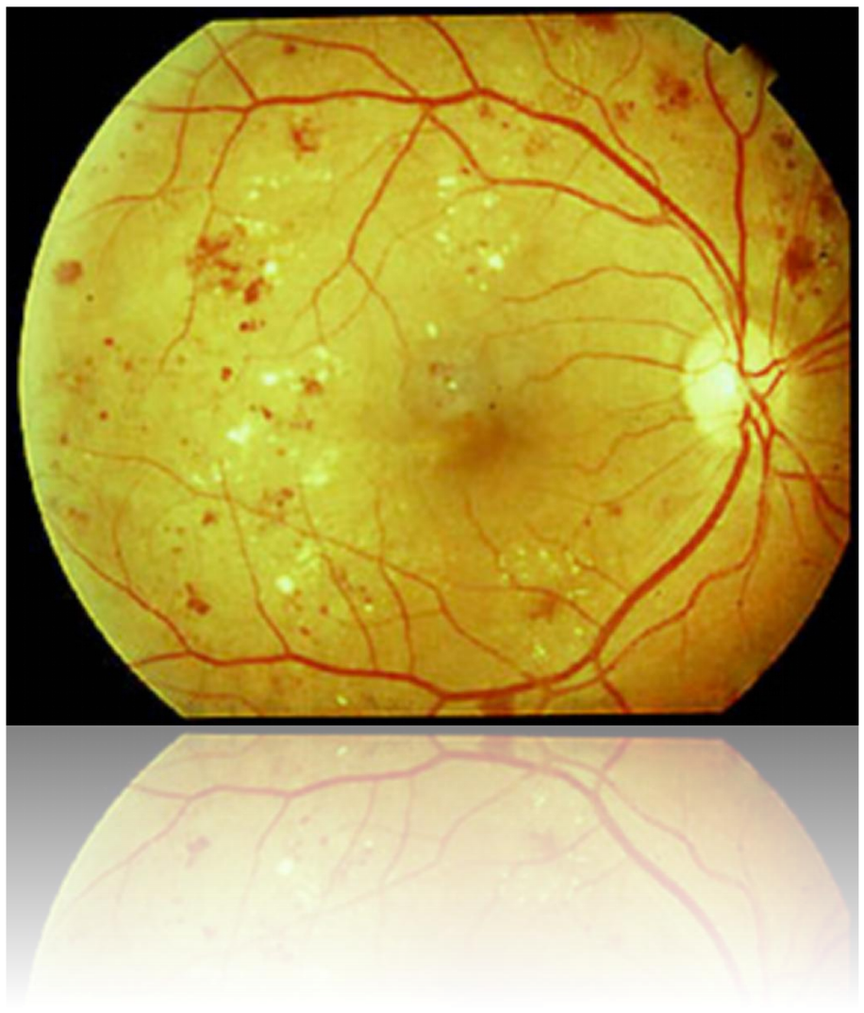
# Epidemiology



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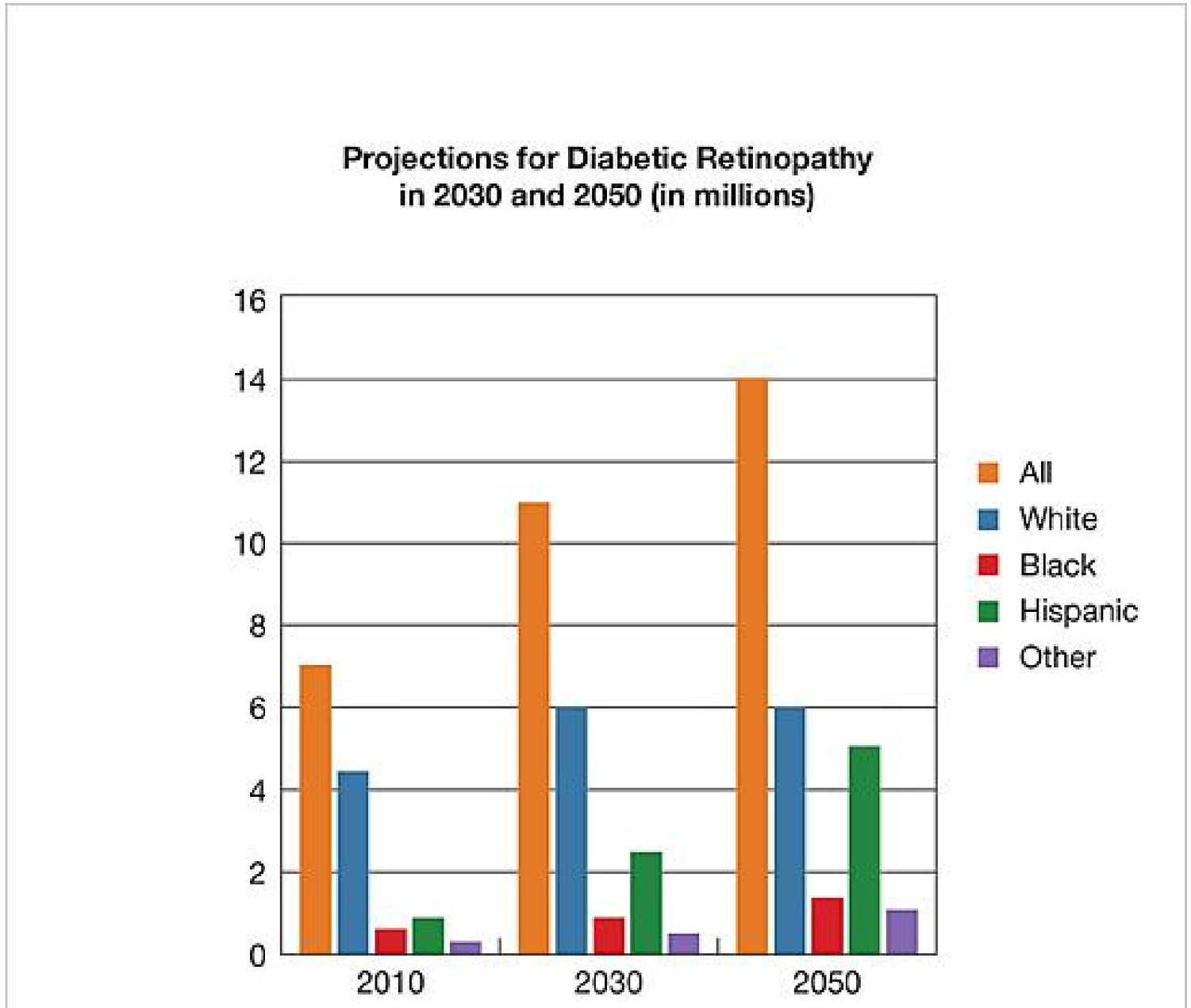



Graph courtesy of National Eye Institute

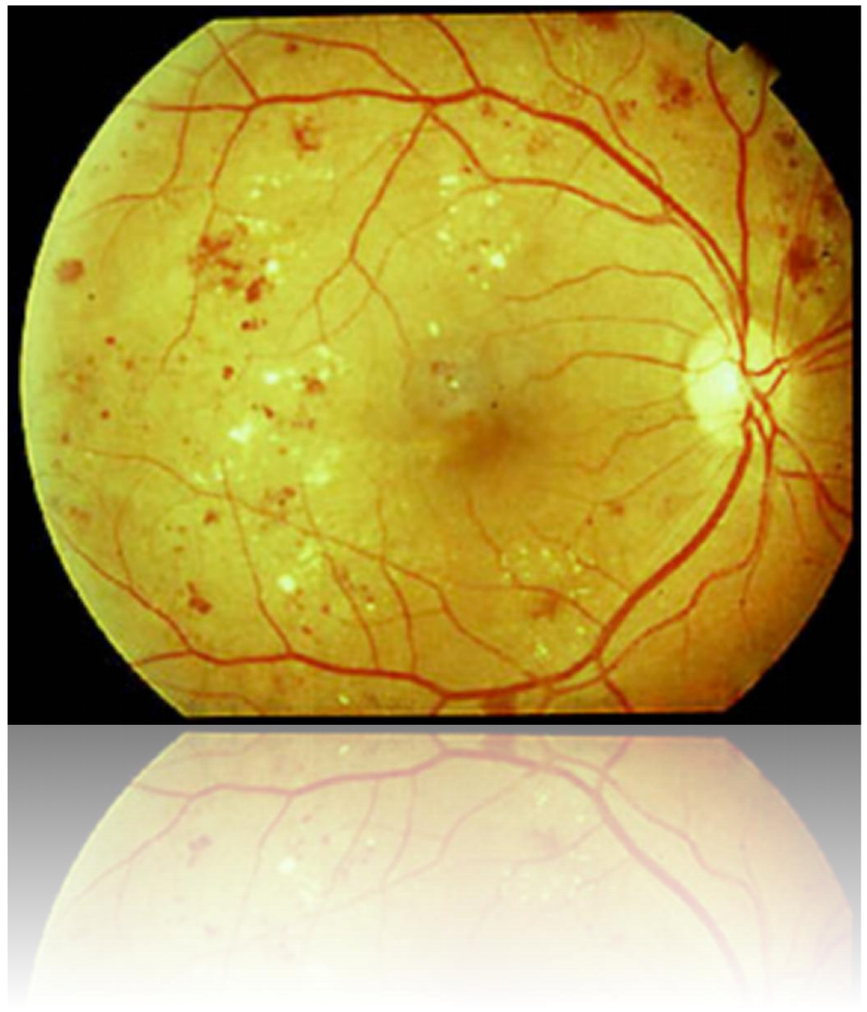
# The Wisconsin Epidemiological Study of Diabetic Retinopathy

- Ongoing epidemiological study on progression of diabetic retinopathy (DR)
- Duration of DM correlated with prevalence of DR
- After 20 years, ***99%*** of Type 1 & ***60%*** of Type 2 pts have DR
- Note: Study limited to Caucasian pts from northern European descent

# Diabetes Control and Complications Trial United Kingdom Prospective Diabetes Study

- Studied intensive glucose control in Type 1 & 2 DM: HgbA1C<6%
- Risk of developing DR reduced by ***75%***; Risk of progression of DR reduced by ***50%***

# Pathophysiology



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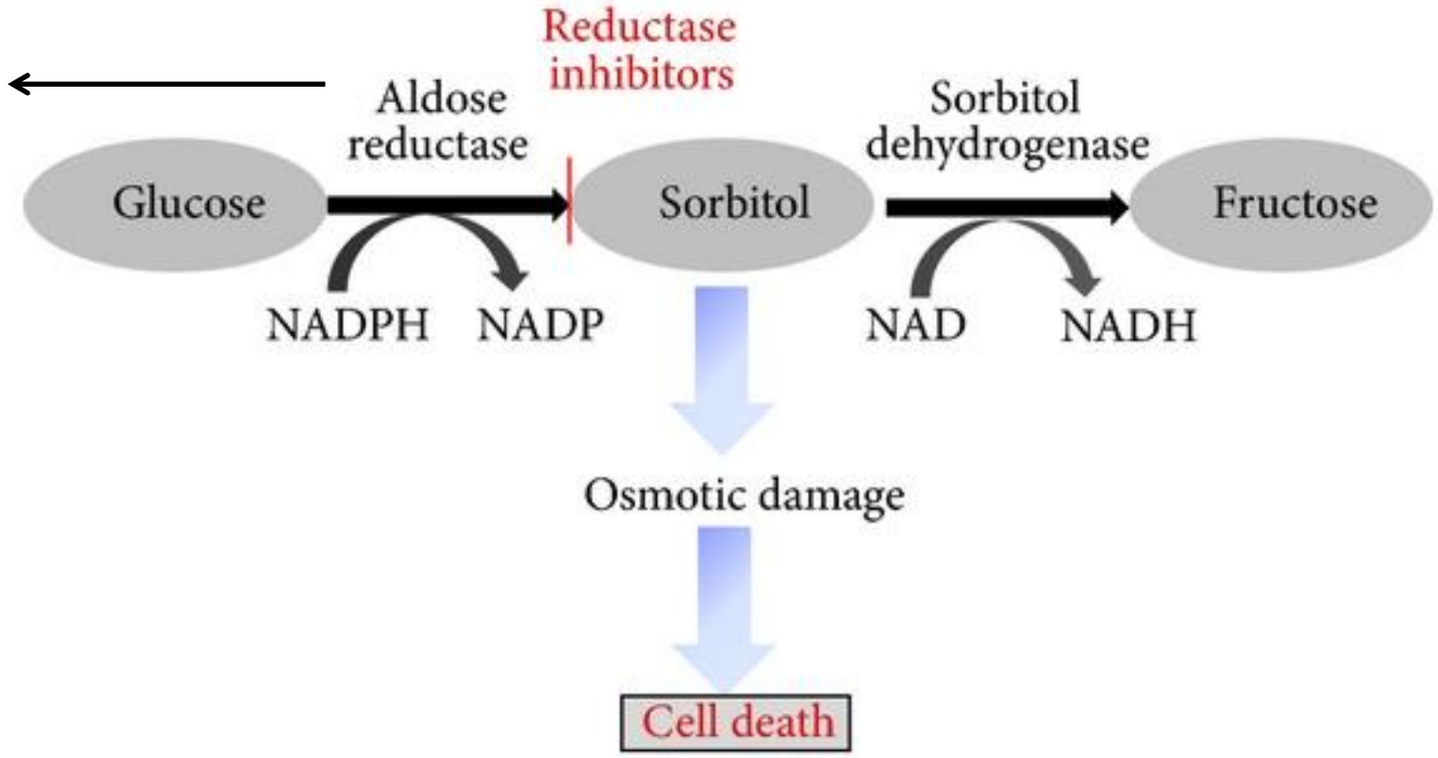
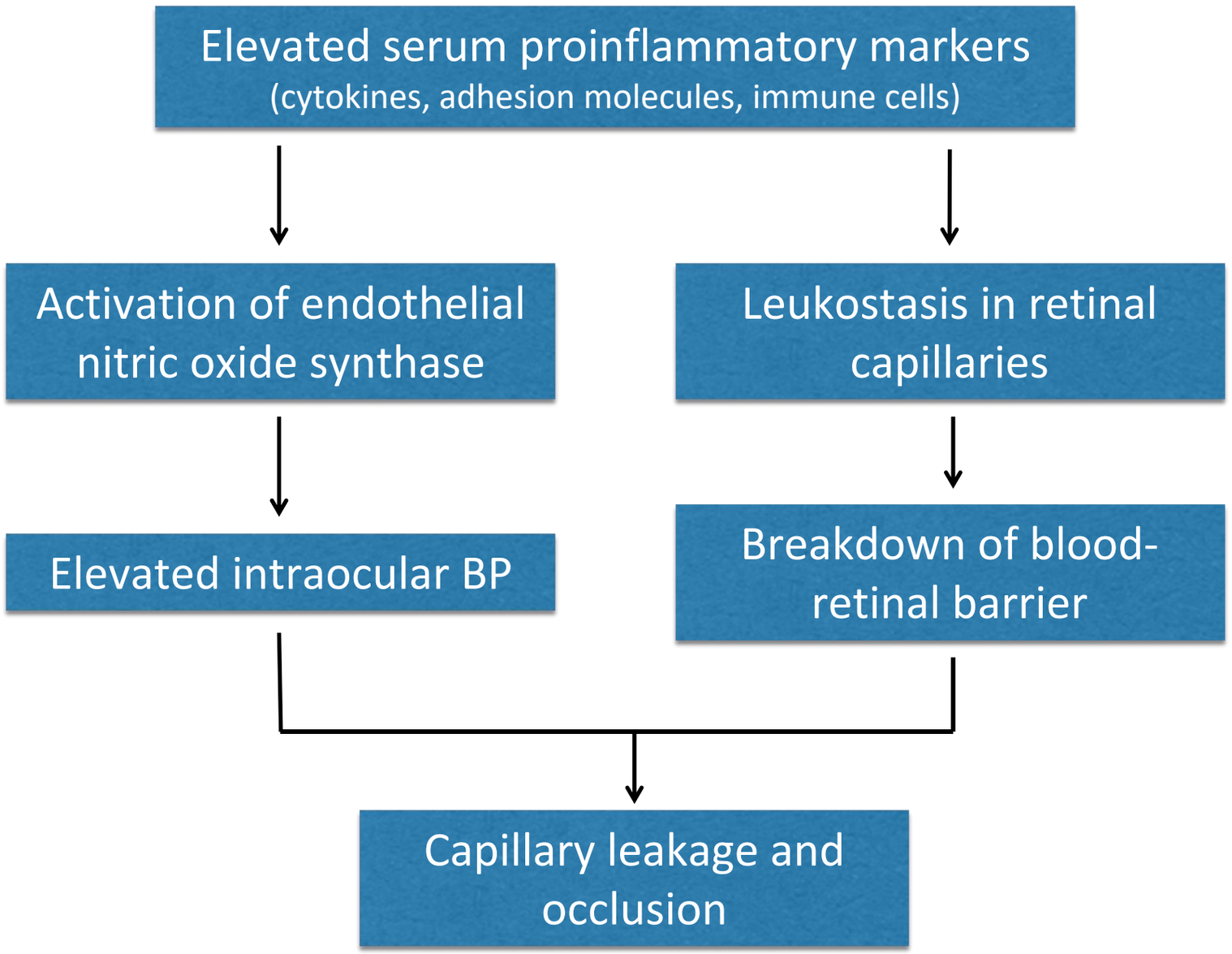
**Found in high concentrations:**

**Pericytes**
**Endothelial cells**
**Ganglion cells**
**Mueller cells**
**RPE**




- Excessive sorbitol and fructose in retinal cells causes osmotic damage
- Loss of NADPH increases risk of oxidative damage
- Thickening of retinal capillary basement membrane
- Breakdown of blood retinal barrier

# Role of Inflammation



# Role of VEGF

Capillary damage leads to retinal ischemia

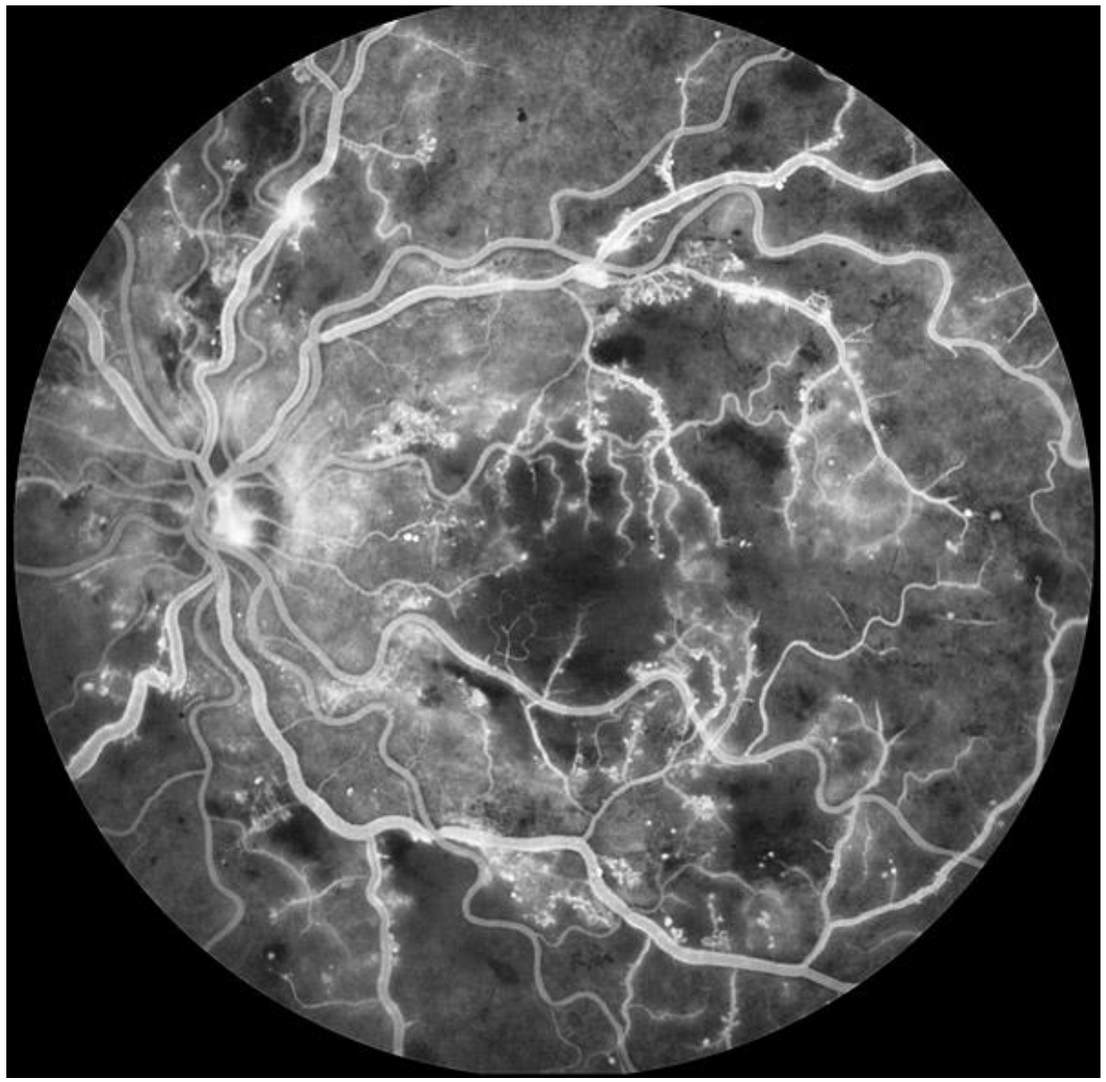
→

Upregulation of **Vascular Endothelial Growth Factor (VEGF)**

→

- Promotes angiogenesis
- Breakdown of blood-retinal barrier
- Stimulation of endothelial growth
- Neovascularization
- Vascular permeability

- **Hyperglycemia over time leads to endothelial damage, loss of pericytes, and basement membrane thickening**
- **Leads to capillary occlusion, non-perfusion, and leakage**

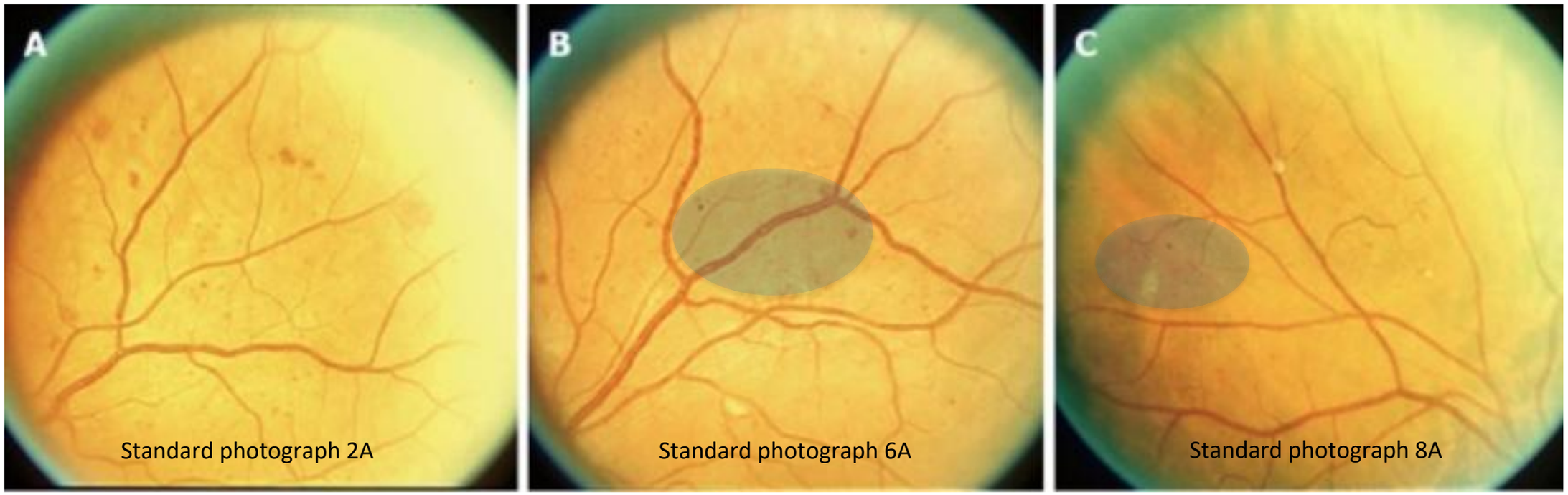


# Clinical Definitions

# Historical Perspective

- In 1968, Airlie House classification created: 13 levels (way too complex)
- These criteria were used/modified in Diabetic Retinopathy Study (DRS) Early Treatment of Diabetic Retinopathy Study (ETDRS)
- In 2003, classification was simplified by the International Clinical Disease Severity Scale for Diabetic Retinopathy
- 5 stages were created

1. **No apparent retinopathy**
2. **Mild NPDR**
3. **Moderate NPDR**
4. **Severe NPDR**
5. **PDR**




Standard photograph 2A

Standard photograph 6A

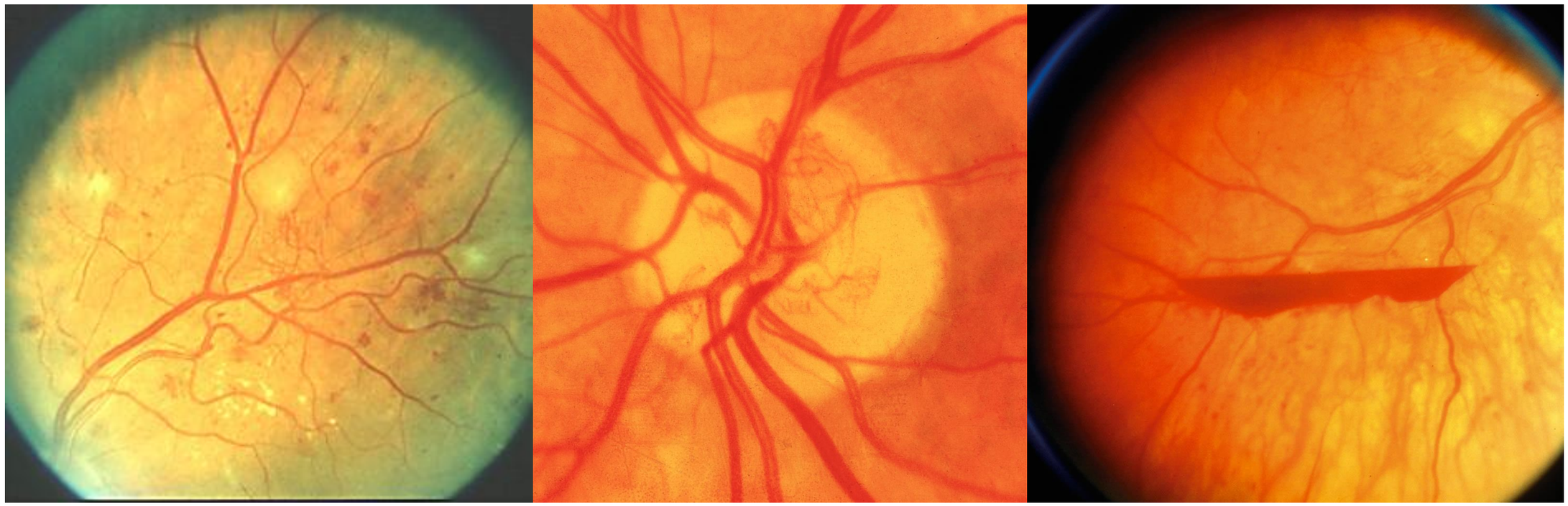
Standard photograph 8A

## 4:2:1 Rule of Severe NPDR

4 quadrants of Dot-Blot Hemorrhages
2 quadrants of Venous Beading
1 quadrant of Intraretinal Microvascular Anomalies

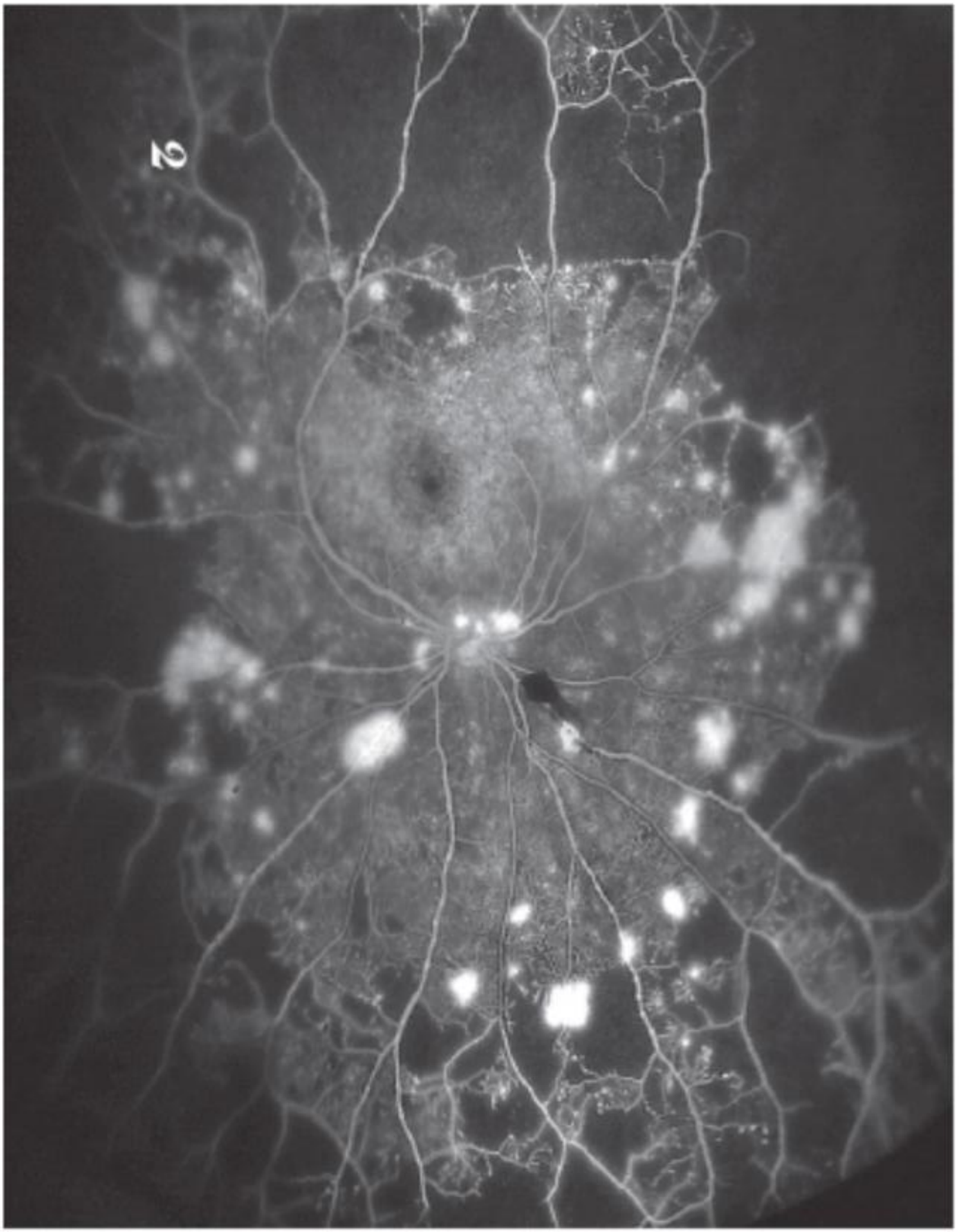
Need 1 of 3 to be severe NPDR: 15% risk of progression to high risk PDR in 1 year

Need 2 to be very severe NPDR: 45% risk of progression to high risk PDR in 1 year



## High-risk Proliferative Diabetic Retinopathy

Neovascularization of disc <1/4 disc area with associated vitreous hemorrhage
Neovascularization of disc >1/4 disc area
Neovascularization elsewhere> ½ disc area with associated vitreous hemorrhage




COURTESY: JOHN W. KITCHENS, MD

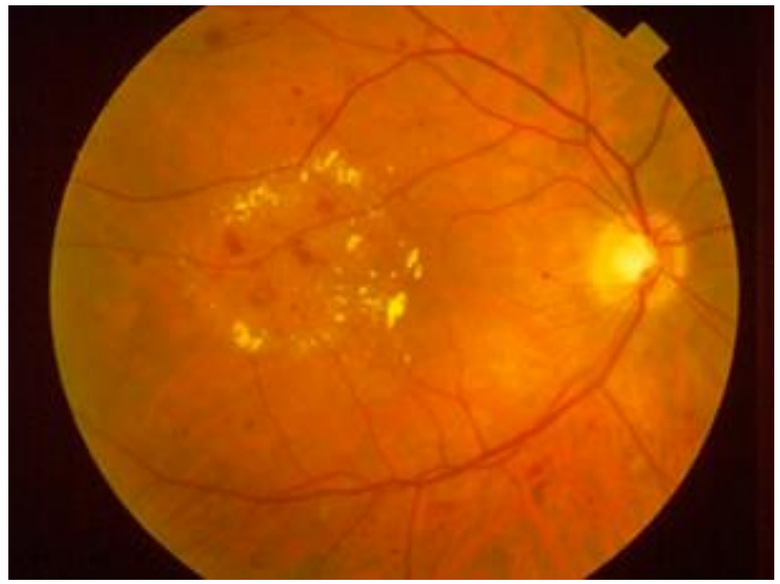
# Causes of Vision Loss

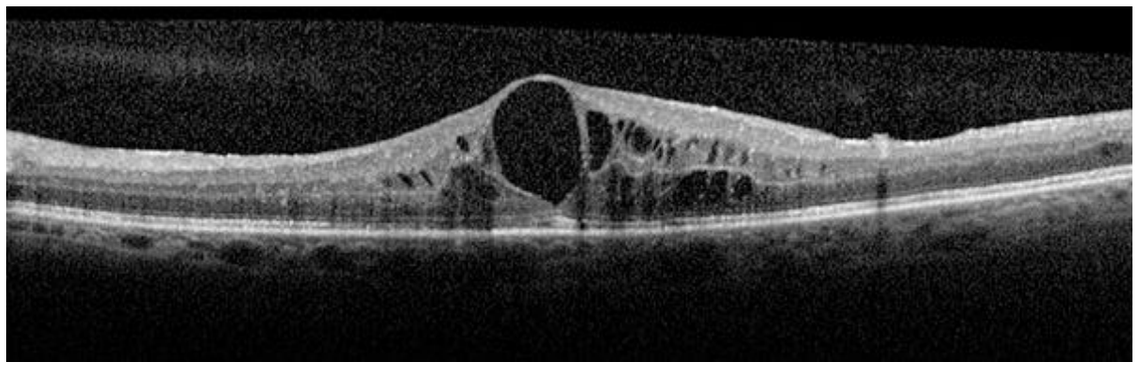
- Macular edema
- Macular ischemia
- Vitreous hemorrhage
- Retinal detachment

# Clinically significant macular edema

- Defined by ETDRS study
- Leading cause of vision loss in diabetic retinopathy

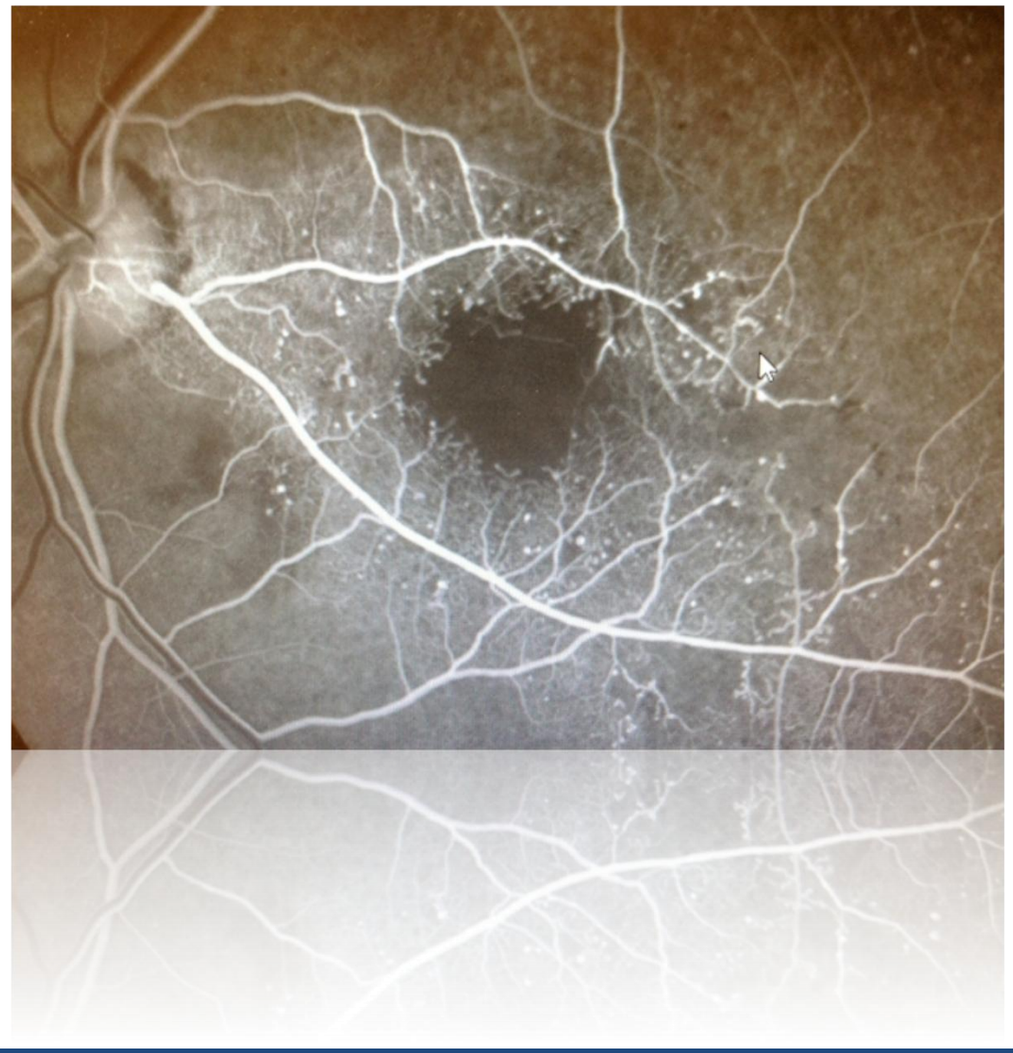
1. Retinal edema within 500um of foveal center
2. Exudates within 500um of foveal center with adjacent retinal thickening
3. Zone of thickening larger than 1 disc area within 1 disc diameter of foveal center

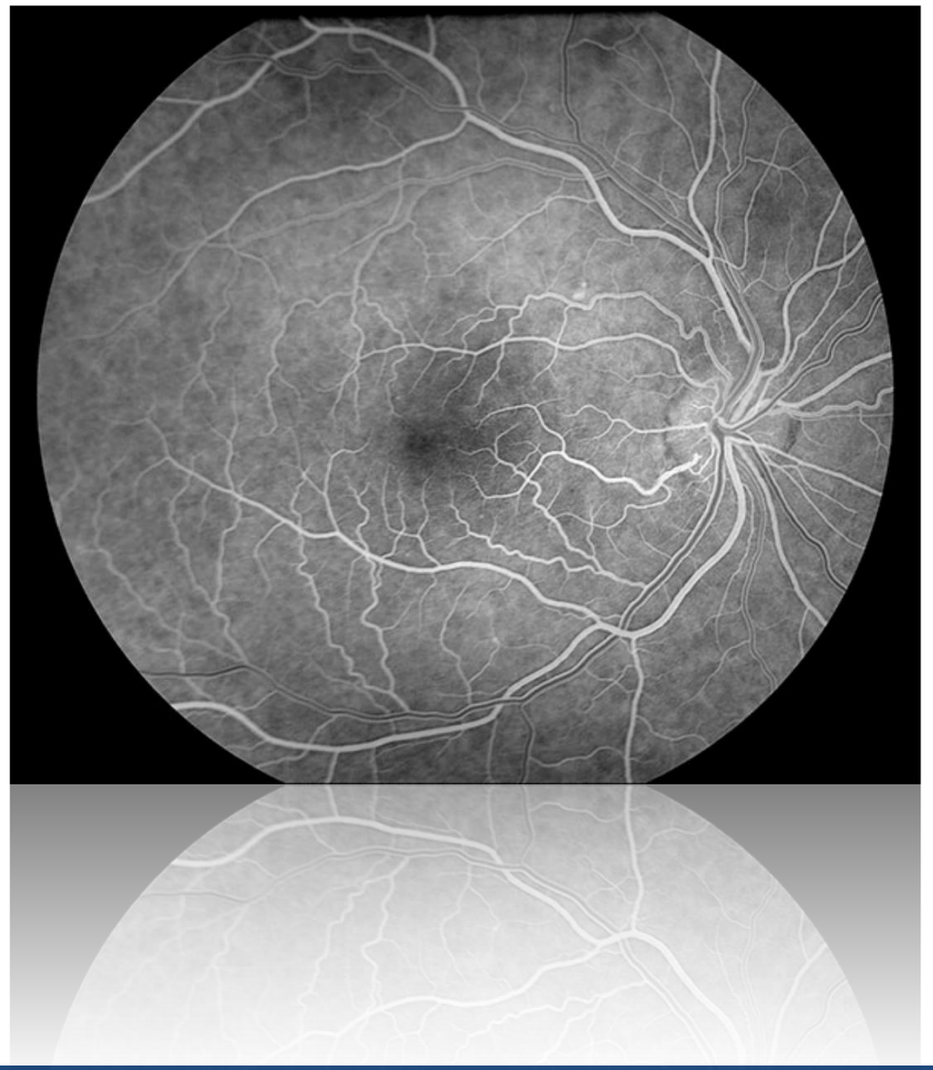




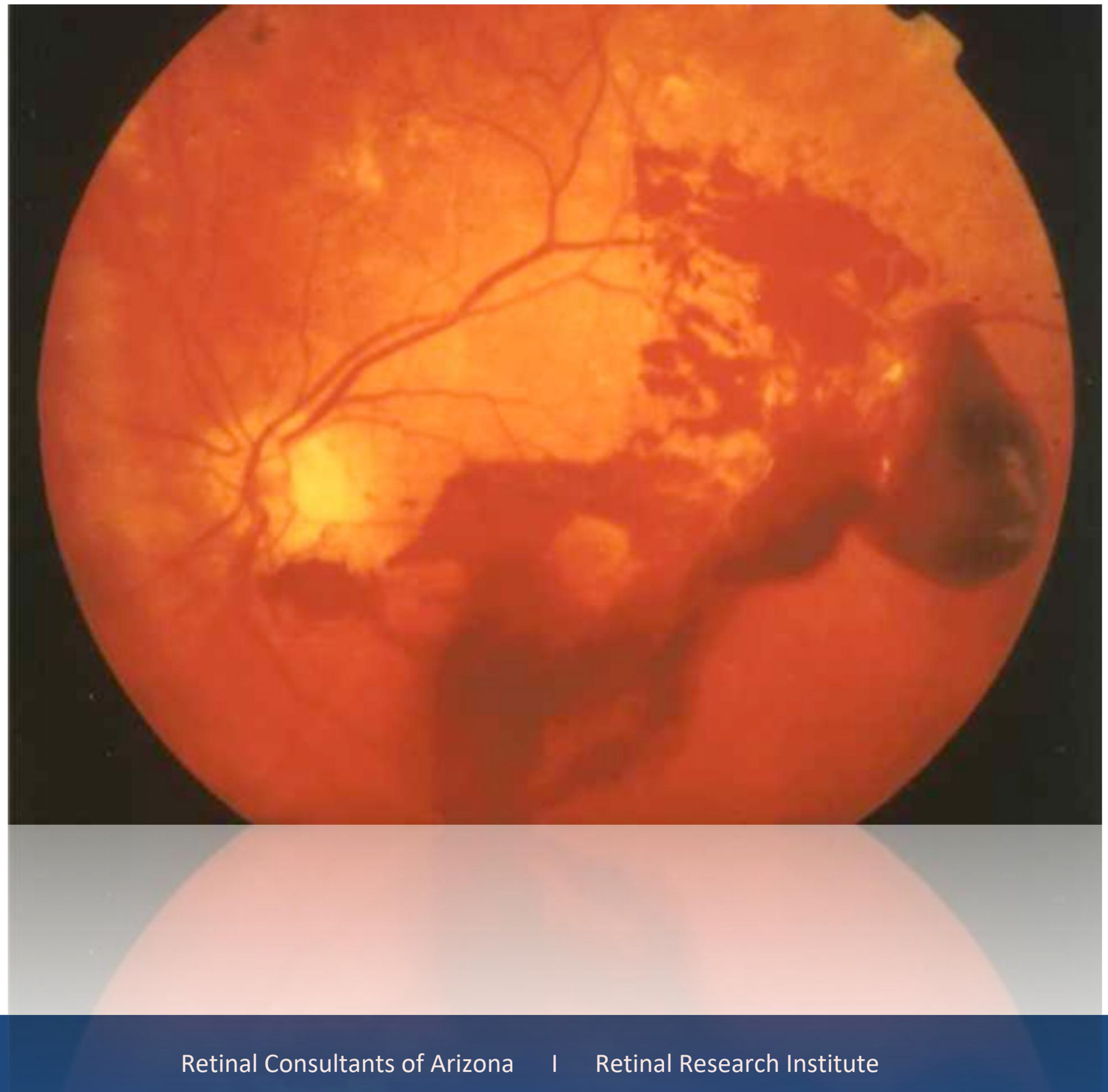
# Macular Ischemia

Due to capillary non-perfusion

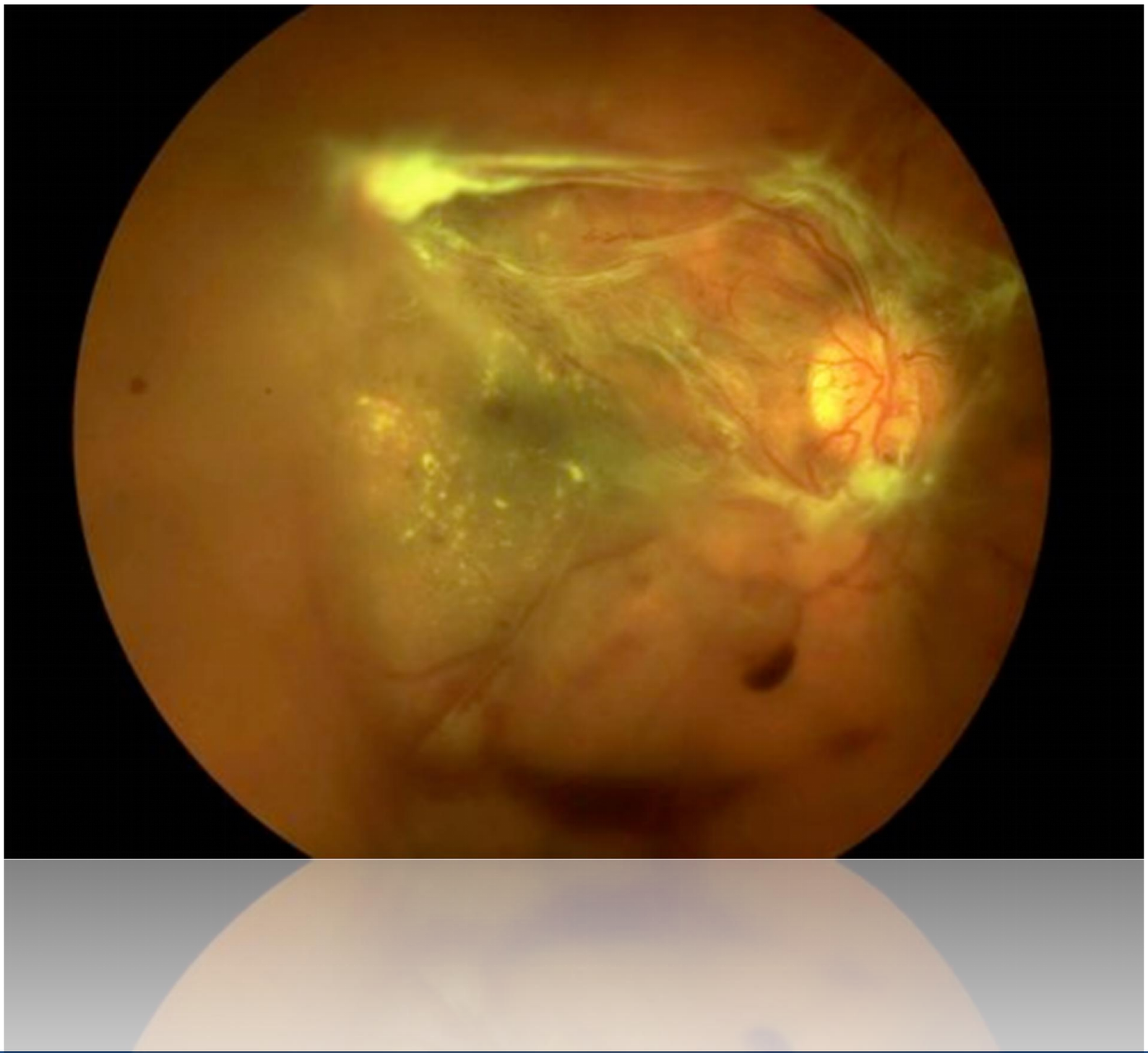




# Vitreous Hemorrhage



# Tractional Retinal Detachment



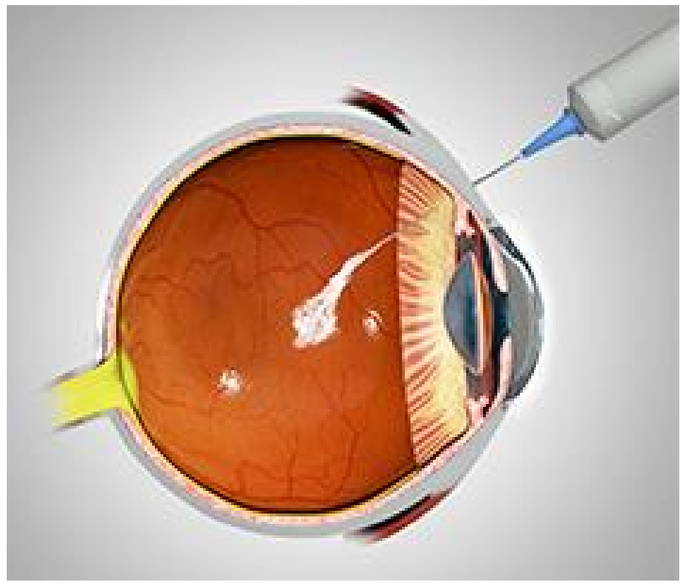
# Treatment Options

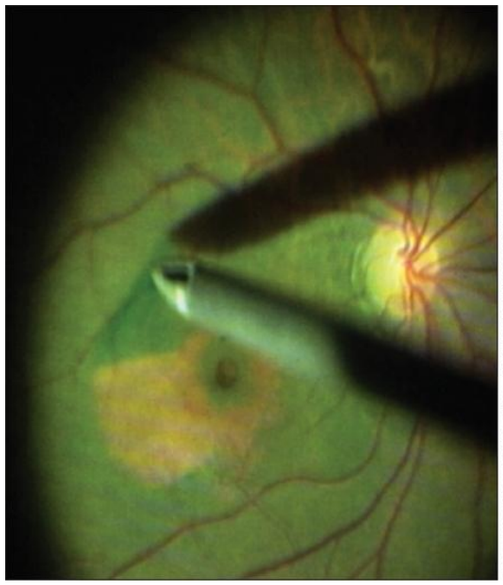
# Diabetic Macular Edema

According to ETDRS, 1/3 of patients with DME will lose >3 lines of vision in 3 years

**Treatment options:** ⟶

- Focal Laser
- Intravitreal Anti-VEGF
- Intravitreal steroid
- Vitrectomy with ILM peel

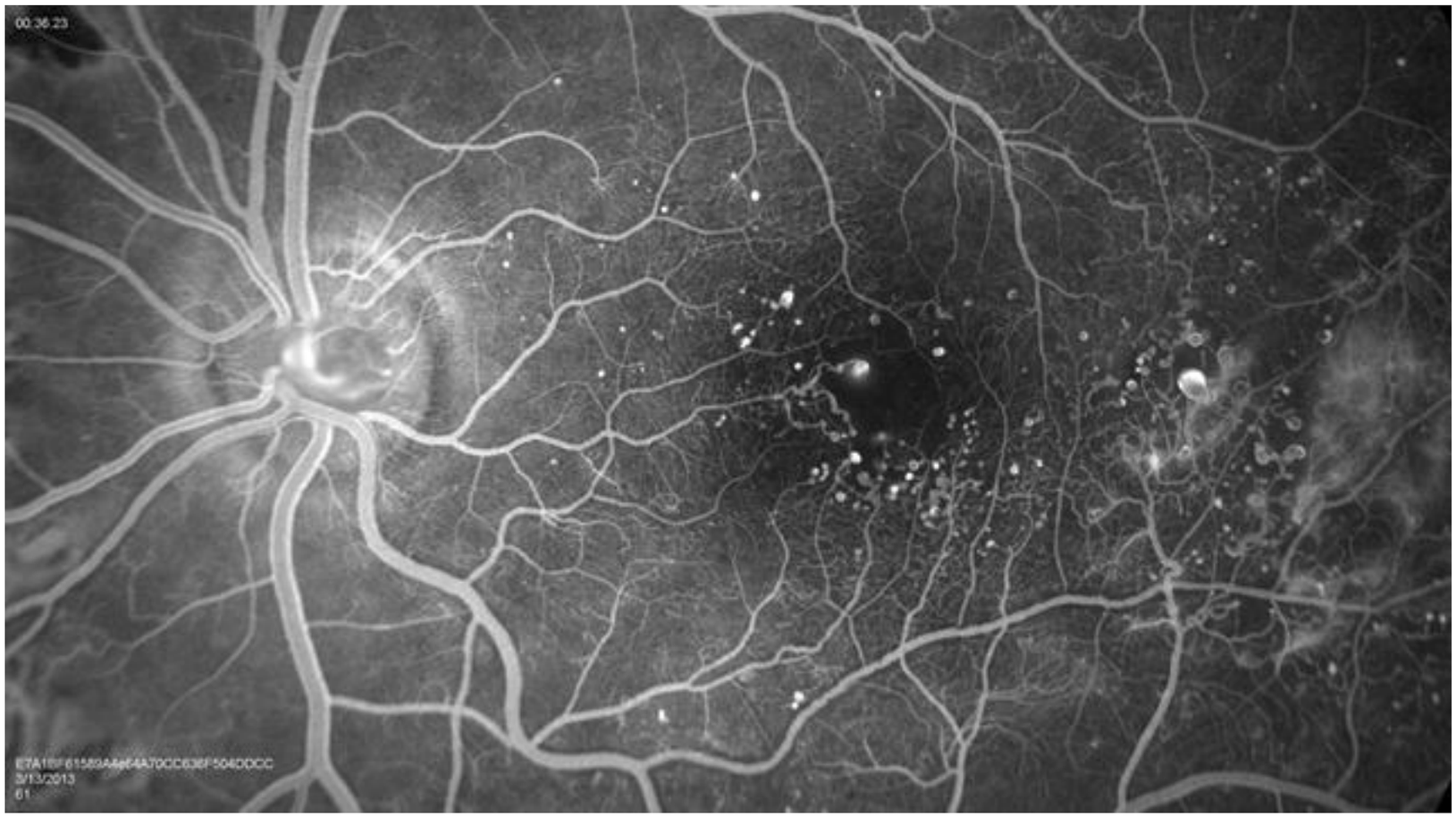





REPRINTED FROM MEYER CH, ED. VITAL DYES IN VITREORETINAL SURGERY – CHROMOVITRECTOMY. BASEL, SWITZERLAND: KARGER; 2006. WITH PERMISSION FROM KARGER.

# Focal/Grid Laser

- ETDRS established focal laser as standard of care for treatment of DME
- Low power laser is either applied directly to leaking microaneurysms or in a grid pattern to stimulate RPE to re-absorb edema
- Reduced risk of >3 lines of vision loss by 50% compared to observation in ETDRS



## Risks:

Cannot treat central leaking microaneurysms
Risk of scotoma
“Laser creep”
Risk of CNV w/“hot” burns

# Intravitreal Bevacizumab

- Bevacizumab is a monoclonal full length antibody that binds all isoforms of VEGF-A

## DRCR Protocol H

- 5 Groups: A-Laser @ baseline; B-1.25mg Avastin @ baseline & 6wks; C-2.5mg Avastin @baseline & 6wks; D-1.25mg Avastin @ baseline; E-1.25mg Avastin @ baseline & 6 wks & focal @ 3wks
- 3 line VA gainers: A-5%; **B-14%; C-13%; D-9%; E-15%**

## BOLT Trial

- Compared Avastin vs focal laser; followed for 2 years
- Avastin group: 1.25mg @ 0, 6, and 12 weeks followed by prn tx
- Focal group: Laser at baseline then prn
- Avg treatment: 13 injections vs 4 lasers
- VA Results: **9 vs 2.5 letters**

# Intravitreal Ranibizumab

- Ranibizumab is a cleaved $F_{ab}$ fragment of bevacizumab that has a 5- to 20-fold enhanced affinity

## DRCR Protocol I

- Sham injection & prompt laser vs Ranibizumab & prompt laser vs Ranibizumab & deferred laser vs Triamcinolone & prompt laser
- @1 year: higher VA gains in Ranibizumab group (9 vs 3-4 letters)

## READ-2

- Ranibizumab q2months vs focal laser vs combination Ranibizumab and focal
- @ 6 months: VA gains- 21, 0, 6
- @ 24 months (all subjects able to get Ranibizumab)- 24,18, 26

## RISE/RIDE

- 2 parallel trials: Ranibizumab (0.3, 0.5mg) monthly vs sham
- @24 months: 18.1/12.3% sham, 44.8/33.6% 0.3mg, and 39.2/45.7% 0.5mg gained >3-lines of VA
- After 24 months, sham group could be crossed over- showed modest vision gains

# Intravitreal Aflibercept

## DA VINCI

- Phase II study
- 4 groups: Aflibercept 0.5mg q 4wk; 2mg q4wk; 2mg q4wk x 3 doses then q8wk; 2mg q4wk x 3 doses then prn; focal laser
- All aflibercept groups did better than focal laser in terms of VA and macular edema @ 1 year

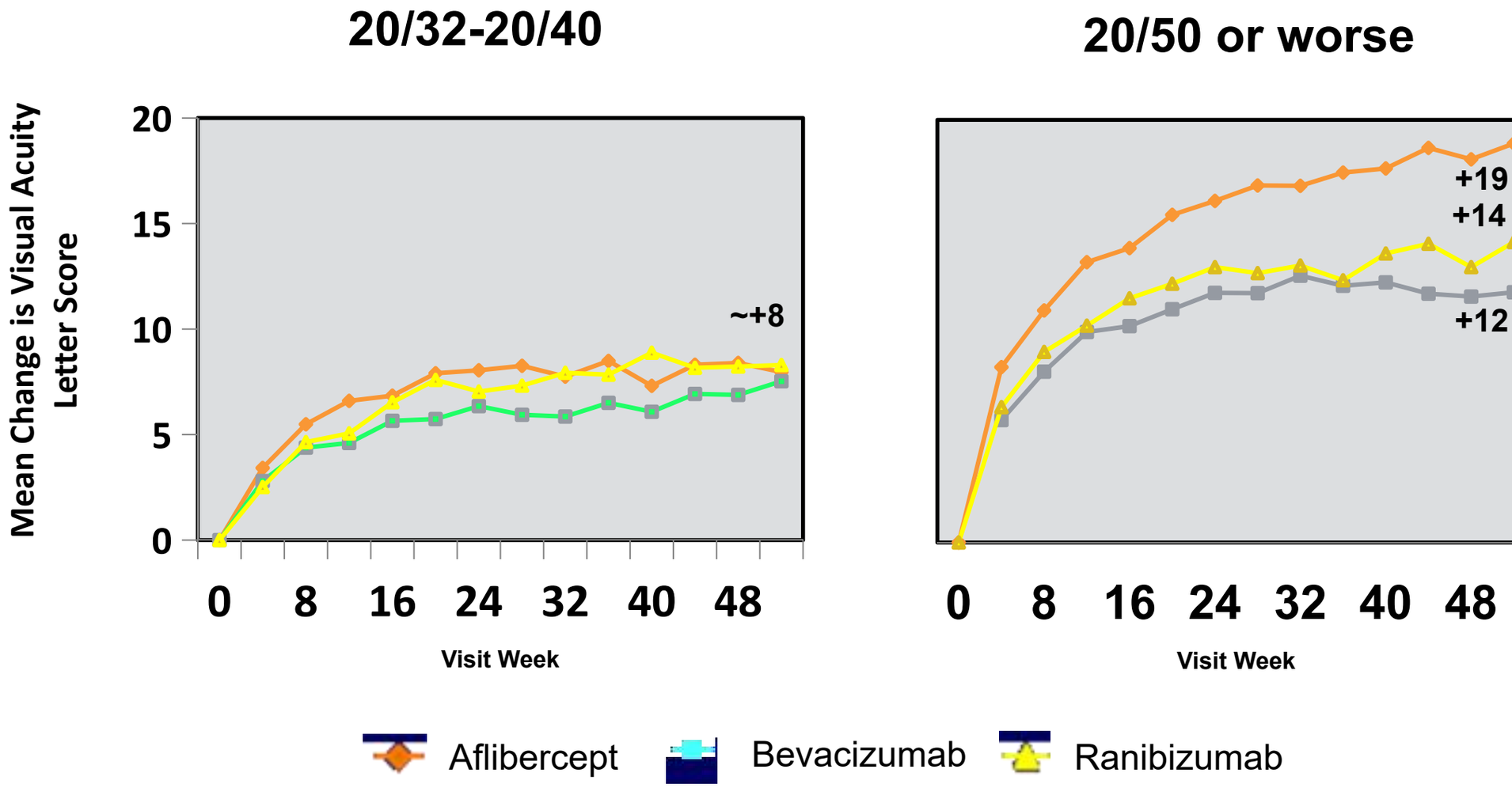
## VISTA/VIVID

- Parallel Phase 3 studies
- 3 groups: Aflibercept 2mg q4wk; 2mg q4wk x 5 doses then q8wk; focal laser
- VA change @ 1 year: 12.5/10.5, 10.7/10.7, 0.2/1.2, respectively
- % gaining >3 lines of vision: 41.6/32.4%, 31.1/33.3%, 7.8/9.1%

# DRCR NETWORK PROTOCOL T

Purpose: Compare safety and efficacy of Bevacizumab, Ranibizumab, and Aflibercept in treatment of DME @ 1 year, 2 years

Methods: Randomized to 1 of 3 drugs; monthly injections x 6 months; then continue treatment if improving/worsening (>1 line VA change from last injection or >10% change in macular thickness)
Hold injections if VA 20/20 and OCT without fluid or stable exam over 2 visits; Rescue focal laser if persistent edema after 6 months




Courtesy of DRCR Network Protocol T

# Treatment Group Comparisons

| | Difference | CI | *P*-Value |
|---|---|---|---|
| **Aflibercept vs Bevacizumab** | **+0.7** | **-1.3 to +2.7** | **0.69** |
| **Aflibercept vs Ranibizumab** | **-0.4** | **-2.3 to +1.5** | **0.69** |
| **Ranibizumab vs Bevacizumab** | **+1.1** | **-0.9 to +3.1** | **0.69** |

VA between 20/30-20/40

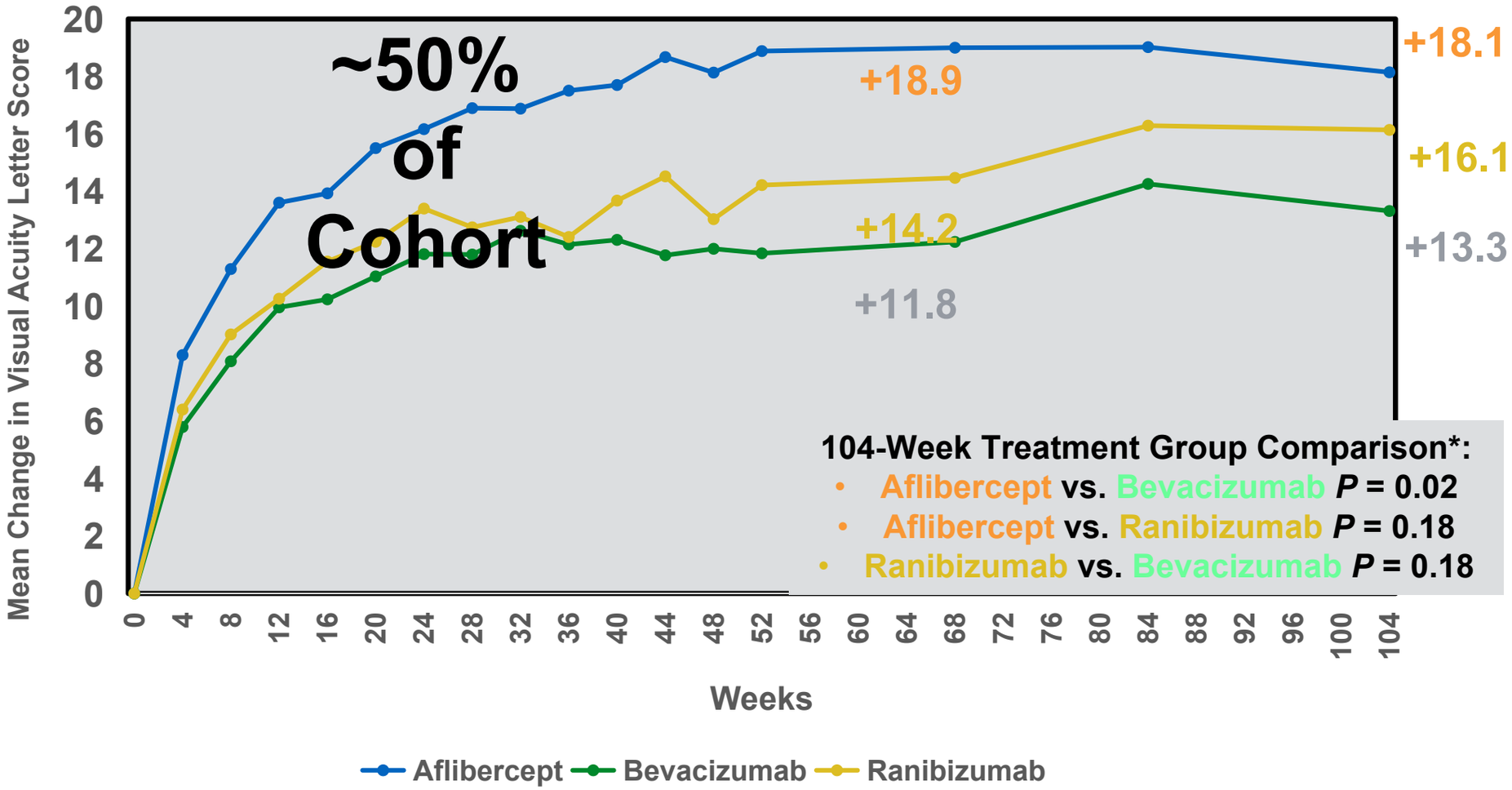
| | Difference | CI | *P*-Value |
|---|---|---|---|
| **Aflibercept vs Bevacizumab** | **+6.5** | **+2.9 to +10.1** | **<0.001** |
| **Aflibercept vs Ranibizumab** | **+4.7** | **+1.4 to +8.0** | **0.0031** |
| **Ranibizumab vs Bevacizumab** | **+1.8** | **-1.1 to +4.8** | **0.21** |

VA worse than 20/50

Courtesy of DRCR Network Protocol T

# Mean Change in Visual Acuity Over 2 Years

*Visual Acuity 20/50 or Worse*



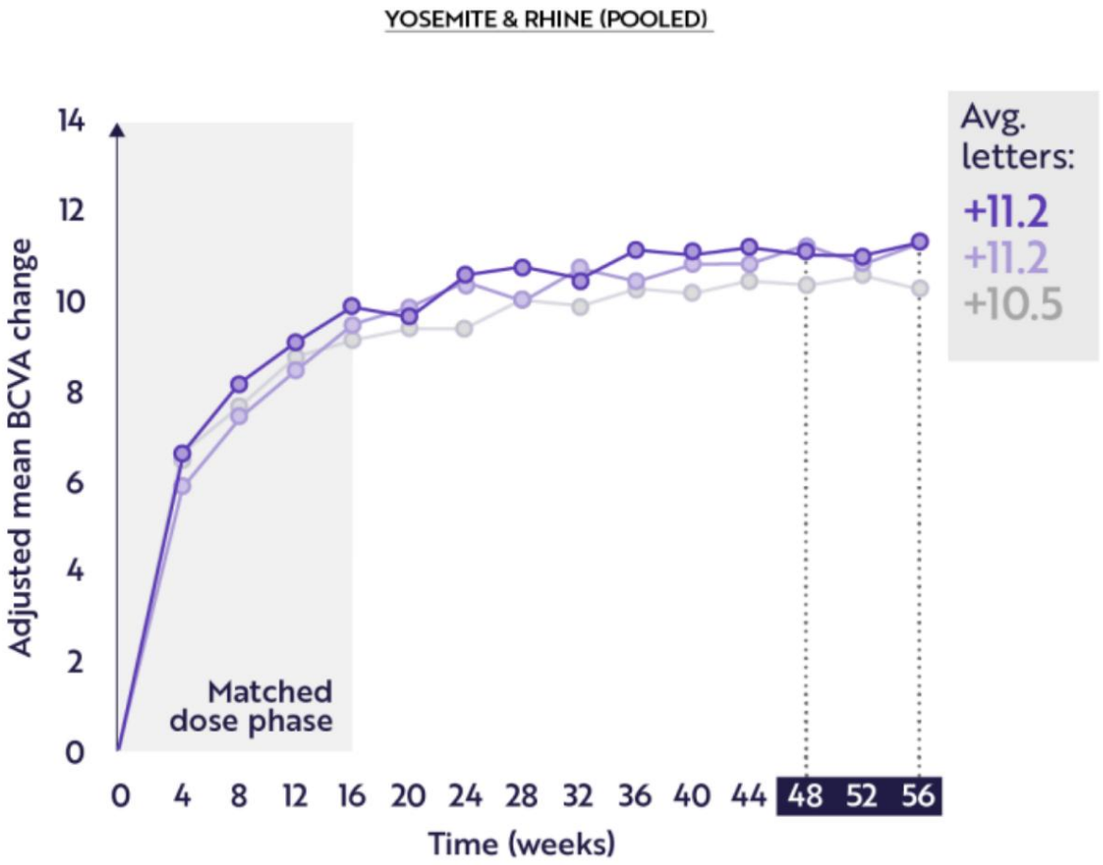

**104-Week Treatment Group Comparison*:**

- **Aflibercept vs. Bevacizumab *P* = 0.02**
- **Aflibercept vs. Ranibizumab *P* = 0.18**
- **Ranibizumab vs. Bevacizumab *P* = 0.18**

[52-Week: A vs. B *P* < 0.001 / A vs. R *P* = 0.003 / R vs. B *P* = 0.21]

* *P*-values adjusted for baseline visual acuity and multiple comparisons

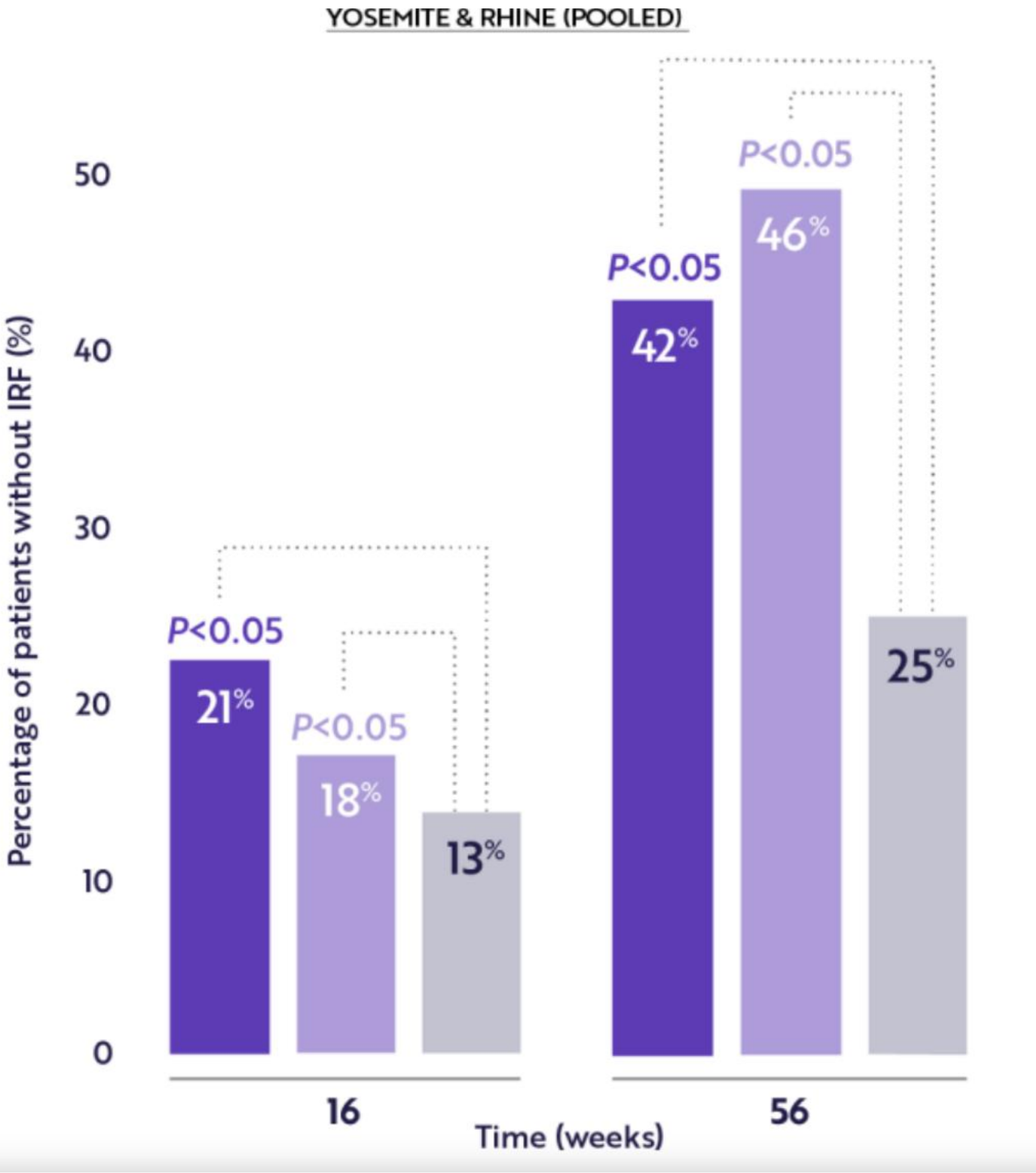
# Intravitreal Faricimab

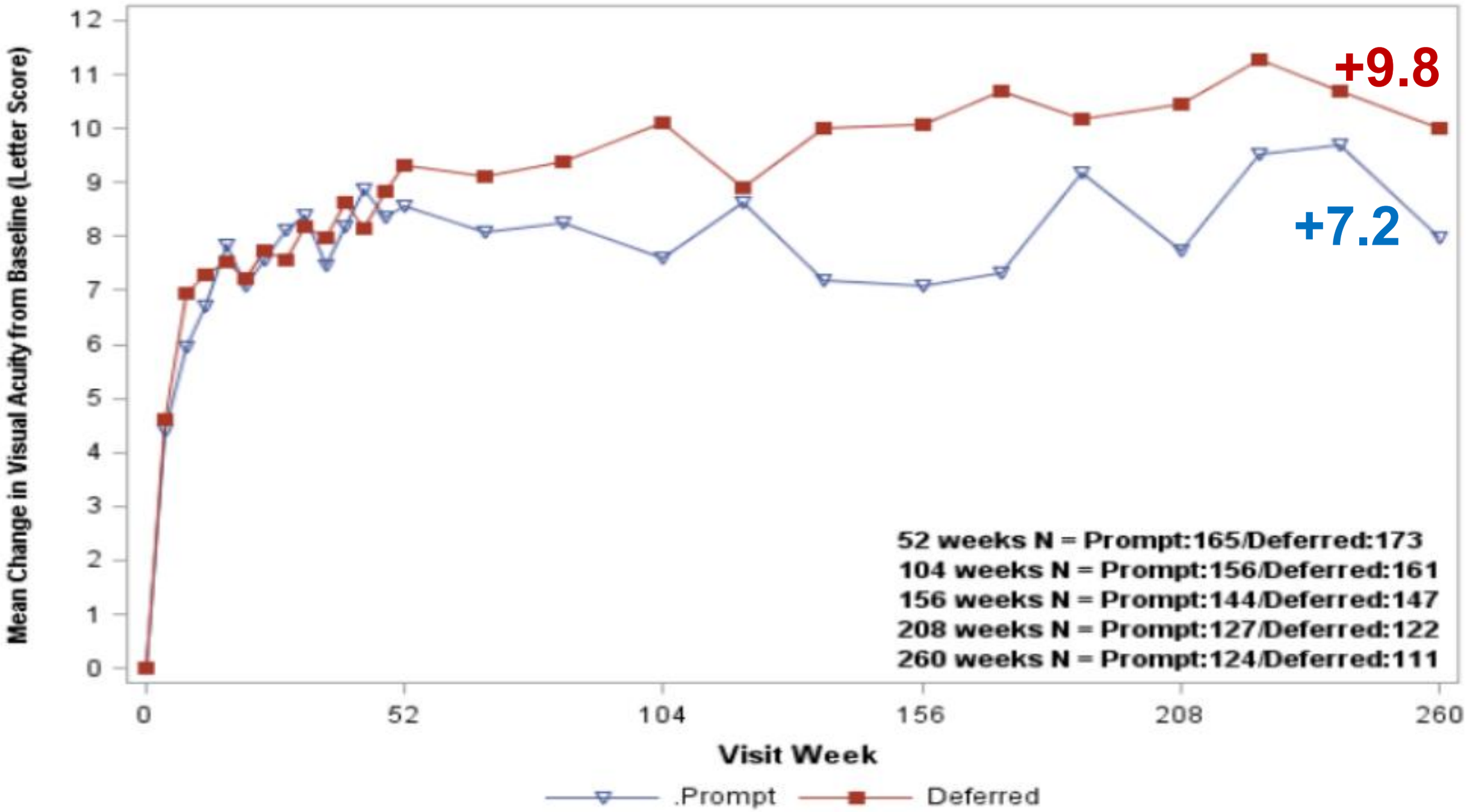



| VABYSMO 6 mg Q4W-Q16W | n=632 | VABYSMO 6 mg Q8W | n=632 | Aflibercept 2 mg Q8W (ref) | n=627 |
|---|---|---|---|---|---|

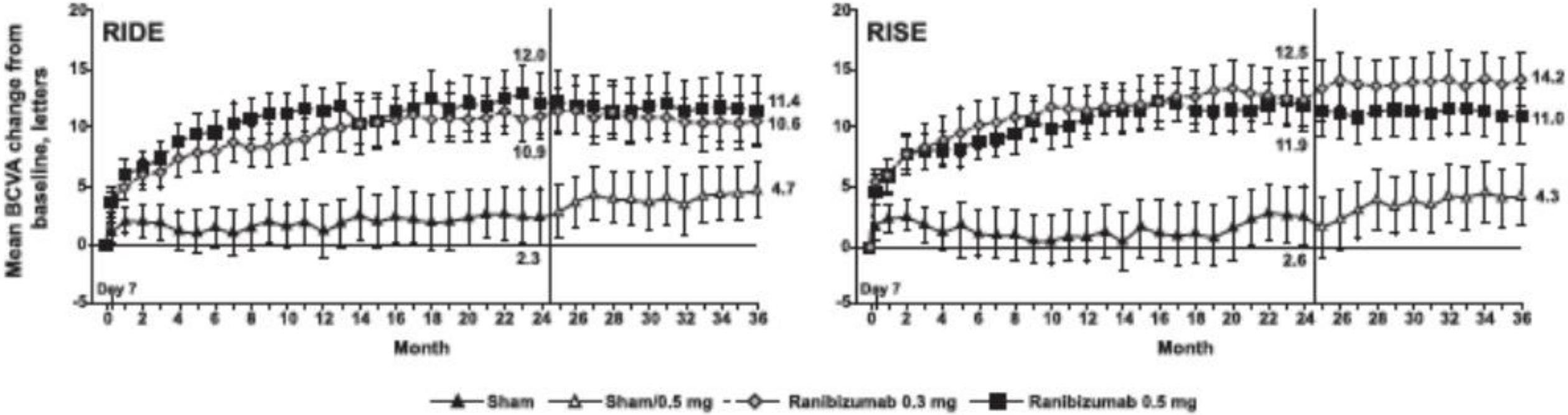
ITT population

| Proportion of VABYSMO Variable arm patients on a Q4W, Q8W, Q12W, or Q16W treatment interval at week 52 (pooled)[12] | |
|---|---|
| Q16W | 51.9% |
| Q12W | 20.5% |
| Q8W | 15.5% |
| Q4W | 12.1% |






Courtesy of DRCR Network Protocol I

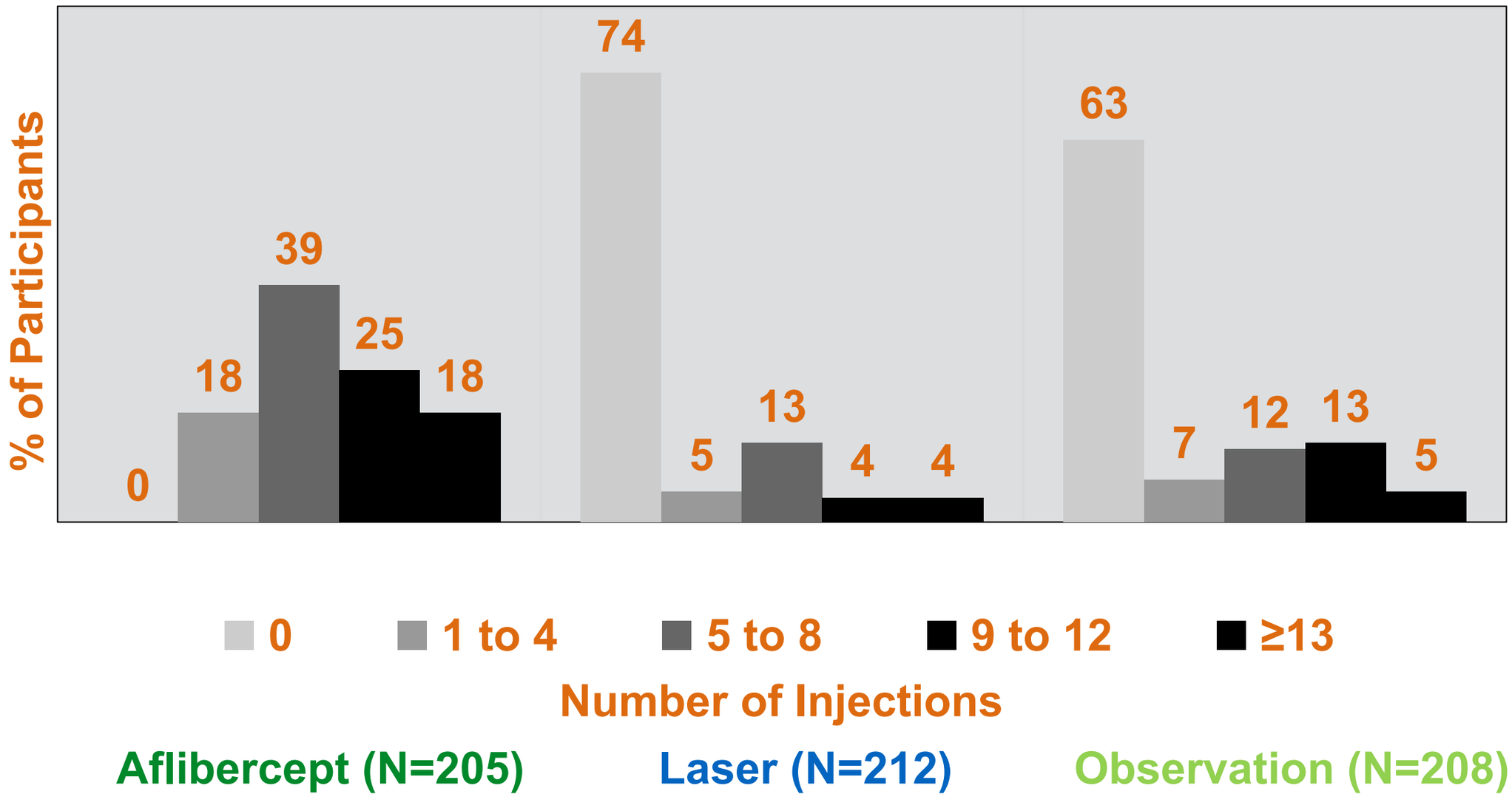

RIDE
RISE
Mean BCVA change from baseline, letters
Month
Day 7
12.0
10.9
11.4
10.6
4.7
2.3
12.5
11.9
14.2
11.0
4.3
2.6
Sham
Sham/0.5 mg
Ranibizumab 0.3 mg
Ranibizumab 0.5 mg

| | 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% |

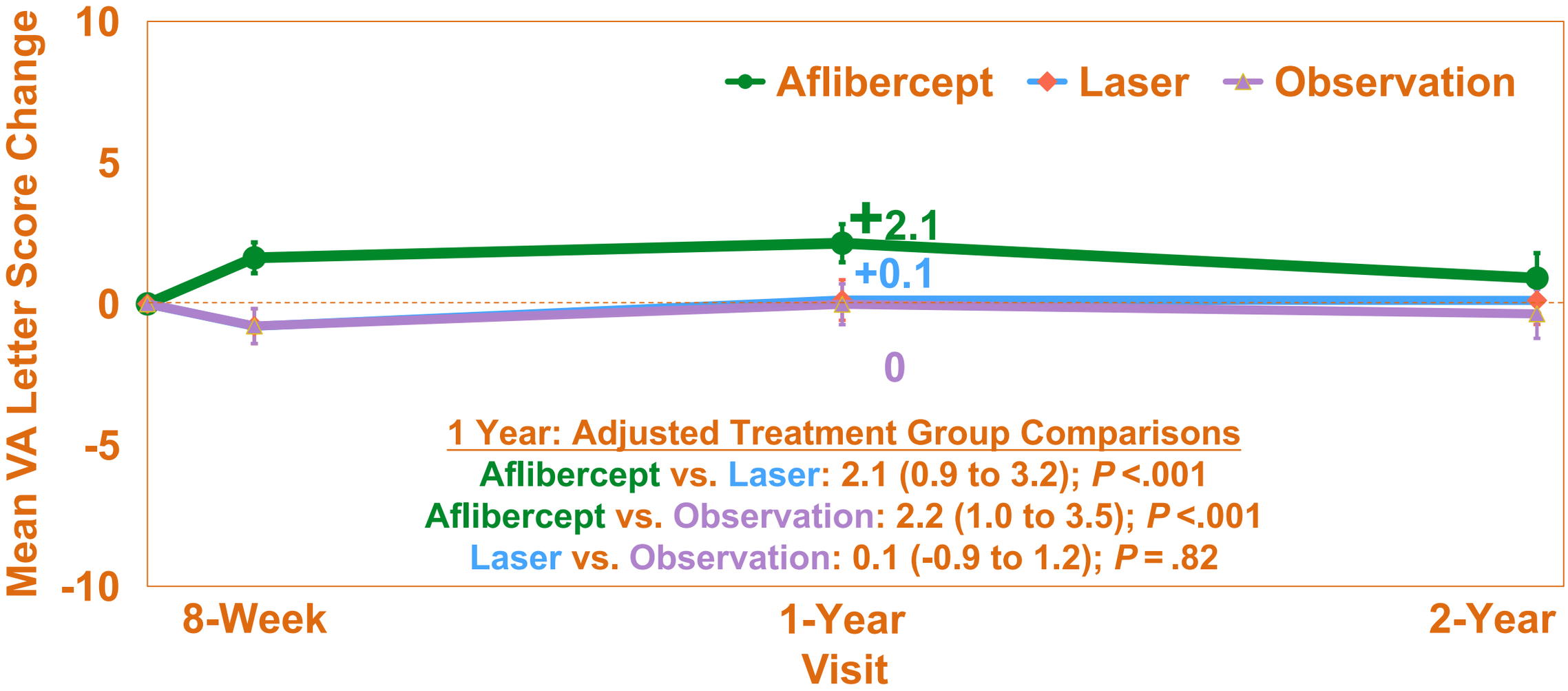
Courtesy of DRCR Network Protocol I

# DRCR NETWORK PROTOCOL V

Purpose: Compare aflibercept, Focal laser and PRN aflibercept, and observation and PRN aflibercept in eyes with DME and 20/25 or better VA



# Mean VA Letter Score Change from Baseline

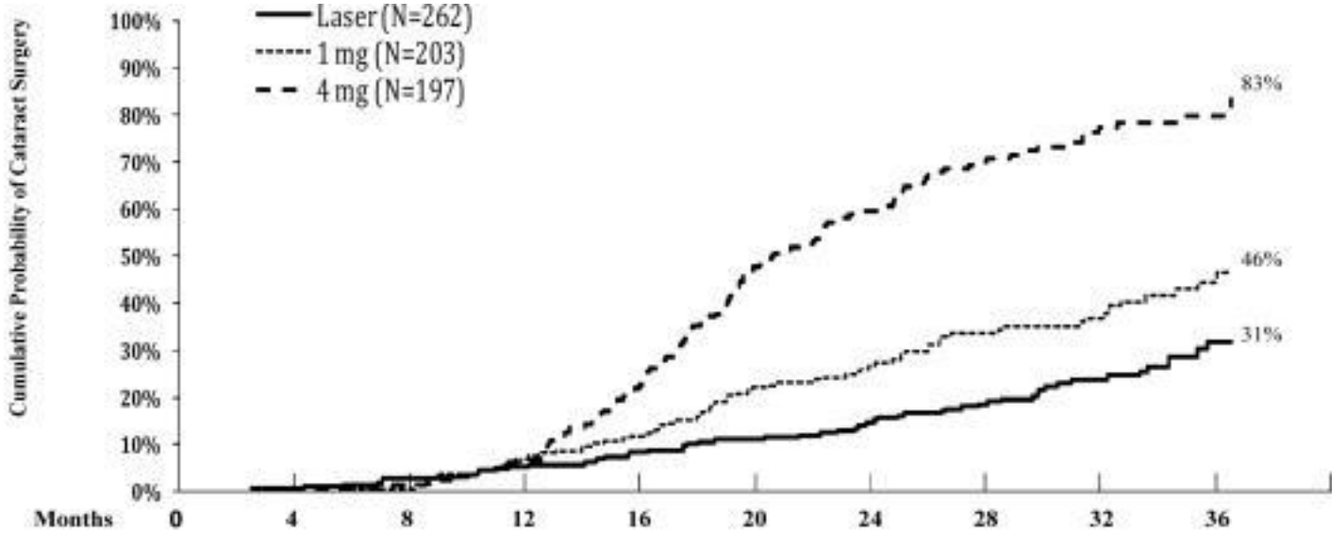


# Intravitreal Triamcinolone

- DRCR Protocol B: compared focal laser vs intravitreal Triamcinolone (1mg, 4mg)
- Subjects followed for 3 years

## Results:

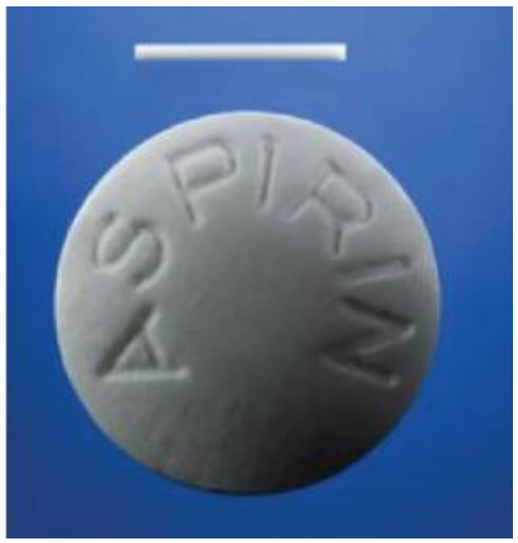
- Avg # of tx: 3.1 vs 4
- >15 letter gain: 26% vs 21%
- Risk of IOP meds: 3% vs 12% (4mg group)
- Risk of cataract: 31%vs 84% (4mg group)




# Intravitreal Dexamethasone Implant

MEAD

- 3 groups: Dexamethasone 0.7mg implant, 0.35mg implant, sham
- Followed patients for 3 years
- Retreatment done no more often than every 6 months
- Mean number of tx: 4.1, 4.4, 3.3, respectively
- >3 line improvement @ 3 years: 22.2%, 18.4%, 12%
- Risk of cataract: 67.9%, 64.1%, 20.4%
- >10mm Hg IOP change: 28% vs 4% (42% of study drug patients required IOP meds)

# Intravitreal Fluocinolone Acetonide Implant

## FAME

- Enrolled patients with persistent DME despite at least 1 focal laser treatment
- 3 groups: 0.2ug/day, 0.5ug/day, or sham
- Rescue treatment with focal laser > 6wks or retreatment with implant after 1 year
- 3-line VA gain @ 3 years: 27.8%, 28.7%, 18.9%
- Nearly all phakic patients developed cataract
- Risk of incisional glaucoma surgery: 4.8%, 8.1%, 0.5%
- DME> 3 years: 34% (low-dose), 28.8% (high-dose), 13.4% (sham) gained >3-lines VA
- DME< 3 years: 22.3% (low-dose), 26.4% (high-dose), 27.8% (sham) gained >3-lines VA

## Advantages of Anti-VEGF

- Lower risk of glaucoma and cataract progression

## Advantages of Corticosteroids

- More effective in chronic DME
- Sustained release implants of longer duration of efficacy

# When to try something other than anti-VEGF

## DRCR Protocol I Post-hoc Analysis

| | Mean change in BCVA | |
|---|---|---|
| Cohort | Mean letters gained at **3 months** | Mean letters gained at 3 years |
| 0-4 letters | -0.3 | 3.0 |
| 5-9 letters | 6.9 | 8.2 |
| >10 letters | 15.2 | 13.8 |

# Proliferative Diabetic Retinopathy

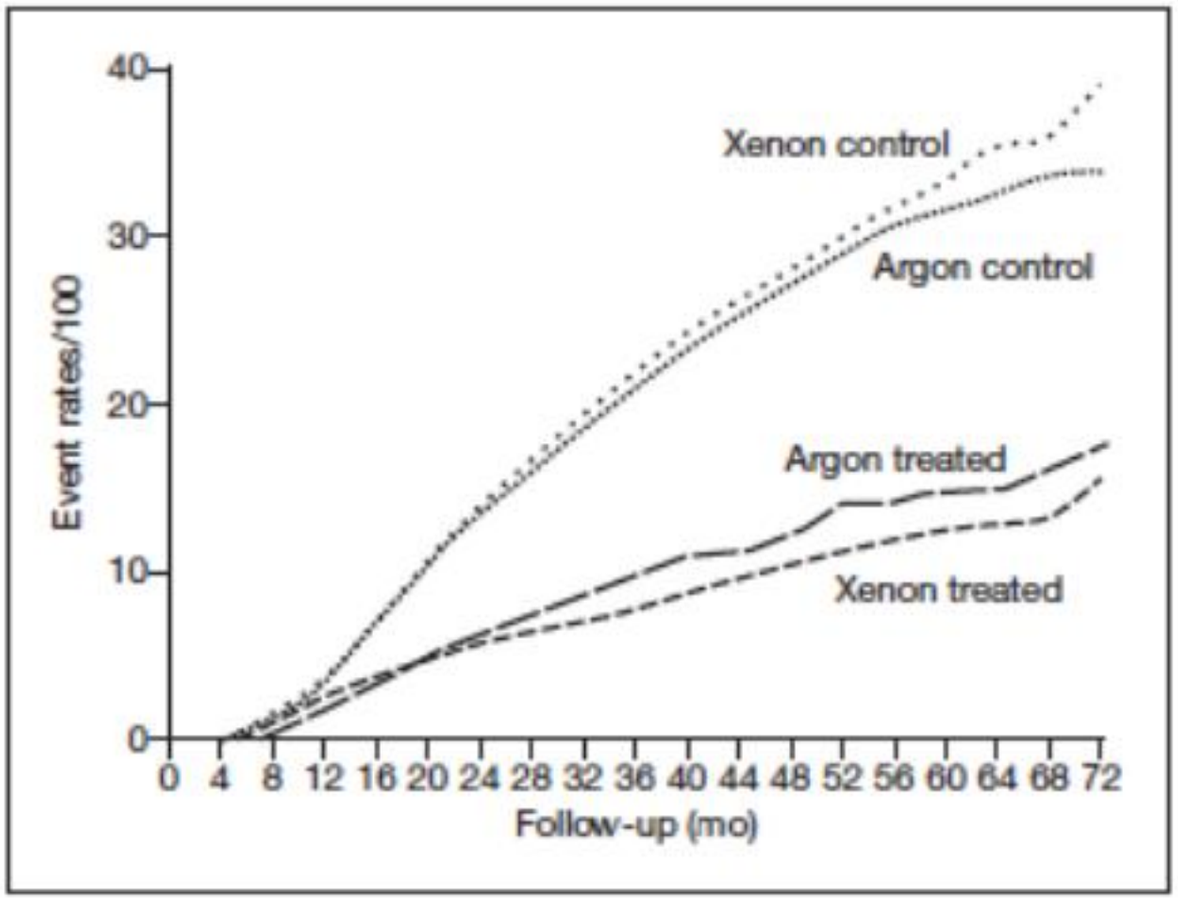
- 1950s- Meyer-Schwickerath used xenon arc photocoagulation to apply laser burns directly on NV vessels
- Idea of PRP came from observation that eyes with extensive chorioretinal scarring (secondary to myopia, retinal degeneration etc…) do better
- Theories why PRP works…
    1. Peripheral ischemic retina produces angiogenic growth factors
    2. Photocoagulation injury may cause retinal cells to produce growth inhibiting factors
    3. Laser scars produce retinal thinning increasing diffuse of oxygen from choroid

# Proliferative Diabetic Retinopathy

- 1970s- 2 randomized clinical trials created:  British trial using xenon arc photocoagulation and NEI sponsored Diabetic Retinopathy Study comparing xenon arc to argon photocoagulation to observation

## Diabetic Retinopathy Study

- Enrolled patients with PDR in 1 eye or severe NPDR in both eyes
- 1 eye was randomized to xenon arc or argon laser; fellow eye was observed
- Laser technique: Laser spots from arcades to equator spaced ½ burn width apart
- 2 year results: risk of severe vision loss (<5/200) was **15.9%** in *control eyes* and **6.4%** in *treated eyes*
- Established definition of *high-risk disease*



# PRP is not a perfect treatment

- Peripheral retinal ablation
- Loss of peripheral vision
- Loss of night vision
- Can exacerbate diabetic macular edema

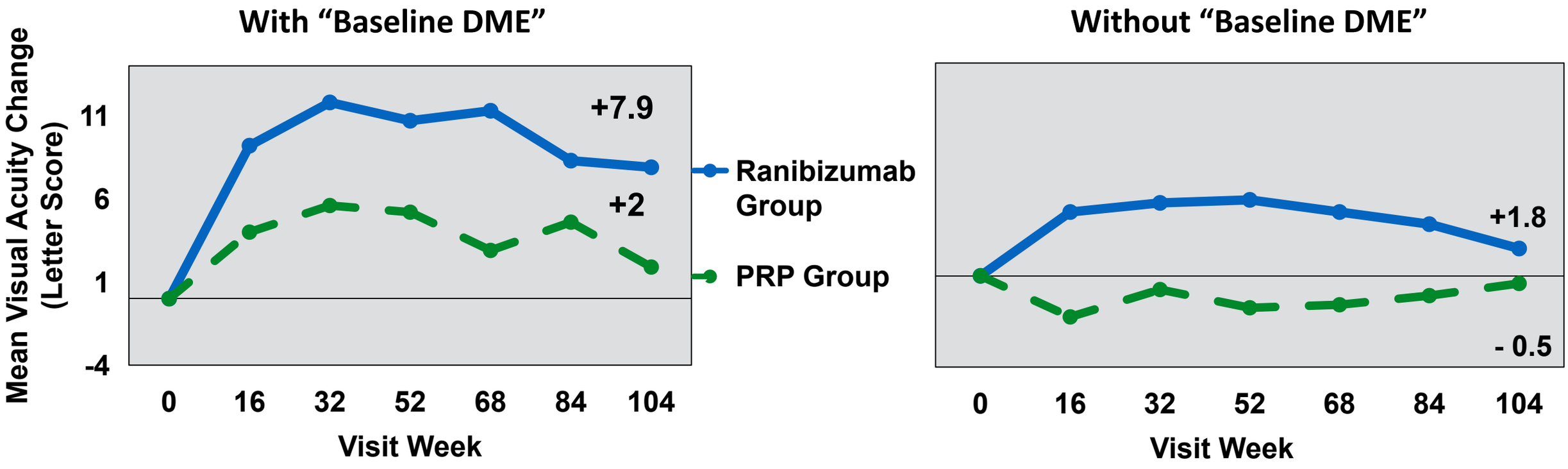
# Diabetes Retinopathy Clinical Research Network Protocol S

Primary Objective: Compare efficacy/safety of PRP vs Ranibizumab 0.5mg in treating PDR @ 2 years

PRP Group: Full laser treatment in 1-3 sessions. Followed every 4 months.
Ranibizumab Group: Treated with 6 monthly treatments then followed monthly for 1st year and then extend visits in 2nd year if stable

DME treatment in both groups per discretion of investigator

Results:
PRP Group: 45% needed additional laser during follow up
Ranibizumab Group: Median of 10 injections in eyes without baseline DME and 14 in eyes with baseline DME




| | Ranibizumab Group (N = 142) | Prompt PRP Group (N = 148) | |
|---|---|---|---|
| **Fundus Photos Graded by Reading Center*** | | | **0.41** |
| **No PDR** | **35%** | **30%** | **-** |
| **Regressed NV** | **23%** | **24%** | **-** |
| **Active NV** | **42%** | **46%** | **-** |

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Keck School of Medicine
University of Southern California

# At 2 years

| | Ranibizumab Group (N = 191) | PRP Group (N = 203) | |
|---|---|---|---|
| **Any retinal detachment** | **6%** | **10%** | **0.08** |
| **Neovascular glaucoma** | **2%** | **3%** | **0.50** |
| **Iris neovascularization** | **1%** | **1%** | **0.96** |
| **Vitreous hemorrhage** | **27%** | **34%** | **0.09** |
| **Vitrectomy** | **4%** | **15%** | **< 0.001** |

## Advantages of PRP

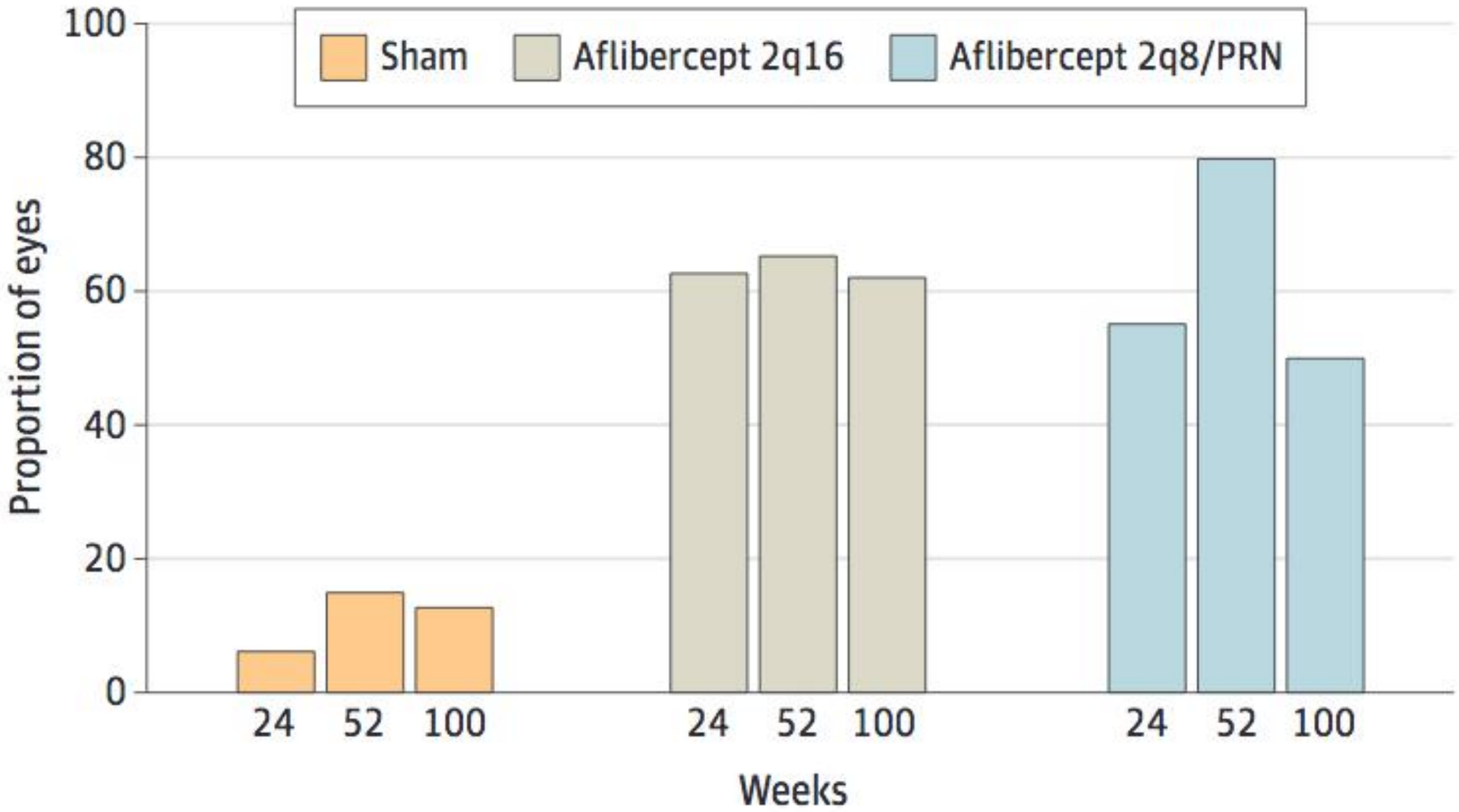
- Completed in a few visits
- *Permanent* effect
- Lower cost
- No risk of endophthalmitis
- No risk of systemic exposure of anti-VEGF

## Advantages of Ranibizumab

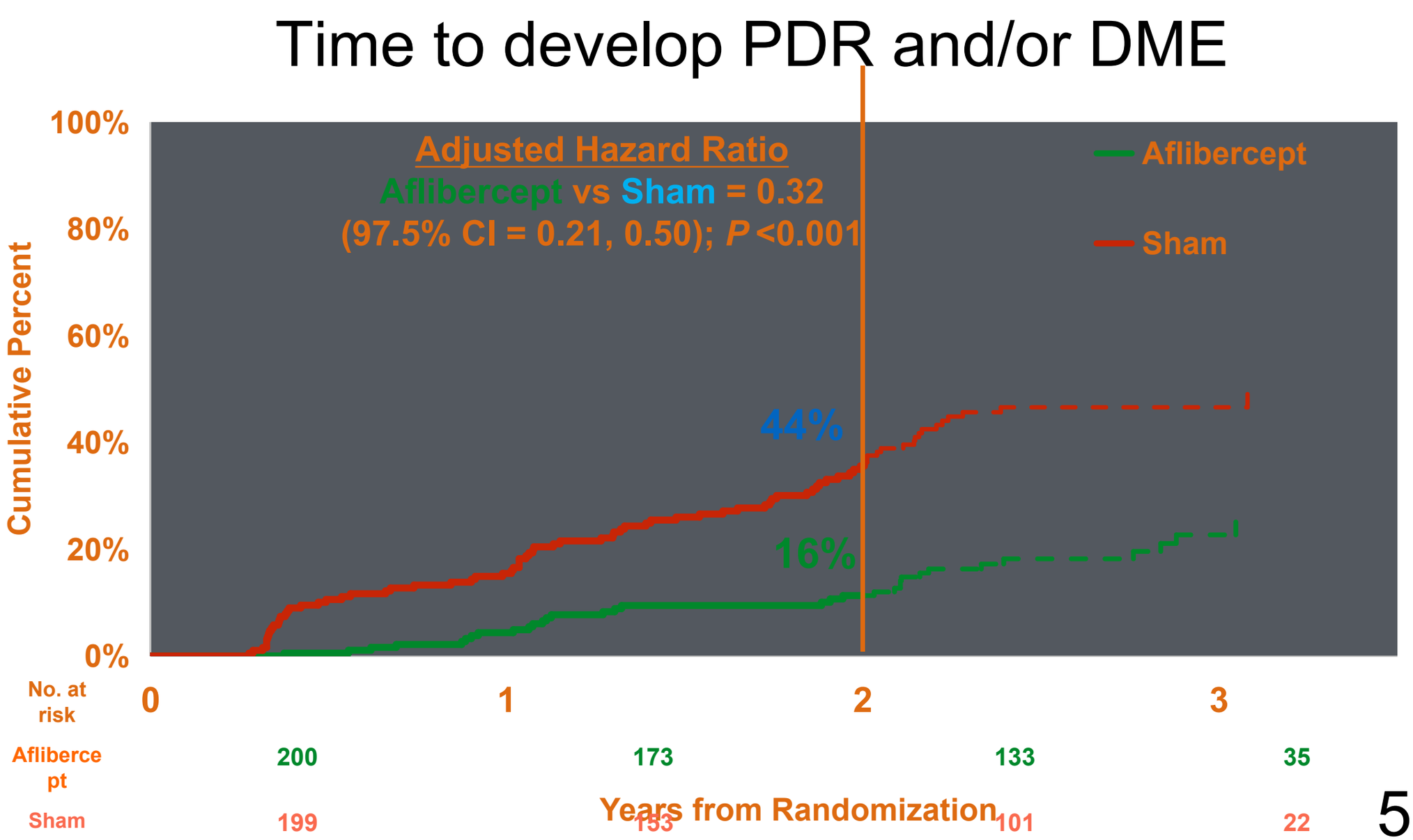
- Better mean VA over course of 2 years
- Better visual field outcomes
- Reduced risk of vitrectomy
- Reduced risk of DME

# What about NPDR without DME?

# Panorama Study



# Protocol W


Time to develop PDR and/or DME
Adjusted Hazard Ratio
Aflibercept vs Sham = 0.32
(97.5% CI = 0.21, 0.50); P <0.001
Aflibercept
Sham
44%
16%
Cumulative Percent
100%
80%
60%
40%
20%
0%
No. at risk
0
1
2
3
Aflibercept 200 173 133 35
Sham 199 153 101 22
Years from Randomization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