Retinopatia Diabetica

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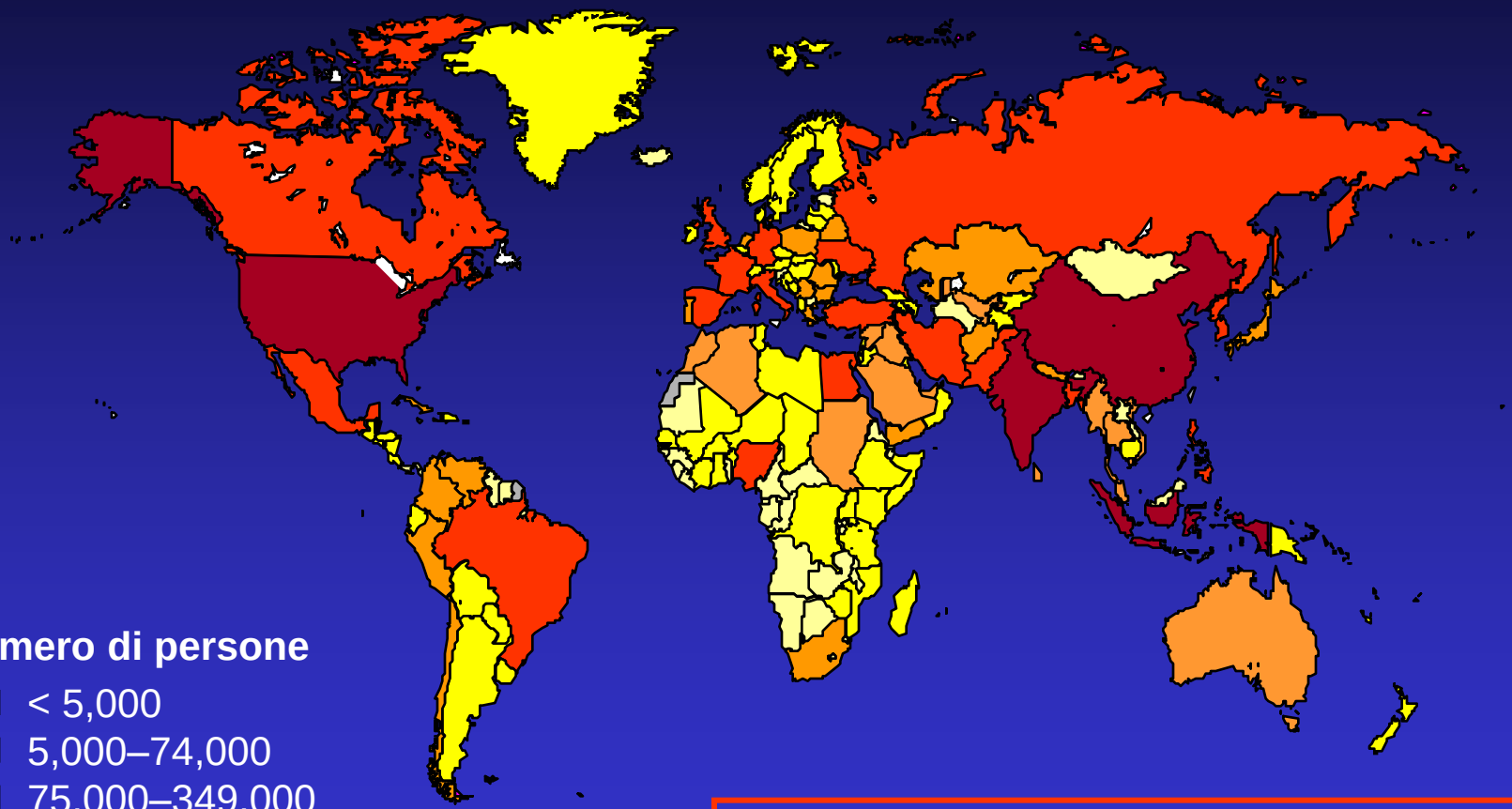
Presentation Outline

- Epidemiologia
- Patogenesi
- Classificazione
- Imaging
- Terapia

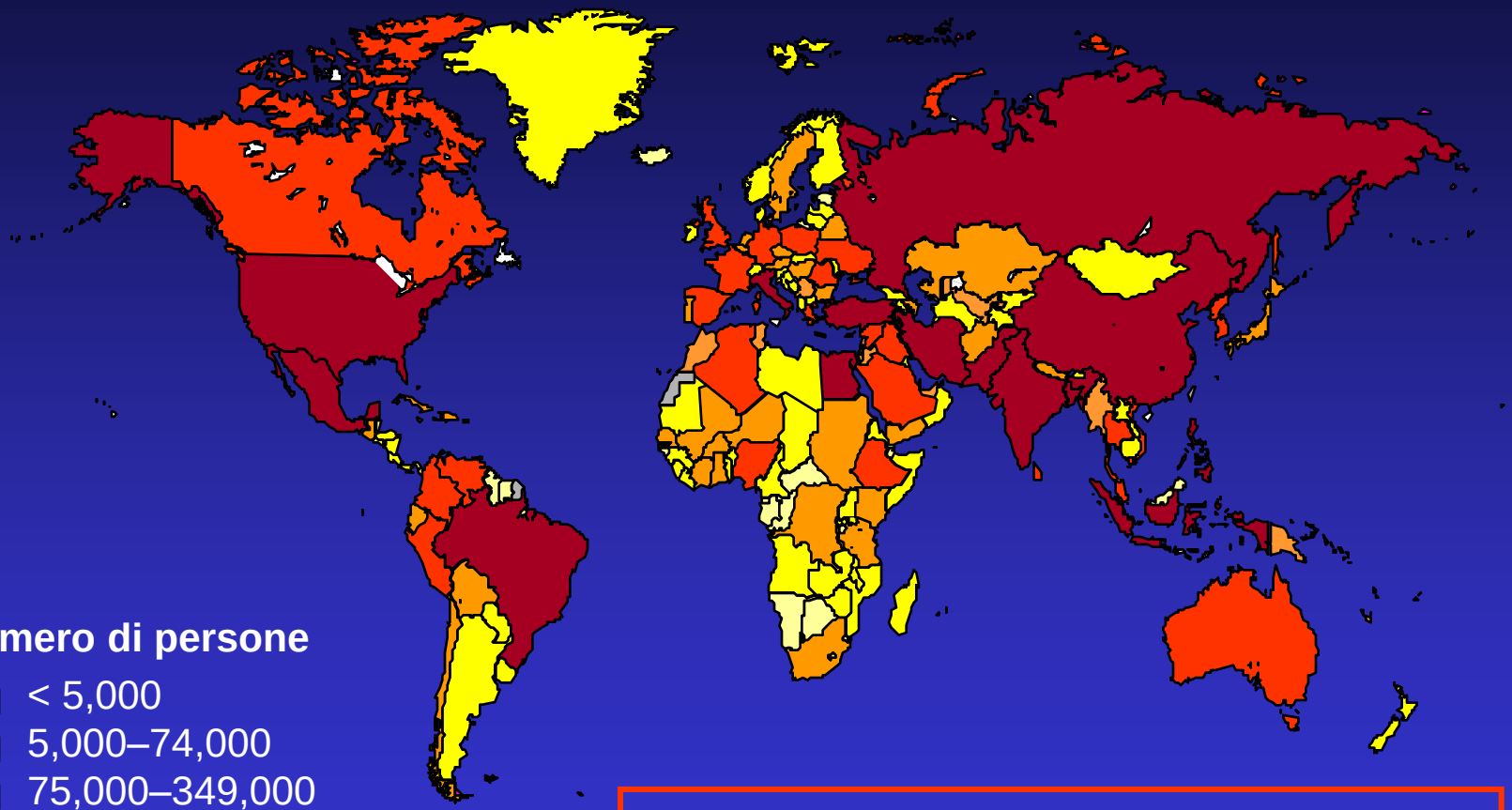
Prevalenza Globale del Diabete nel 2000



Numero totale di casi: 150 milioni

Adapted from WHO Diabetes Programme Facts and Figures: www.who.int/diabetes/facts/world_figures/en. Accessed 1 August, 2006.

Prevalenza Globale del Diabete nel 2030 (proiezione)



Numero di persone

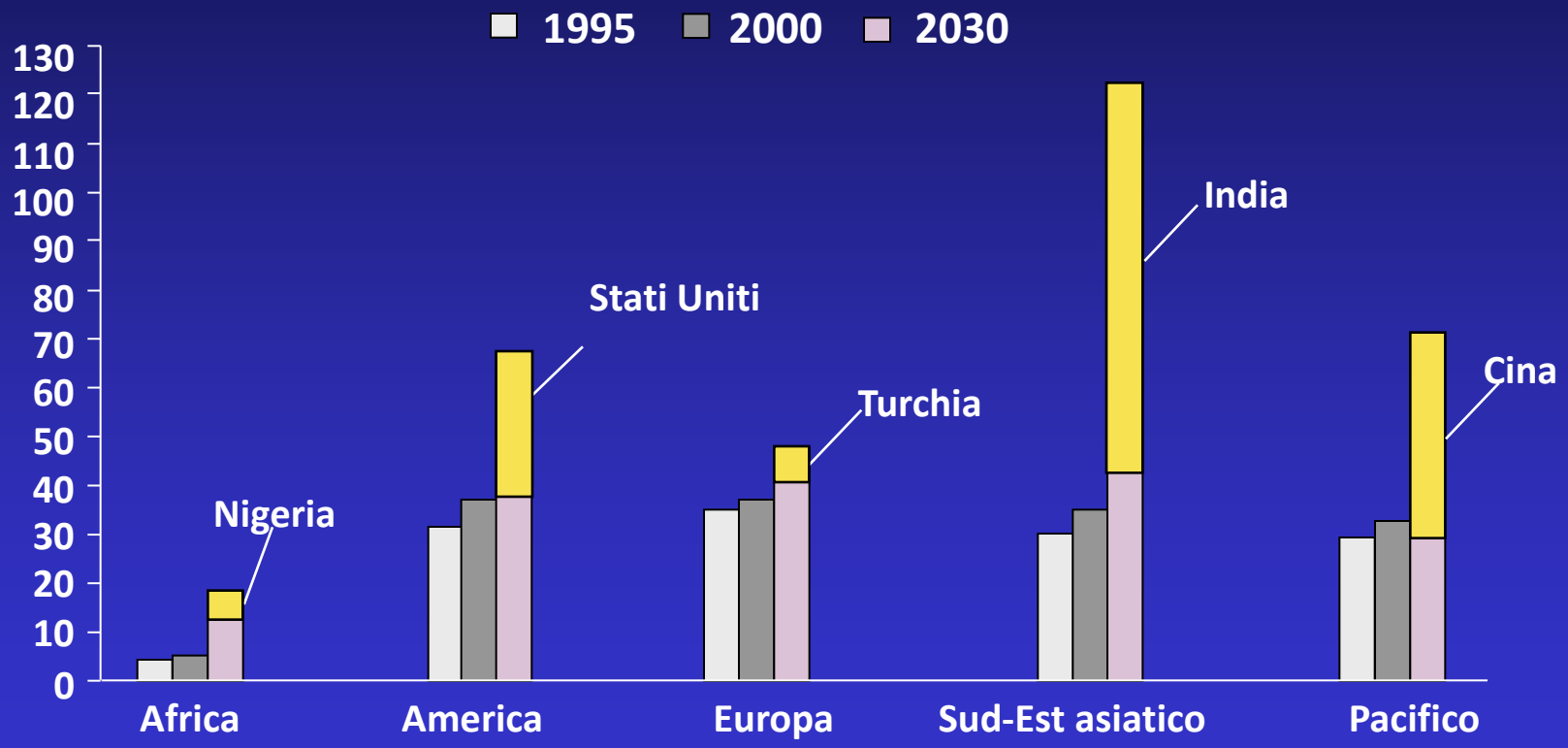
- < 5,000
- 5,000–74,000
- 75,000–349,000
- 350,000–1,499,000
- 1,500,000–4,999,000
- > 5,000,000
- Dati non disponibili

Numero totale di casi: 370 milioni

Adapted from WHO Diabetes Programme Facts and Figures: www.who.int/diabetes/facts/world_figures/en. Accessed 1 August, 2006.

Prevalenza Globale del Diabete nel 2030 (proiezione)

150 → 370 milioni di persone



Nazioni con il più alto incremento previsto di casi

Adapted from WHO Diabetes Programme Facts and Figures: www.who.int/diabetes/facts/world_figures/en. Accessed 1 August, 2006.

Trend epidemiologico

Nonostante tutto ciò… la disabilità associata con le complicanze da DM si va riducendo

- In DMT1 prevalence and severity of DR decreased since insulin therapy use

  Over 20 years the cumulative incidence of DR has decreased

  43% (1° WESDR)→ 18% (2° WDR)

- In DMT2, despite its increase, prevalence and severity of DR are decreased

  Improvement in primary care:

Intensive screeening

Early diagnosis

Intensive medical therapy

WDR Study. LeCaire TJ. Diabetes Care 2013
ACCORD Eye Study Group. Ophthalmology 2014

Glycemic Control: How Much Intensive?

- Intensive glycemic control lowers the risk for DR incidence and progression significantly more than conventional therapy

  - Risk of DR: 6.2% vs 23.2% ($p < 0.00001$)
  - Risk of progression over 2 years: 23.2% versus 38.7% ($p < 0.0001$), ***but with an initial worsening in the first year***
  - Highly cost effective strategy
  - Same quality of health-related life

Fullerton B. Cochrane 2014

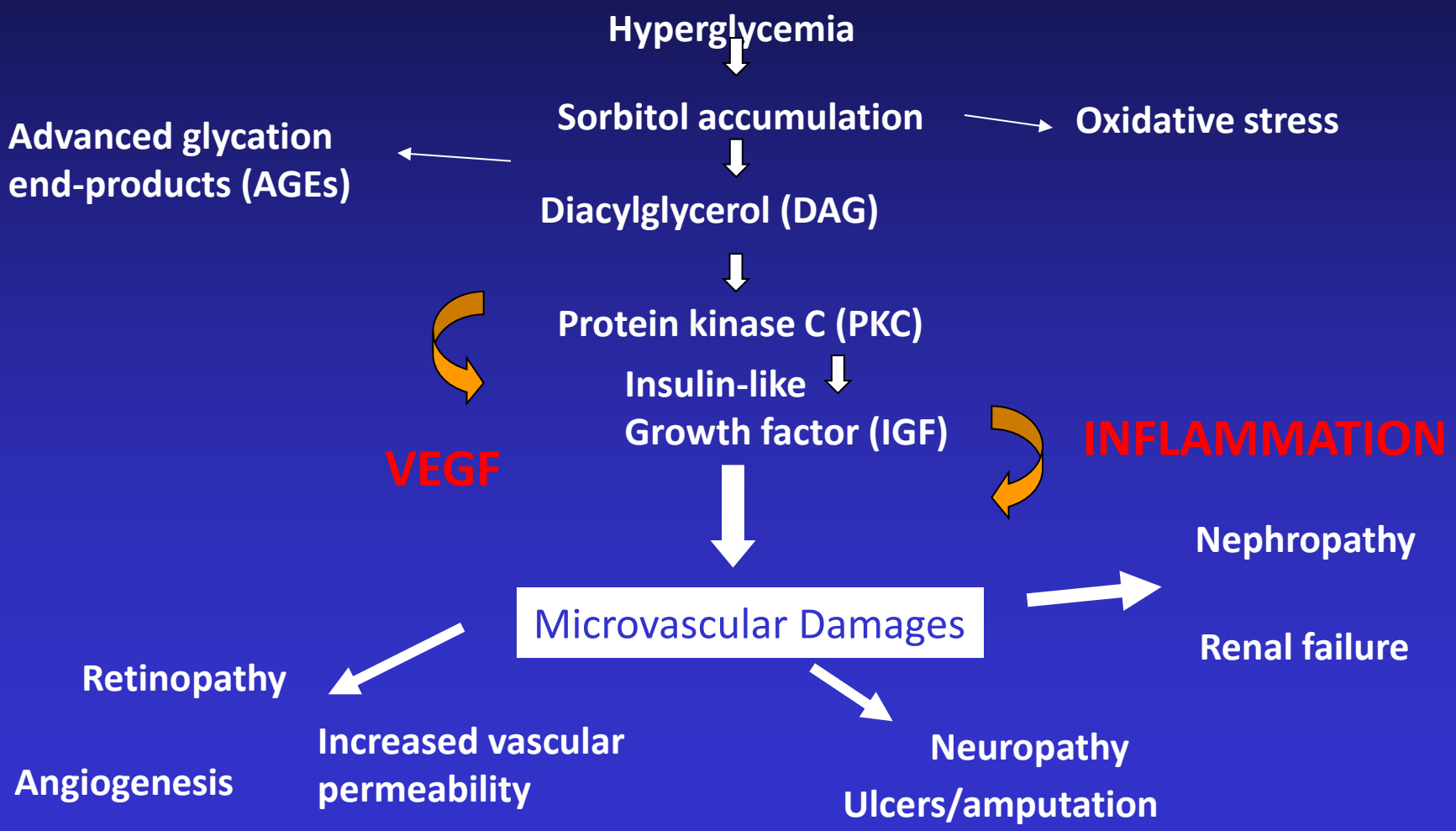
DR Prevalence

Prevalence of DR increases with:

➢ Blood glucose	(DCCT, UKPDS)
➢ Blood pressure	(UKPDS)
➢ Duration of diabetes	(DCCT)
➢ Lipids	(ACCORD)
➢ Pregnancy	(DCCT)
➢ Nephropathy	(UKPDS, WESDR)
- Obesity	(WESDR, SiME)
- Genetics	(GOLDR, TUDR)
- Nutrition	(JDCSG)

Song SJ. Diabetes Metab J 2014

DR Pathogenesis



DME Pathogenesis

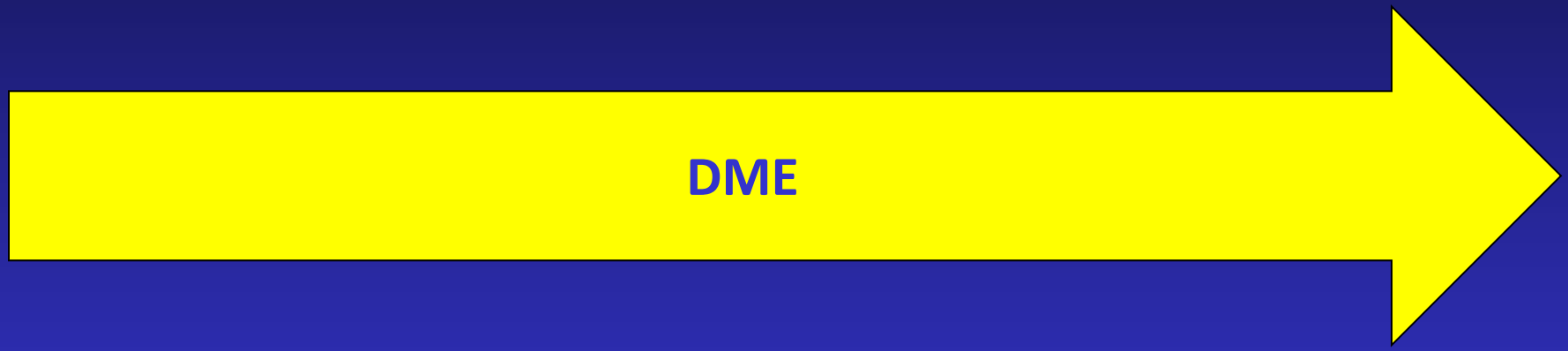
- Increased vascular permeability
- Disruption of the blood-retinal barrier (inner/outer)
- Accumulation of fluid and serum macromolecules in the intercellular space
- Accelerated apoptosis of pericytes and endothelial cells, acellular capillaries, basement membrane thickening, capillary occlusion
- Intracellular retinal cells edema

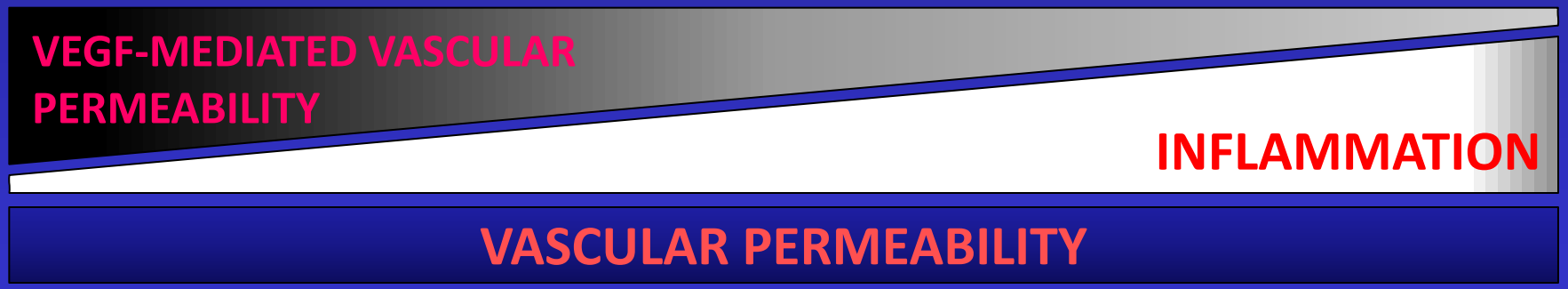
  - Capillary closure / Tissue hypoxia

Bandello F. et al: Dev Ophthalmol. DME. 2010;47:73-110

Life Cycle of DME

Early focal leakage • Diffuse leakage • Fibrosis • Pigmentary changes • Loss of photoreceptor cells





Prasad S, et al. *Prev Med*. 2012;54(Suppl):S29-37

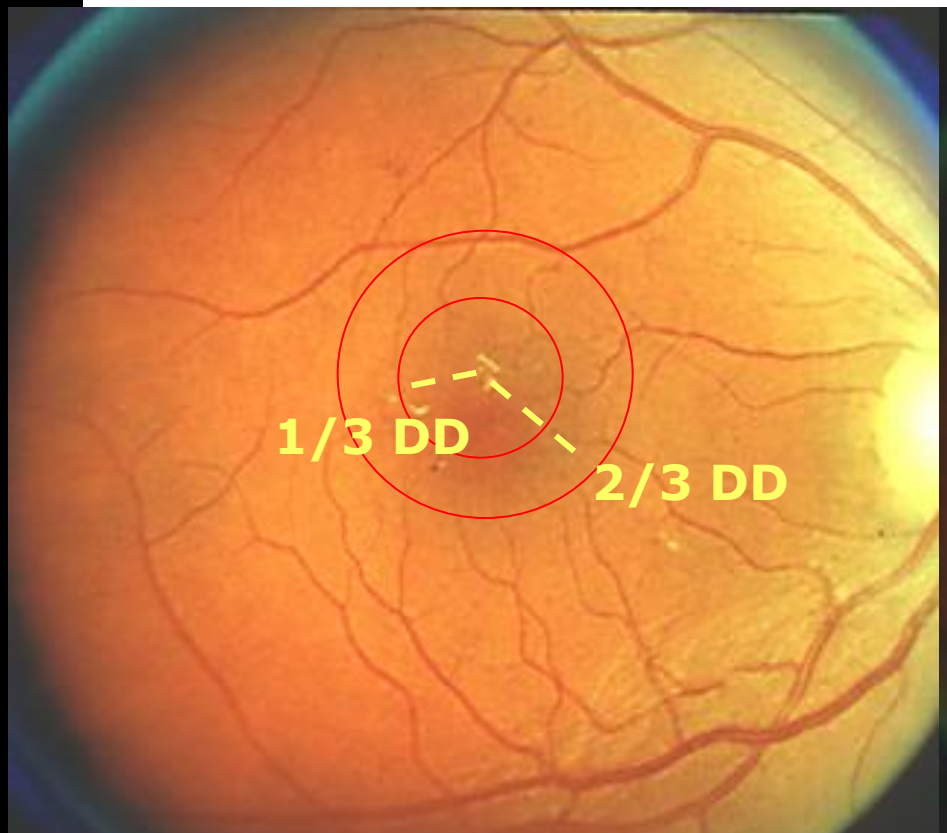
Classificazione della RD

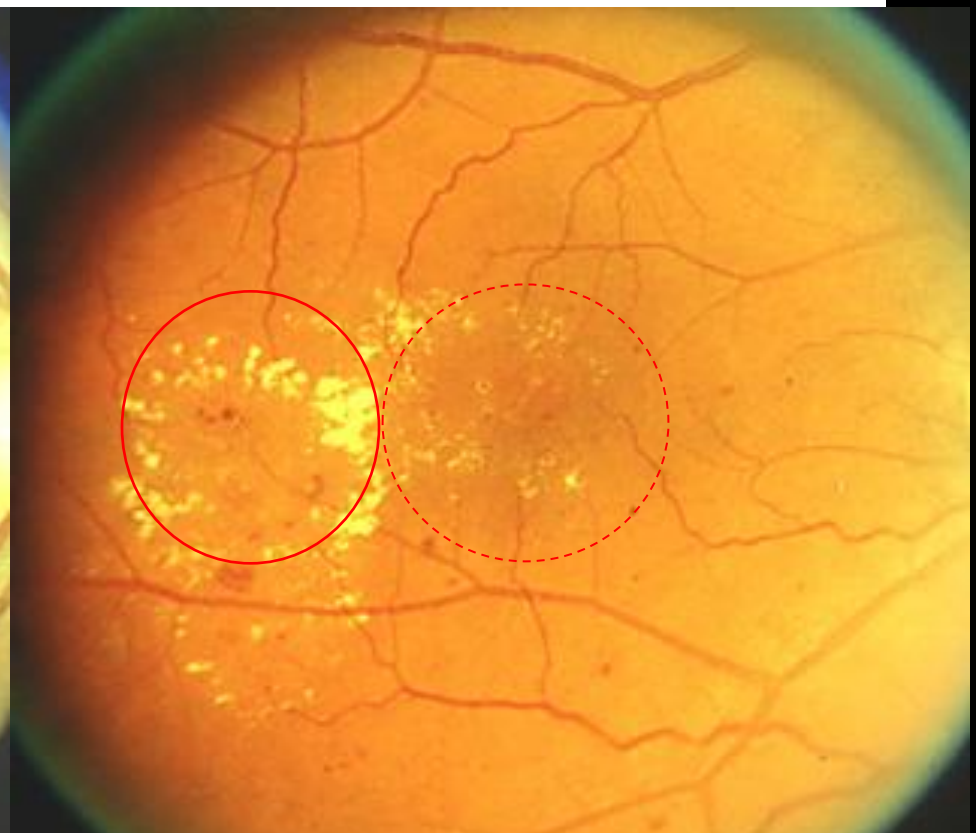
- RD NON PROLIFERANTE
  - Iniziale
  - Moderata
  - Severa (RD Preproliferante)
- RD PROLIFERANTE
  - Iniziale
  - Severa (Alto Rischio)
  - Complicata (emovitreo, distacco di retina secondario, glaucoma neovascolare)

DME ETDRS Classification

Clinically significant diabetic macular edema (ME)

1. Thickening of the retina located ≤500 μm from the center of the macula or
2. HE located ≤500 μm from the center of the macula with thickening of the adjacent retina or
3. A zone of retinal thickening, 1 disk area or larger in size any portion of which is located ≤1 disk diameter from the center of the macula



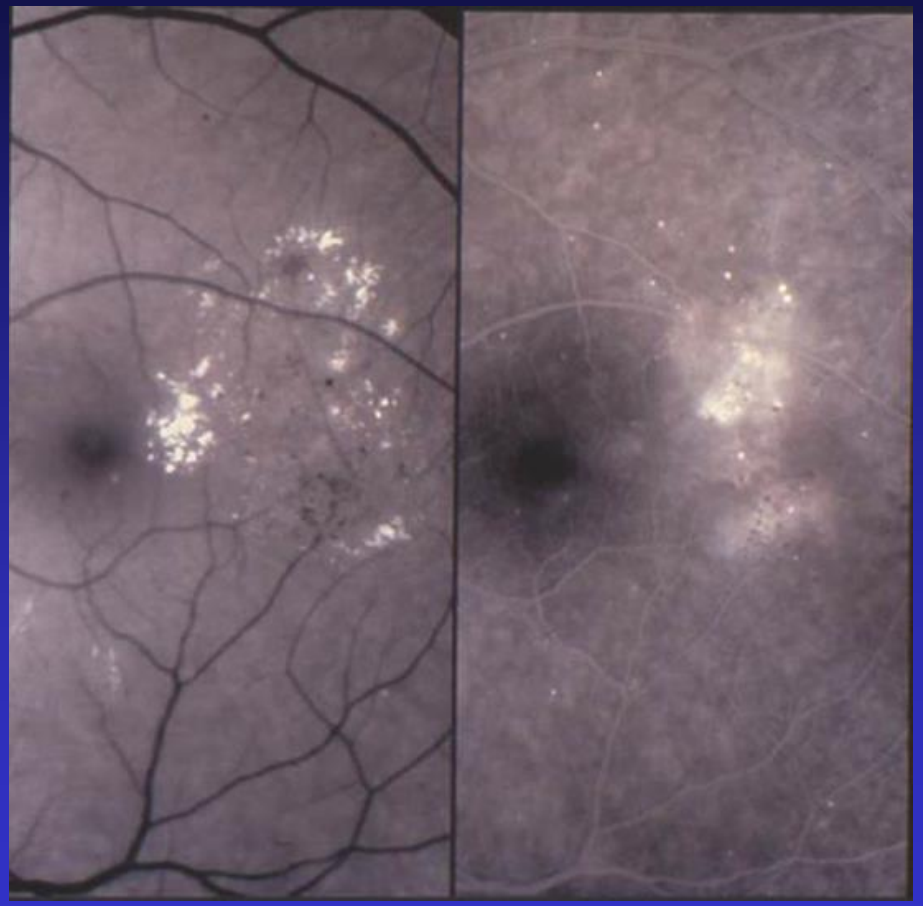


Proposed Simplified DME Classification

- Vasogenic DME
  - Ischemic/Non-Ischemic
- Non-Vasogenic DME
  - Ischemic/Non-Ischemic
- Tractional DME
- Mixed DME

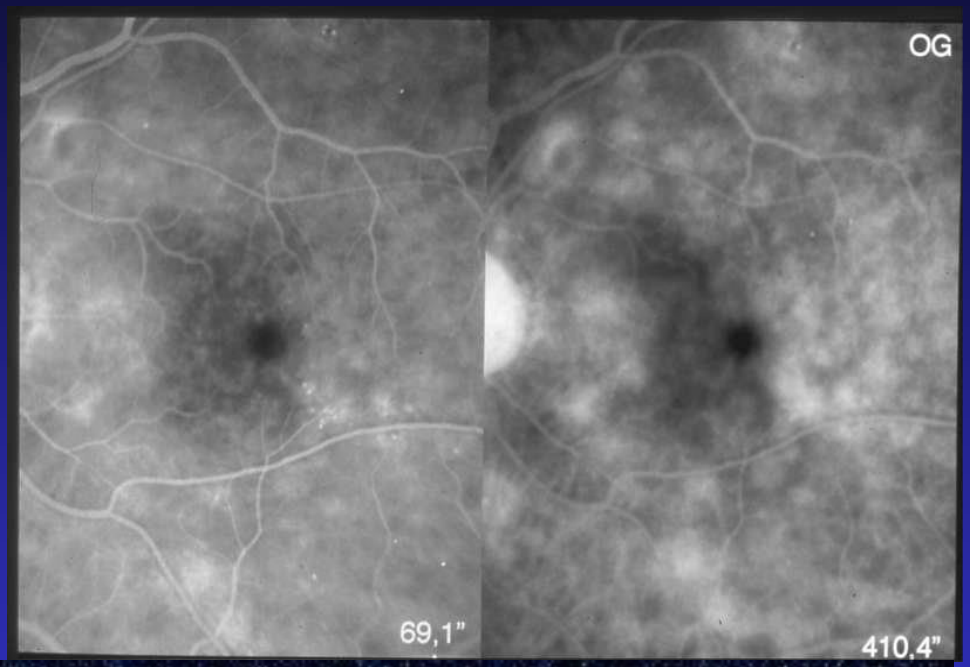
Vasogenic DME

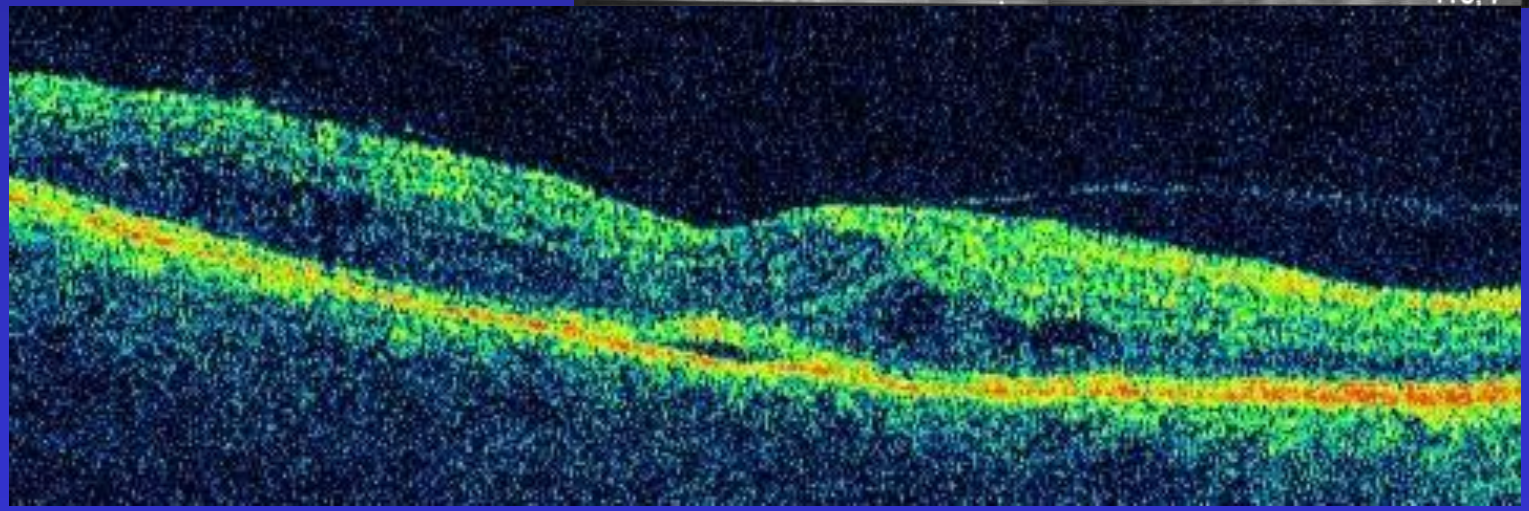
- Localized areas of retinal thickening derived from leakage of mycroaneurisms
- Areas of focal leakage are often demarcated by a partial or complete ring of hard exudates
- FA demonstrates that microaneurysms are the major source of dye leakage



Non-Vasogenic DME

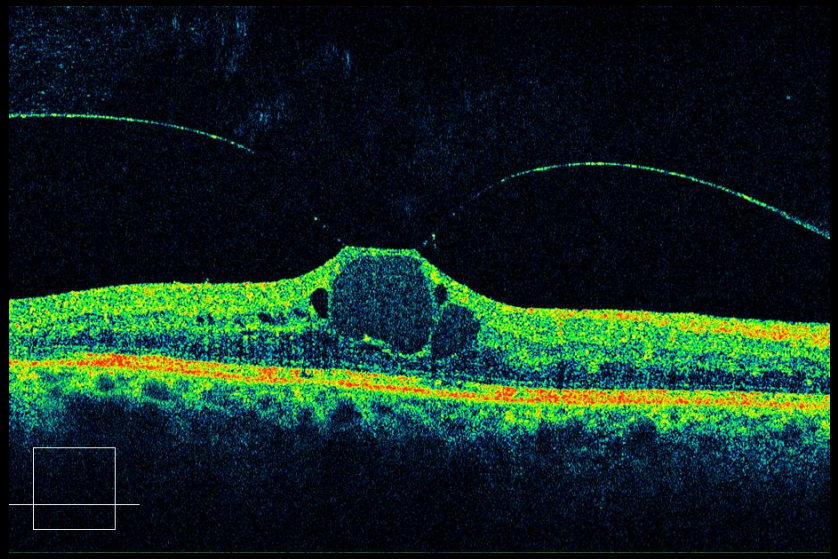
- Limited leaking lesions
- Widespread thickening of the macula

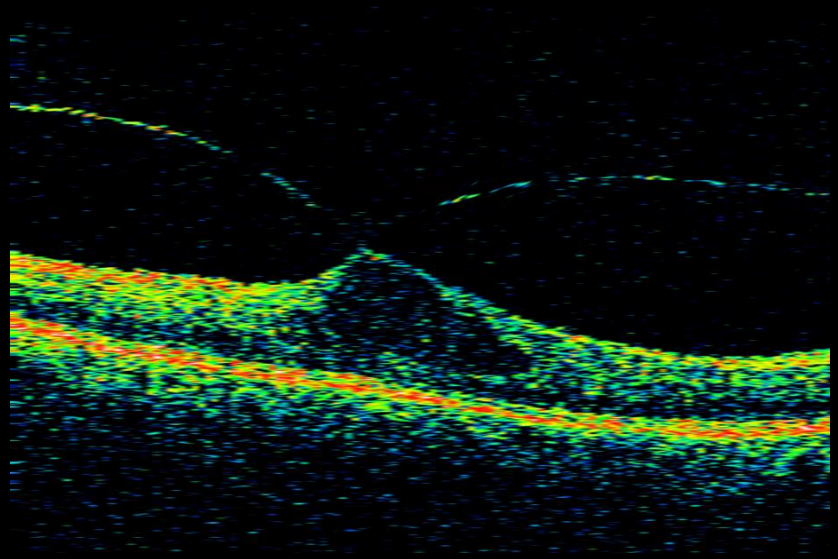




Tractional DME

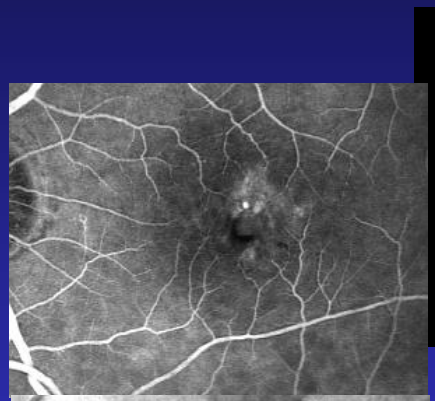
- BIOMICROSCOPY: Thick glistening posterior hyaloid detectable
- FA: Early hypofluorescence and deep, diffuse round late leakage, often vascular arcade to arcade
- OCT: More accurate than biomiscroscopy in determining the status of a posterior hyaloid

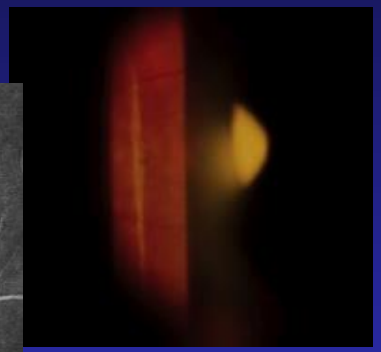


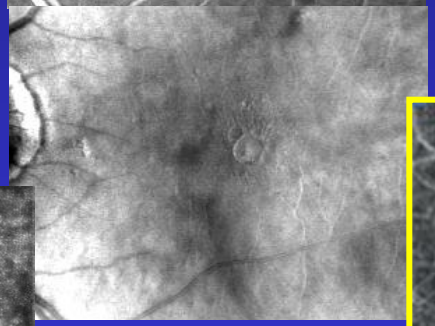


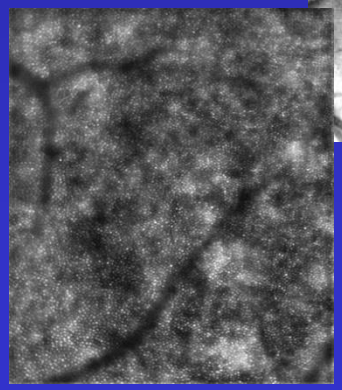
Diagnosis of DR

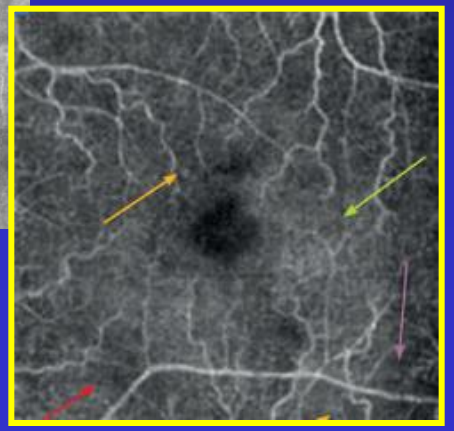
- Biomicroscopic examination with non contact lenses
- Fluorescein angiography
- SD-OCT
- Retromode imaging
- Fundus autofluorescence
- Adaptive optics
- Microperimetry
- Angio-OCT





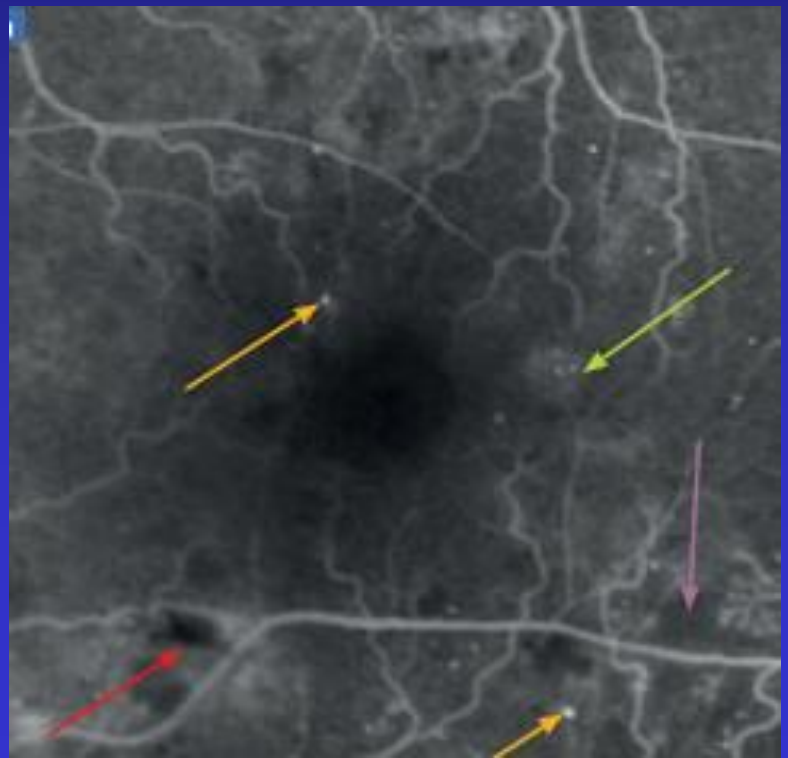


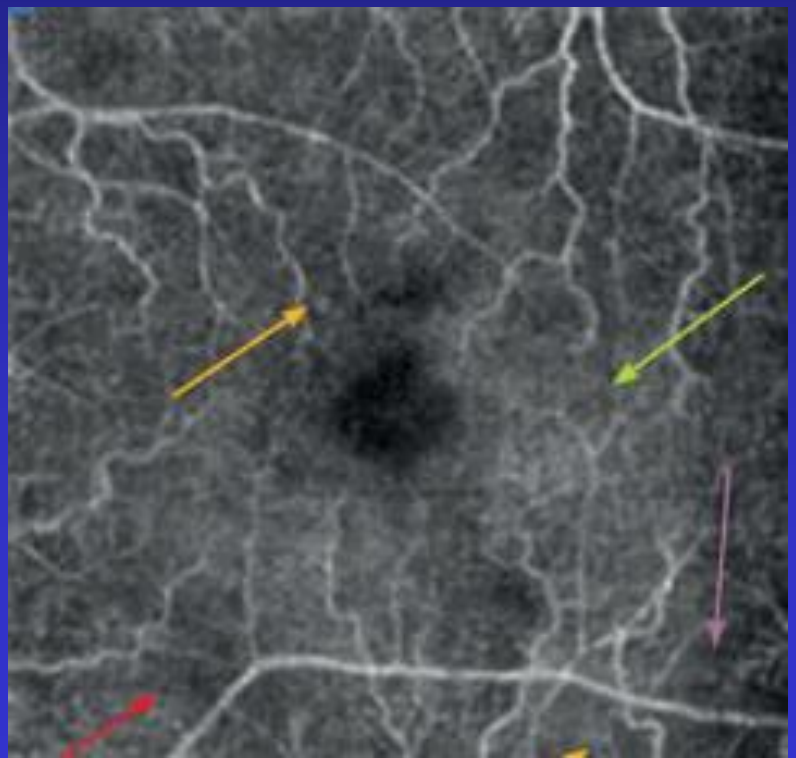




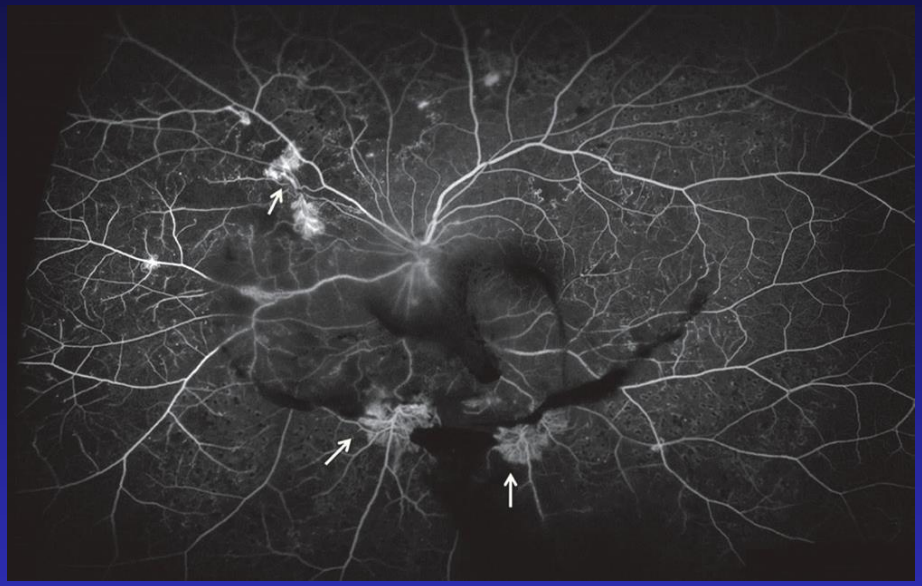
Diagnosis of DR: Angio-OCT

- Non-invasive imaging of retinal vascularization based on blood reflectivity analysis
- Static evaluation (≠ from FA)
- Difficult detection of microaneurysms





Diagnosis of PDR: UltraWide-field fundus fluorescein angiography

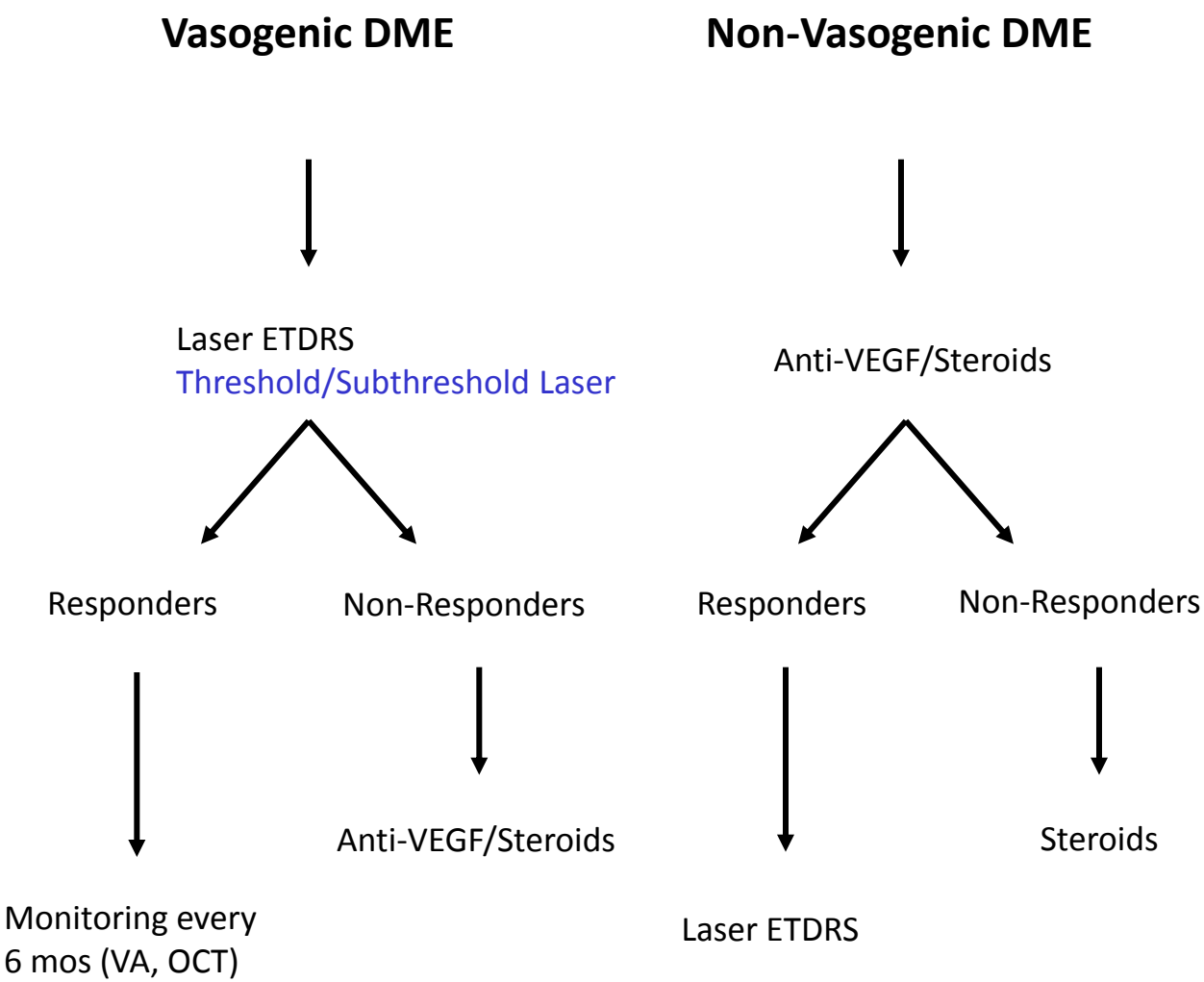


- Used to study the relationship between peripheral capillary nonperfusion and the development of neovascularization, a precursor to PDR
- Visualizes 3.2 times more retinal surface area than the conventional 7-standard fields
- Better management of retinal ischemia (new vessels)

Current Treatment Options for DME

- Towards treatment tailoring
- Laser Treatment
  - Conventional Grid/Focal Laser
  - Light Laser
  - Sub-threshold Laser Treatment
  - Pascal/NAVILAS Photocoagulation
- Steroids
- Anti-VEGF
- Combined Therapies

Proposed Treatment Algorithm for DME

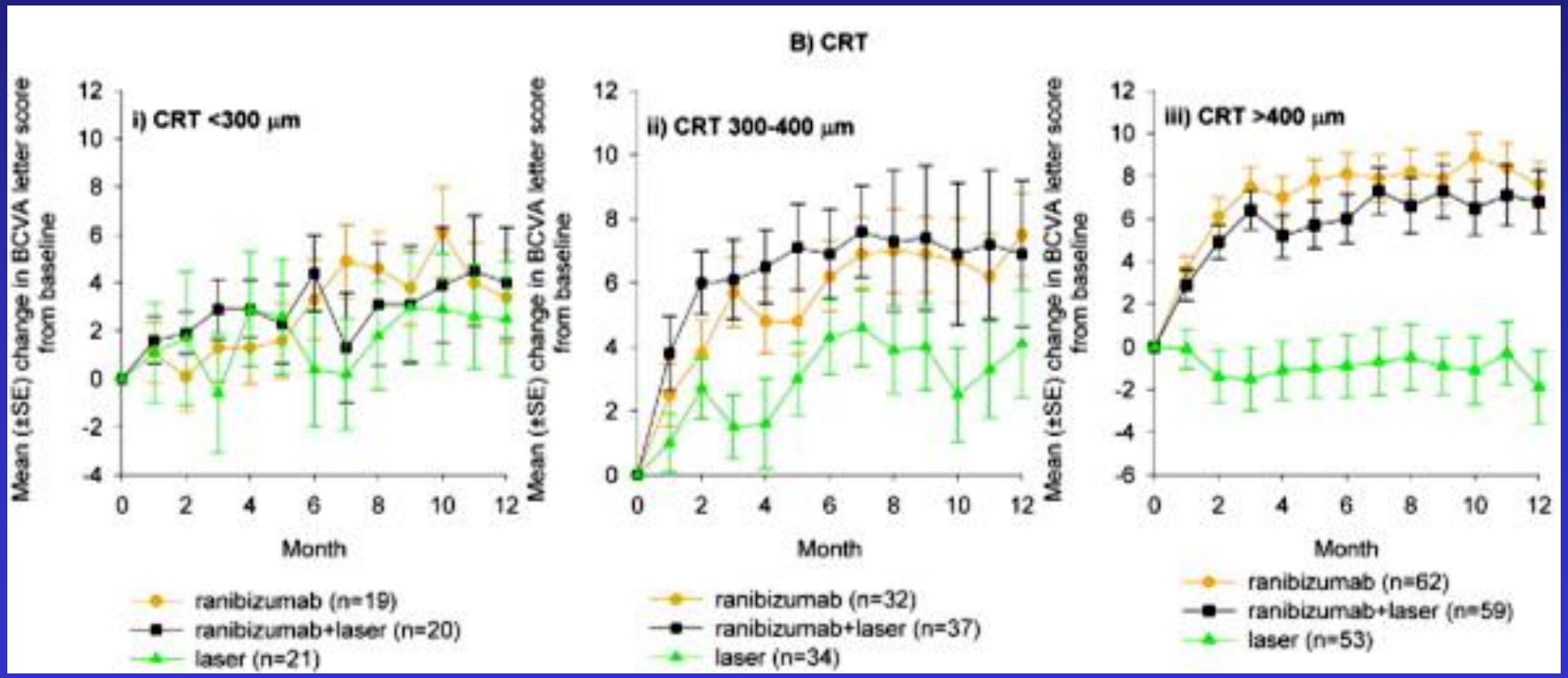


Modified from Bandello F et al. Ophthalmologica 2010

Effect of Retinal Thickness in RESTORE Trial

Difference in VA respons at 12-month:

- 2.2 letters if CRT < 400 micron
- 8.2 letters if CRT > 400 micron



Mitchell P, Bandello F, Schlingheman R. Ophthalmology 2011

DME Subtypes

	Vasogenic	Non-Vasogenic	Mixed	Tractional
Frequency	63% (116/184)	24% (44/184)	7% (13/184)	6% (11/184)
Mean BCVA (LogMAR)	0.43	0.47	0.46	0.64
Mean CRT	458	467	454	483
% < 300µm	22% of whole Vasogenic DME (26/116)	7% of whole Non-Vasogenic DME (3/44)	0%	9% of whole Non-Vasogenic DME (1/11)
% 300 to 400µm	22% of whole Vasogenic DME (25/116)	25% of whole Non-Vasogenic DME (11/44)	30% of whole Mixed DME (4/13)	0%
% within 400 µm	44% of whole Vasogenic DME (51/116)	32% of whole Non-Vasogenic DME (14/44)	30% of whole Mixed DME (4/13)	9% of whole Non-Vasogenic DME (1/11)

DME subtypes frequency from 184 consecutive pts requiring examination in a tertiary centre

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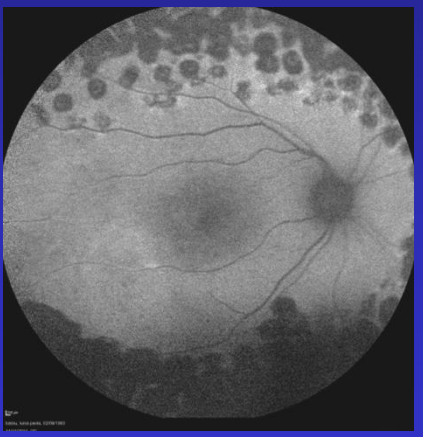
P = 0.03

DME subtypes frequency from 184 consecutive pts requiring examination in a tertiary centre

Current Treatment Options for PDR

- Laser Treatment



Meta-analysis of 5 comparative trials
With no homogeneous cohort
Total N=9503 eyes

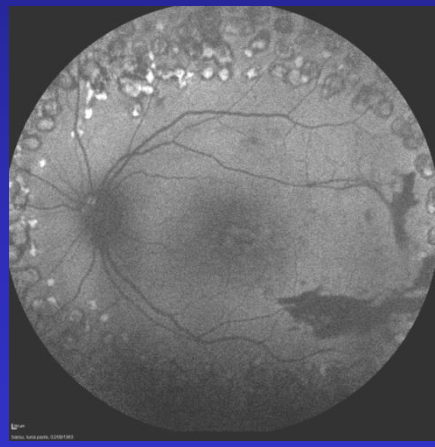
4 studies on PRP (with argon laser)

1 study on selective laser of non-perfused areas

3 studies compared Prompt laser vs no treatment

2 studies compared Prompt laser vs. deferred laser

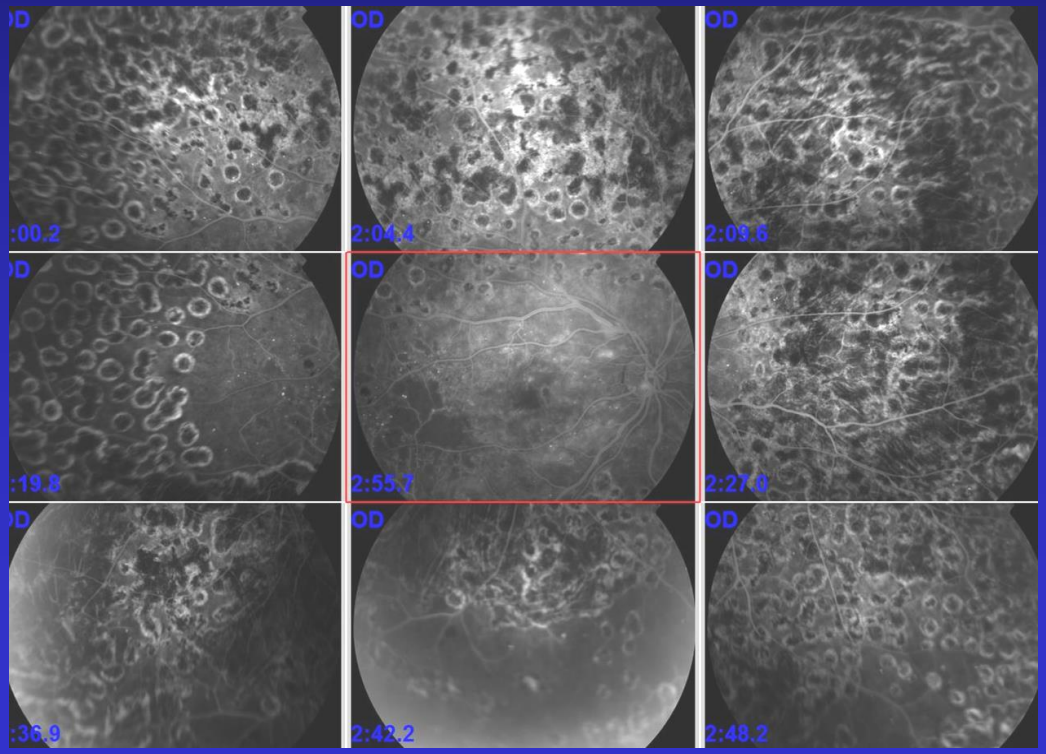
Prompt laser efficacy



Evans MF. Cochrane 2014

Current Treatment Options for PDR

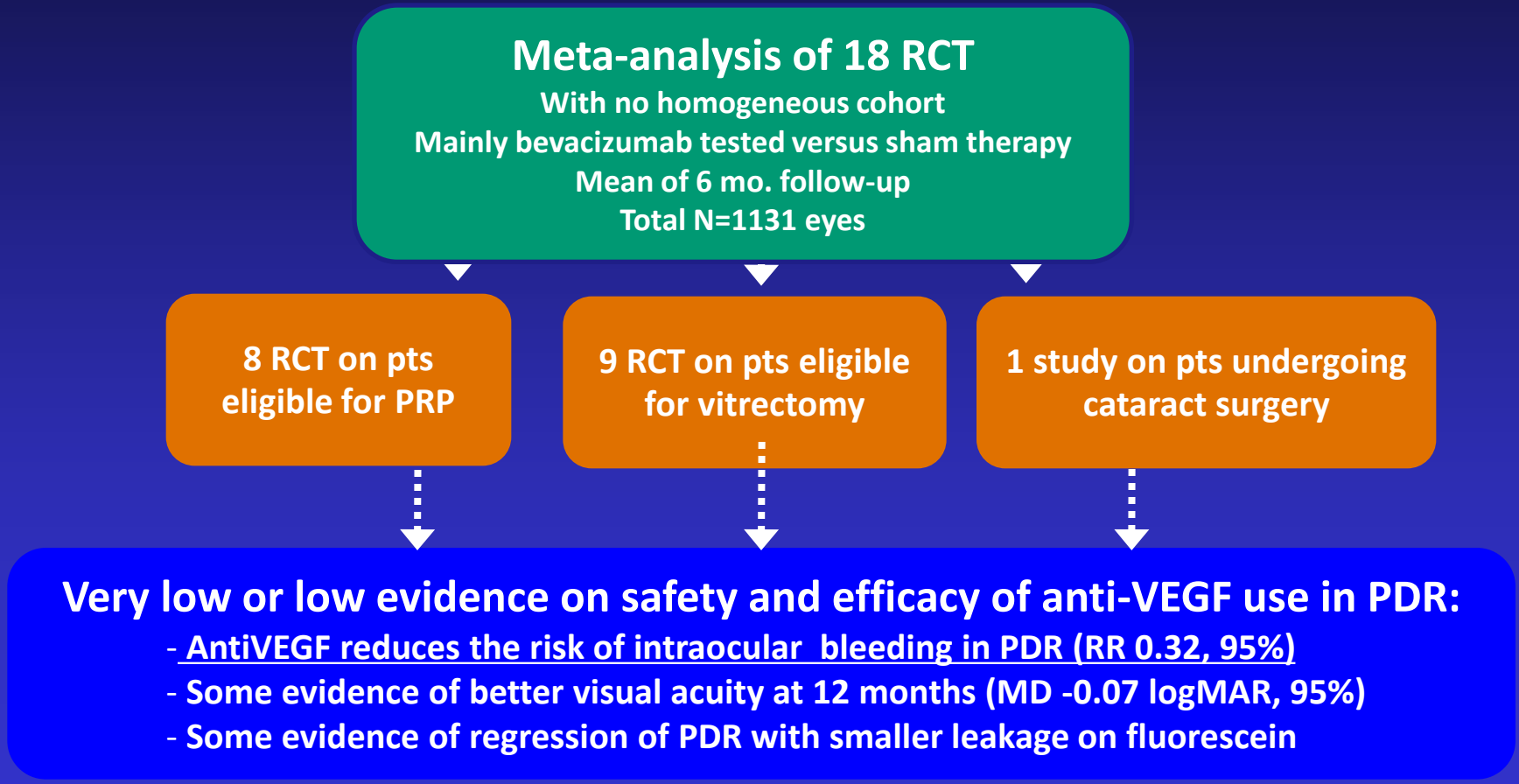
- Over 4 clinical trials, at 12 months, laser therapy significantly:
  - reduced the risk by 50% of severe visual loss (RR 0.46, 95%)
  - reduced the risk by > 50% of DR progression (RR 0.49, 95%)
- Over 2 clinical trials, Reduced the risk of hemovitreous (RR 0.56, 95%)



Evans MF. Cochrane 2014

Current Treatment Options for PDR

- Anti-VEGF



Martinez-Zapata MJ. Cochrane 2014

Current Treatment Options for DME

- Laser Treatment
  - Conventional Grid/Focal Laser
  - Light Laser
  - Sub-threshold Laser Treatment
  - Pascal/NAVILAS Photocoagulation
- Steroids
- Anti-VEGF
- Combined Therapies

Steroids
(Sustained Drug Delivery Systems)

- Dexamethasone
- Fluocinolone

MEAD Study

- 3-year multicenter, RCT
- To evaluate safety and efficacy of dexamethasone (700 or 350 µg) implant vs sham
- 1048 pts – randomization 1:1:1
- BCVA improvement ≥15 letters in:
  - 22% improvement in 700 µg subgroup
  - 18% improvement in 350 µg subgroup
  - 12% improvement in sham subgroup ($p<0.018$)
- Mean retreatment #:
  - 4.1 in 700 µg subgroup
  - 4.4 in 350 µg subgroup

Boyer DS. MEAD Study Ophthalmology 2014

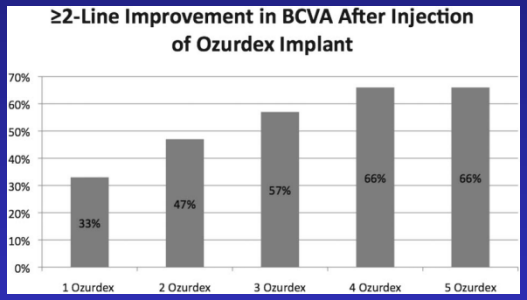
MEAD Study Adverse Events

- Cataract
  - 68% in 700 µg subgroup
  - 64% in 350 µg subgroup
  - 20% in sham subgroup
- Glaucoma Surgery
  - 0.3% in 700 µg subgroup
  - 0.3% in 350 µg subgroup

Boyer DS. MEAD Study Ophthalmology 2014

Ozurdex: Emerging data

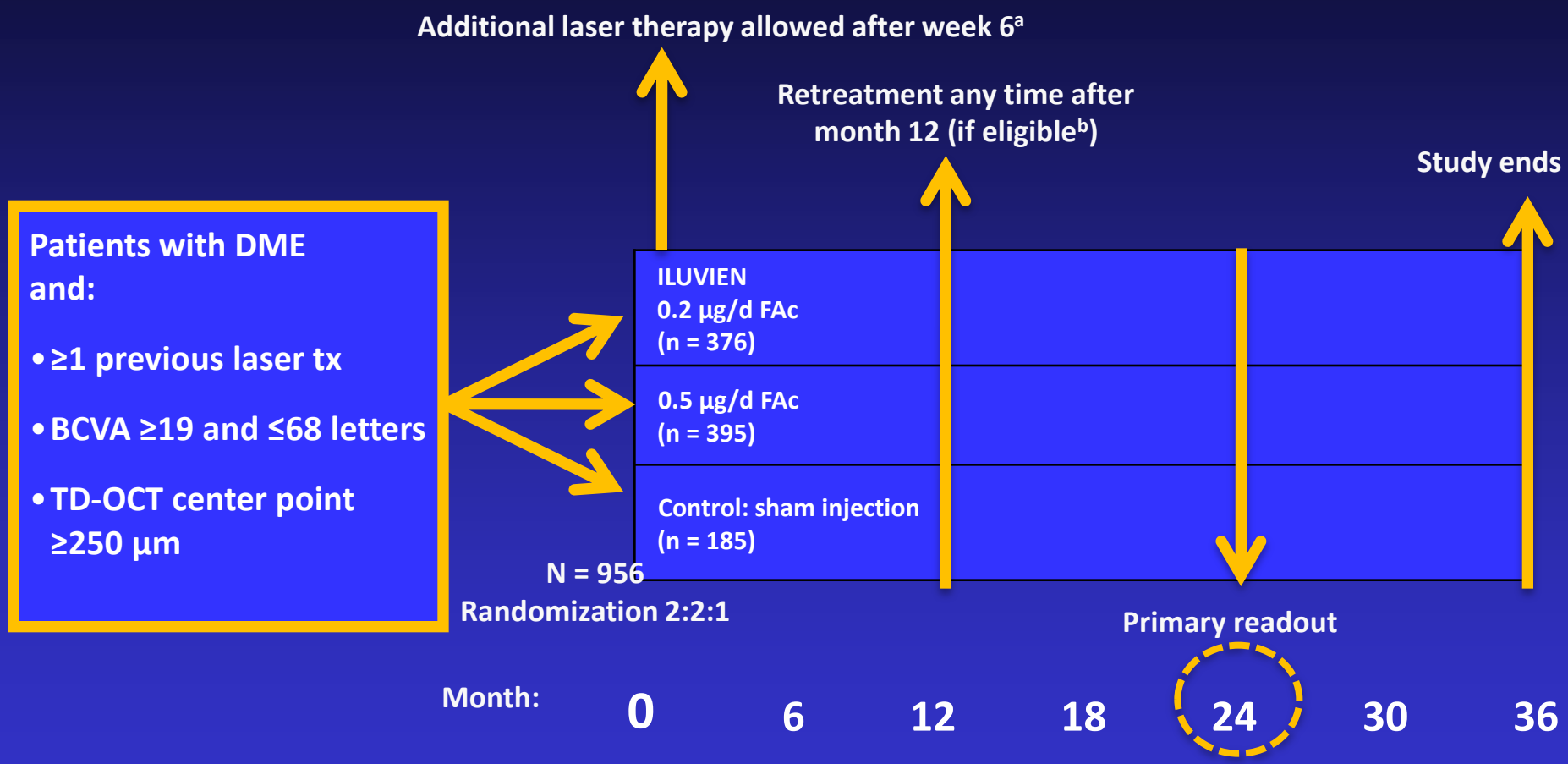
- Repeated Ozurdex on an “as needed” interval produces long-term clinical benefits[1]
- 4 subsequent repeated implants showed to be safe[1]



- Ozurdex vs. Bevacizumab[2]- 88 eyes -randomization 1:1
- BCVA improvement ≥10 letters: 41% vs. 40% (p=0.83)
  - BCVA decrease ≥10 letters: 11% vs. 0% (mostly due to cataract)
  - CRT improvement: 187 µ vs. 122 µ (p=0.015)
  - Mean retreatment # (over 12 months): 2.7 vs. 8.6 injections

1. Scaramuzzi M. Retina 2015
2. Gillies MC. BEVORDEX Study.Retina 2015

Iluvien: Design of Phase 3 FAME Studies



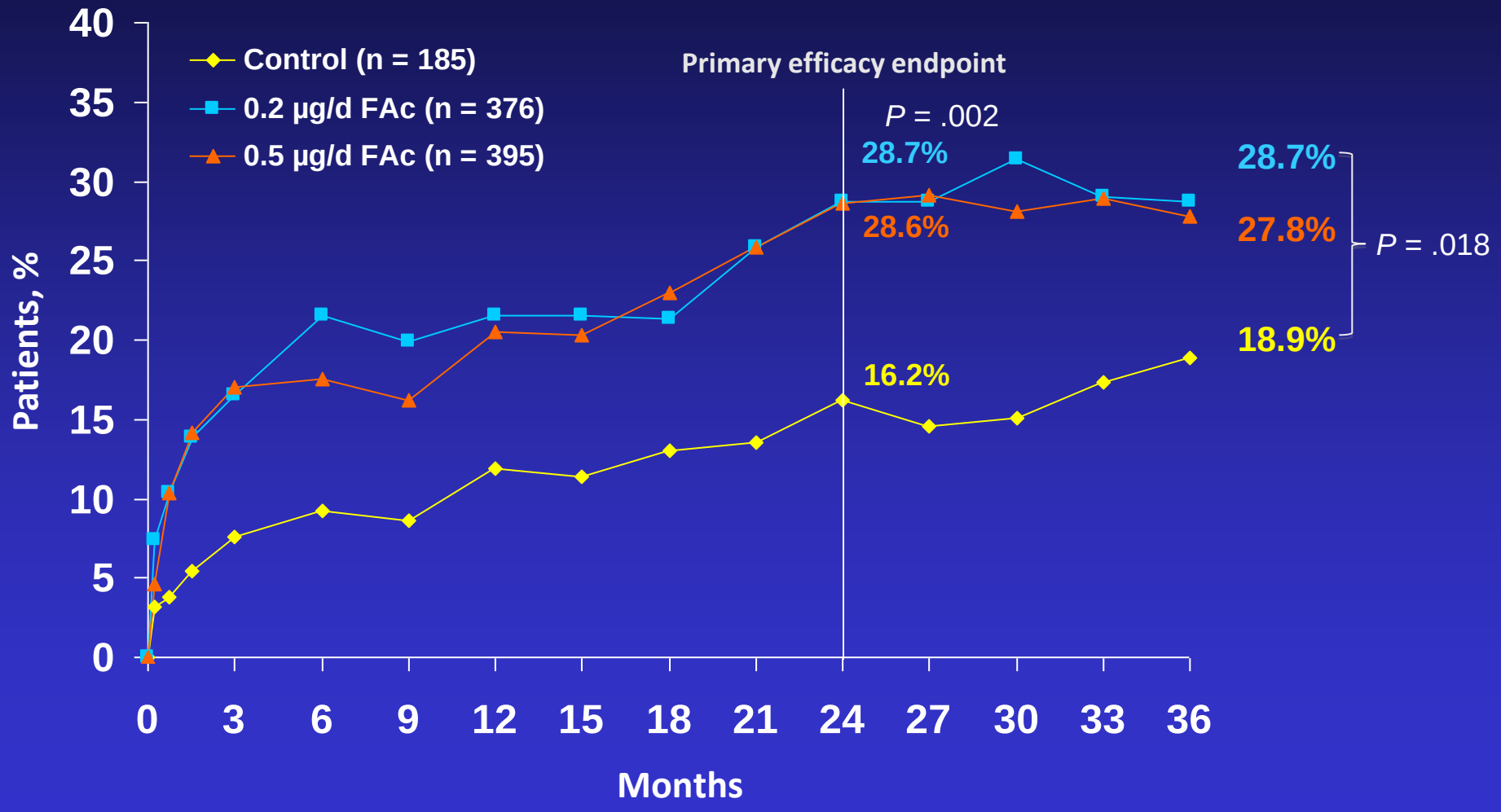
BCVA=best corrected visual acuity; DME=diabetic macular edema; TD-OCT,=time domain optical coherence tomography.

[a] At masked investigator's discretion.

[b] If BCVA loss ≥5 letters or retinal thickening ≥50 µm from best reading in previous 12 months.

Campochiaro P. FAME study group. Ophthalmology 2011

Percentage of Patients With ≥15-Letter Improvement Over Baseline



Fluocinolone Acetonide (Retisert®)

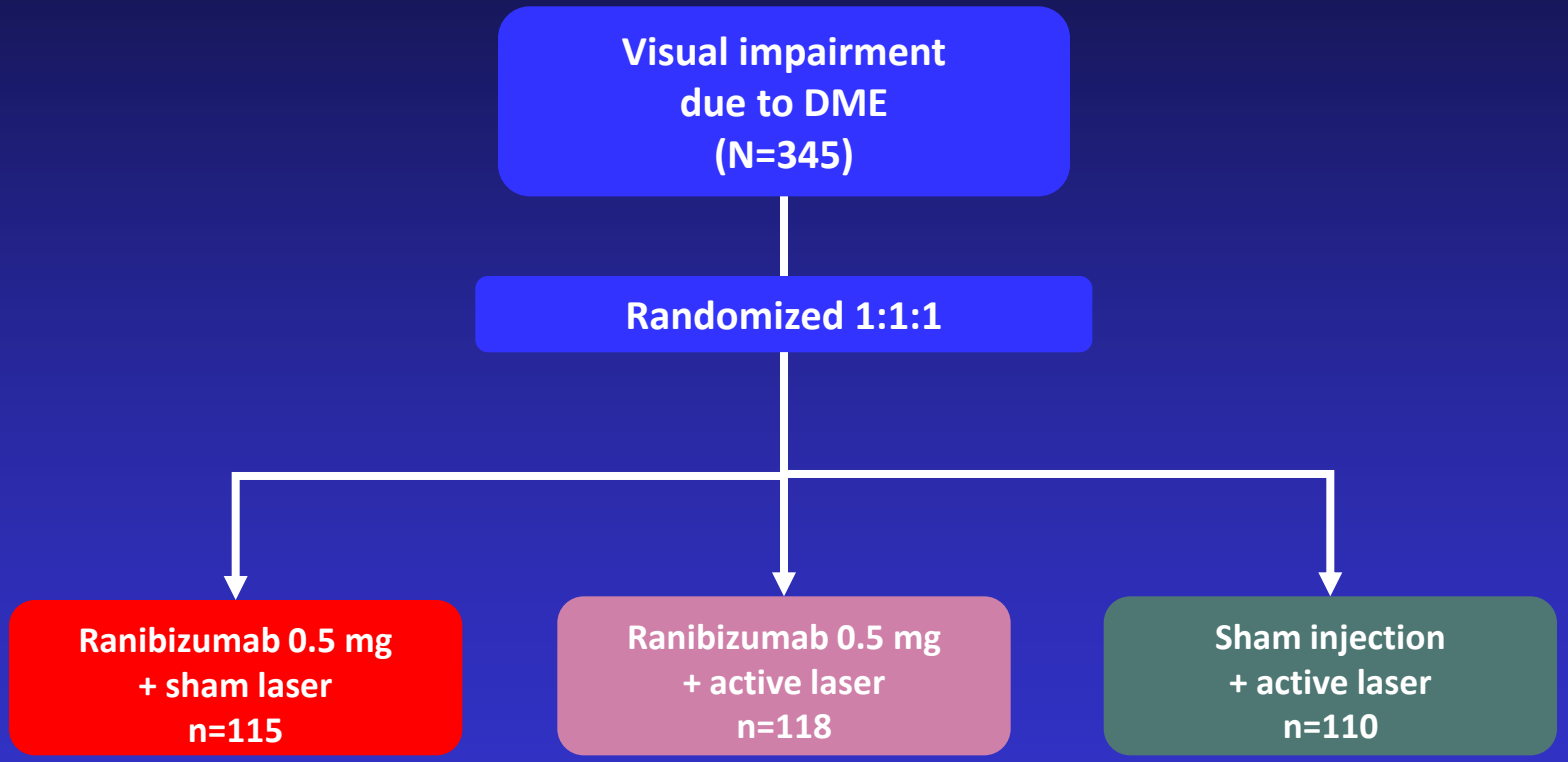
- RCT of 4-year duration including 196 eyes with refractory DME
- Patients randomized 2:1
  - 0.59-mg FA implant (n = 127)
  - standard of care (SOC) -additional laser or observation- (n = 69)
- VA improved ≥3 lines in:
  - 16.8% of implanted eyes at 6 mos (P=0.0012; SOC, 1.4%)
  - 16.4% at 1 year (P=0.1191; SOC, 8.1%)
  - 31.8% at 2 years (P=0.0016; SOC, 9.3%)
  - 31.1% at 3 years (P=0.1566; SOC, 20.0%)
- 61.4% IOP ≥30 mmHg in (SOC, 5.8%) at any time
- 33.8% requiring surgery for ocular hypertension by 4 years
- 91% phakic eyes cataract extraction by 4 years (SOC, 20%)

Pearson PA. Ophthalmology 2011

Anti-VEGF Drugs

- Ranibizumab
- Bevacizumab
- Pegaptanib
- VEGF-Trap

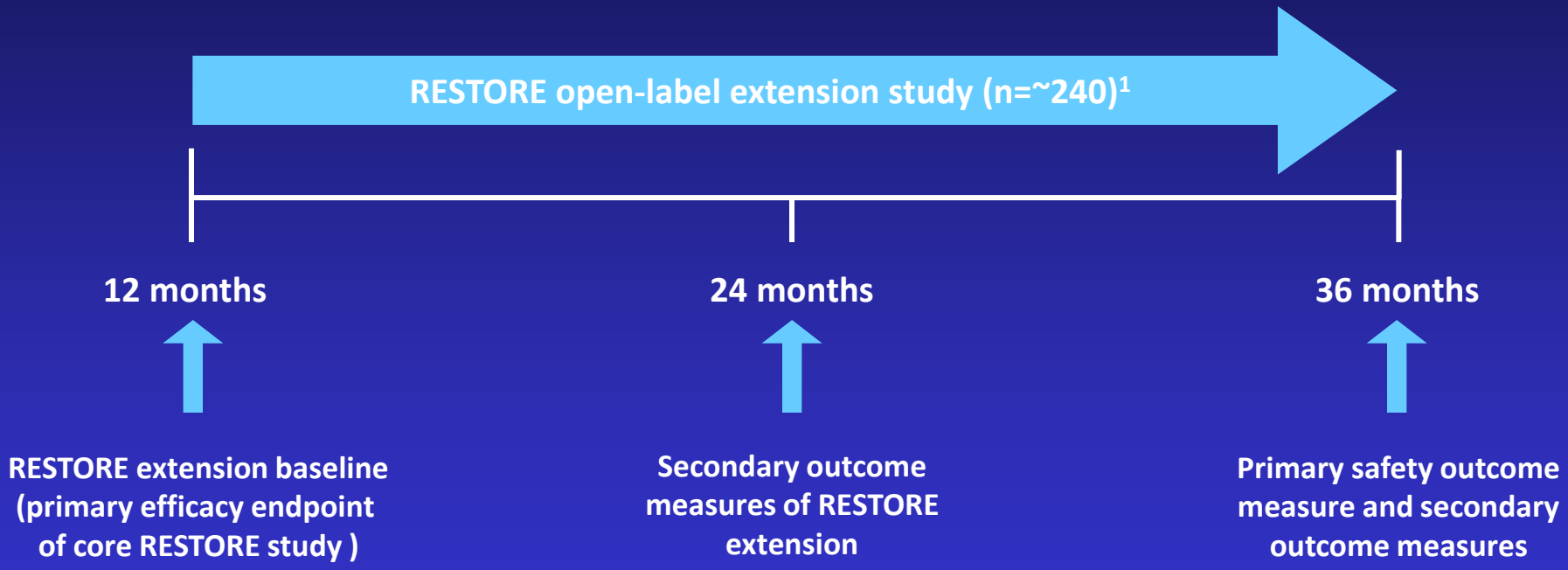
RESTORE: Phase III Trial



Active/sham laser treatment was administered before sham/intravitreal injection on the same day (minimum interval between the 2 treatments was 30 minutes)

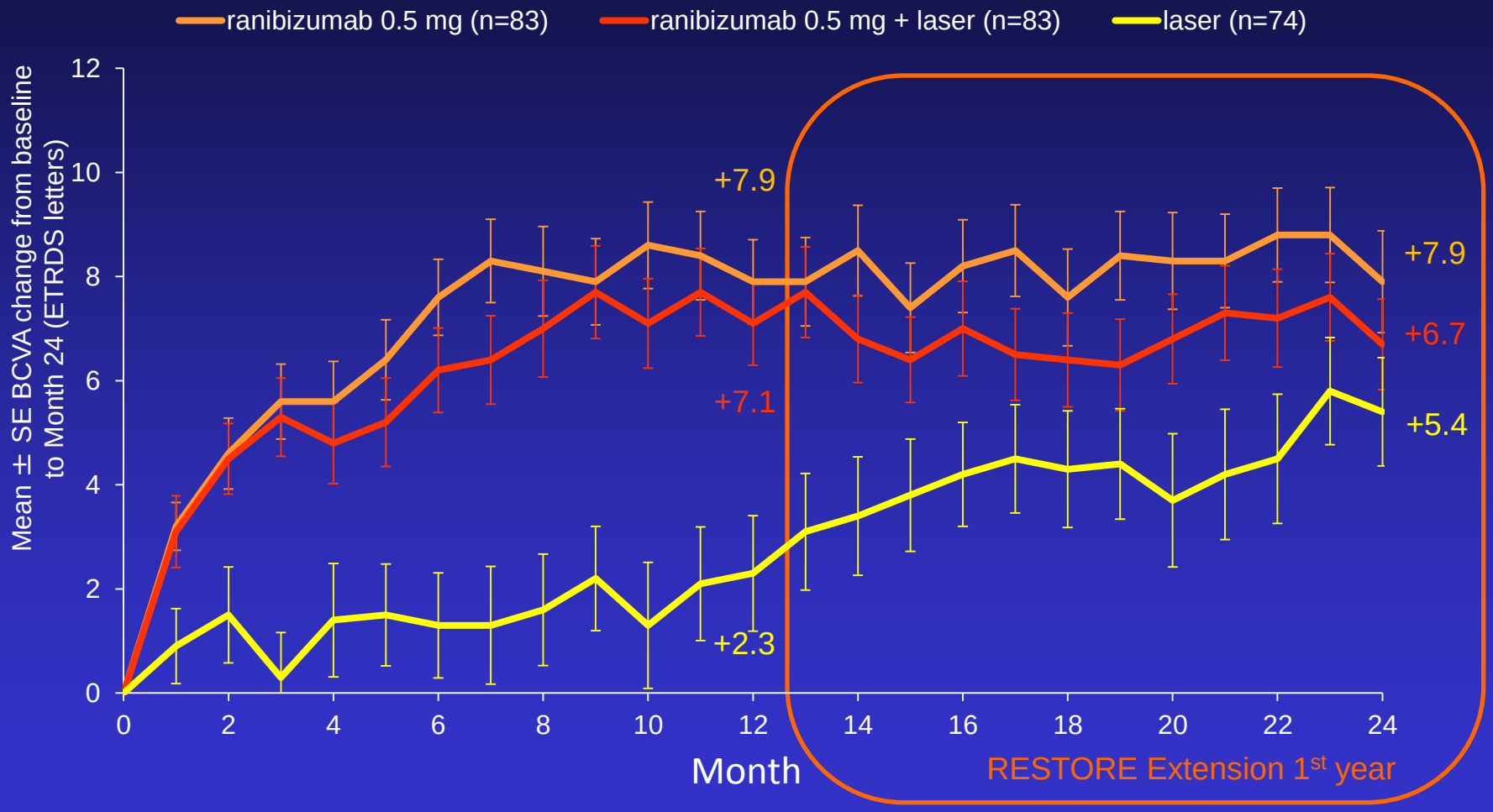
Mitchell P, Bandello F, Schlingheman R. Ophthalmology 2011

Evidence for Long-Term Safety of Ranibizumab: Ongoing RESTORE Extension



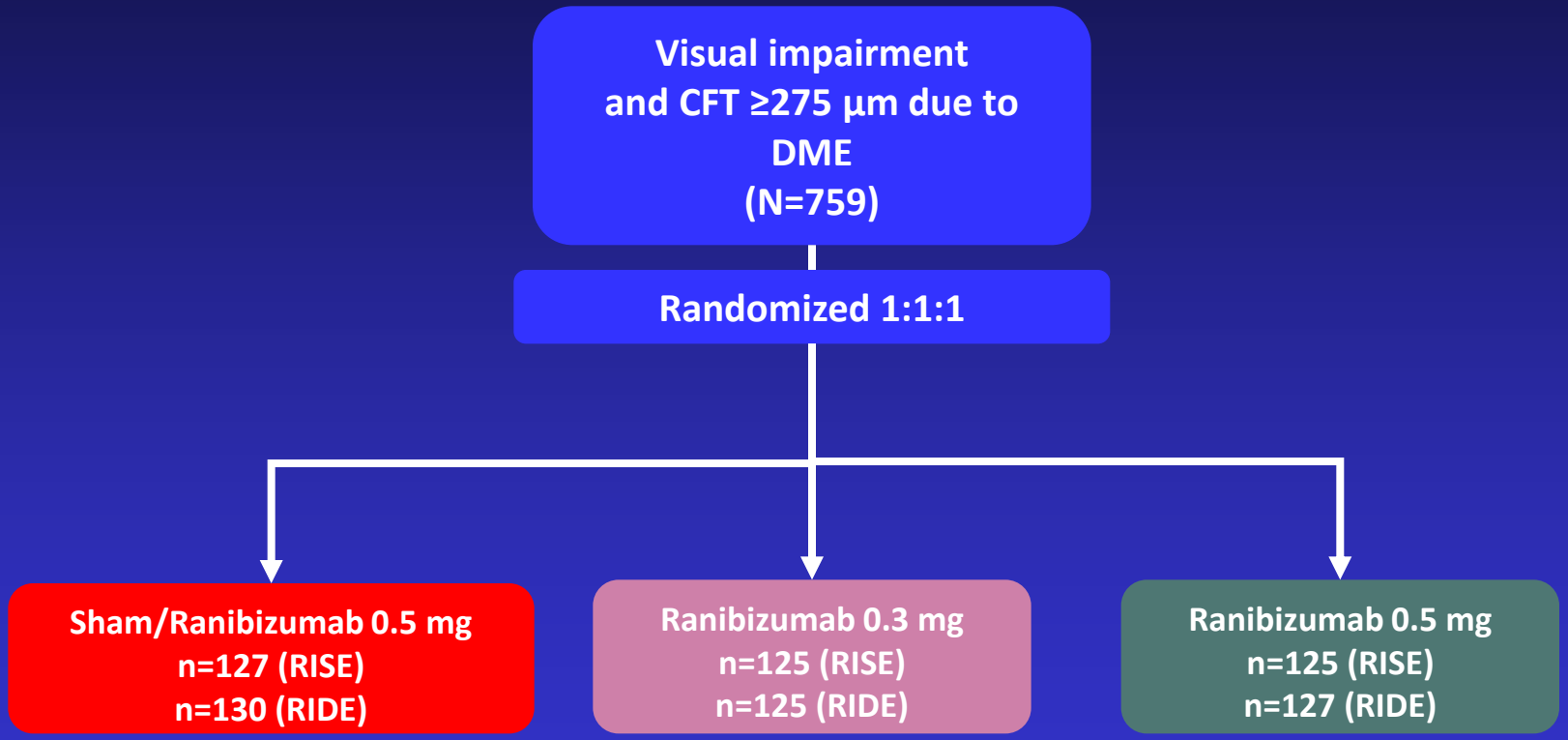
The primary outcome measure is the incidence of AEs during the 24-month extension phase only

Mean BCVA Change from Core Study Baseline Over Time



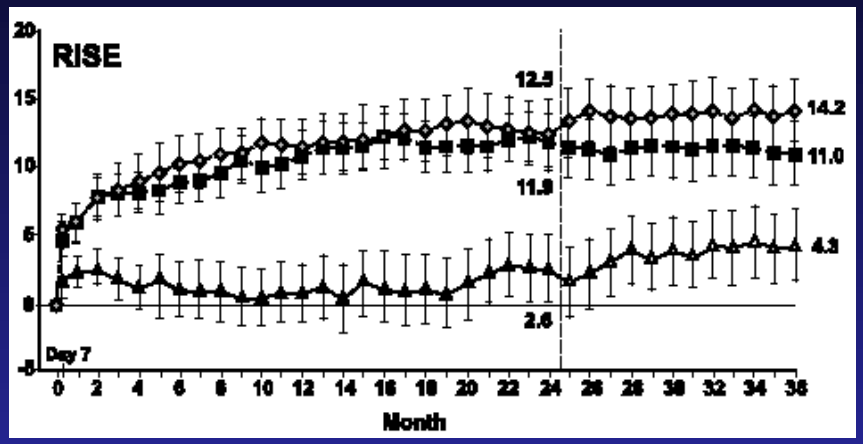
- Study treatment during the extension phase (Month 12 onwards) is open label ranibizumab 0.5 mg intravitreal injections
- Patients in all treatment groups (including “Laser”) can be administered ranibizumab 0.5 mg from Month 12 onwards

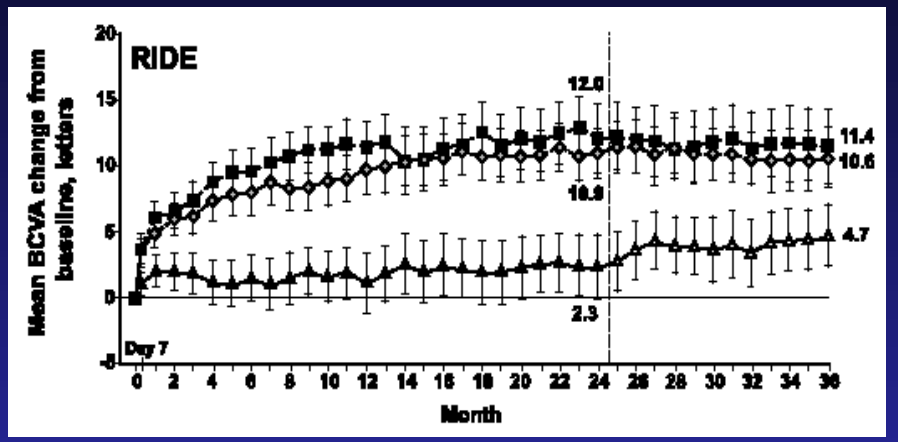
RISE and RIDE: 36-months long-term outcomes from two phase III trials

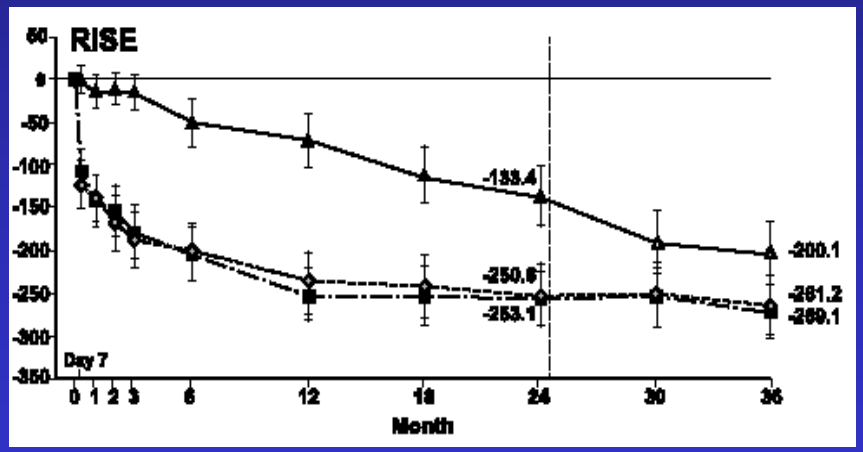


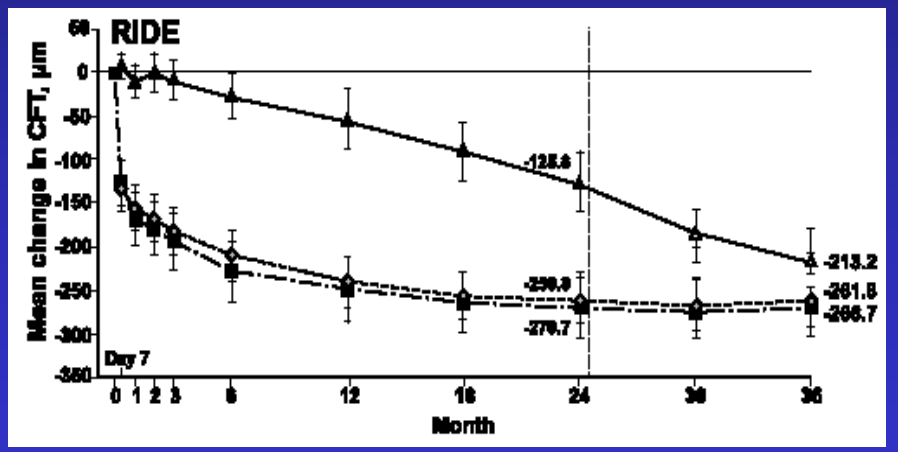
Brown DM. RISE and RIDE Research Group. Ophthalmology 2013

RISE and RIDE Mean BCVA and CFT Changes





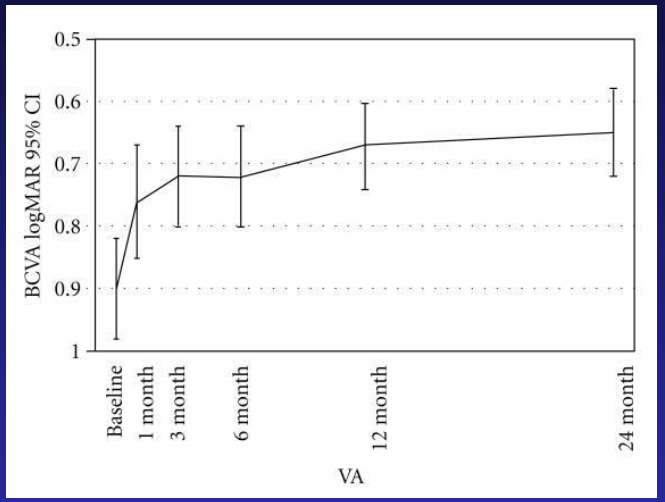




Sham — Sham/0.5 mg — Ranibizumab 0.3 mg — Ranibizumab 0.5 mg

Brown DM. RISE and RIDE Research Group. Ophthalmology 2013

Bevacizumab for Diffuse DME



- Retrospective, multicenter, case series
- 115 consecutive patients (139 eyes)
- At least 1 IVB 1.25 or 2.5 mg
- In 1.25 mg subgroup: BCVA 20/150 → 20/75
- In 2.5 mg subgroup: BCVA 20/168 to 20/114
- No difference between IVB 1.25 or 2.5 mg
- 5.8 mean # IVB injections per eye (range: 1-15)

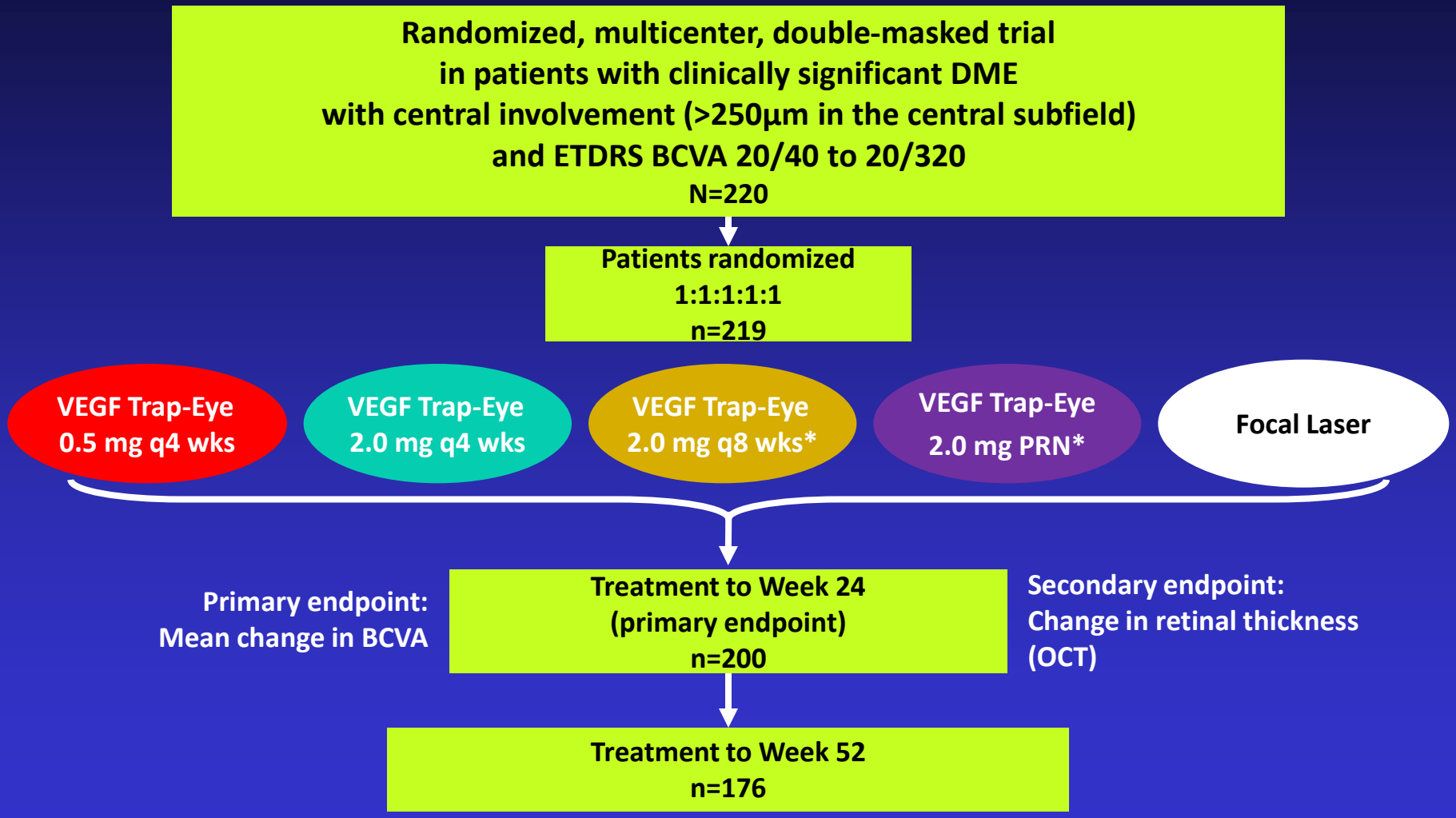
Arevalo JF . Pan-American Collaborative Retina Study Group. Ophthalmology 2010

Bevacizumab vs Laser for DME

- RCT including 80 eyes presenting DME
- 24 months follow-up
- Randomization to:
  - IVB (6 weekly)
  - Grid laser
- IVB group gained a mean of 9 letters
- Grid laser group gained a mean of 2.5 letters
- CMT decreased of 146µm in IVB group, and of 118 in grid laser group
- IVB superior to grid laser treatment

Rajendram R. BOLT study. Arch Ophthalmol 2012

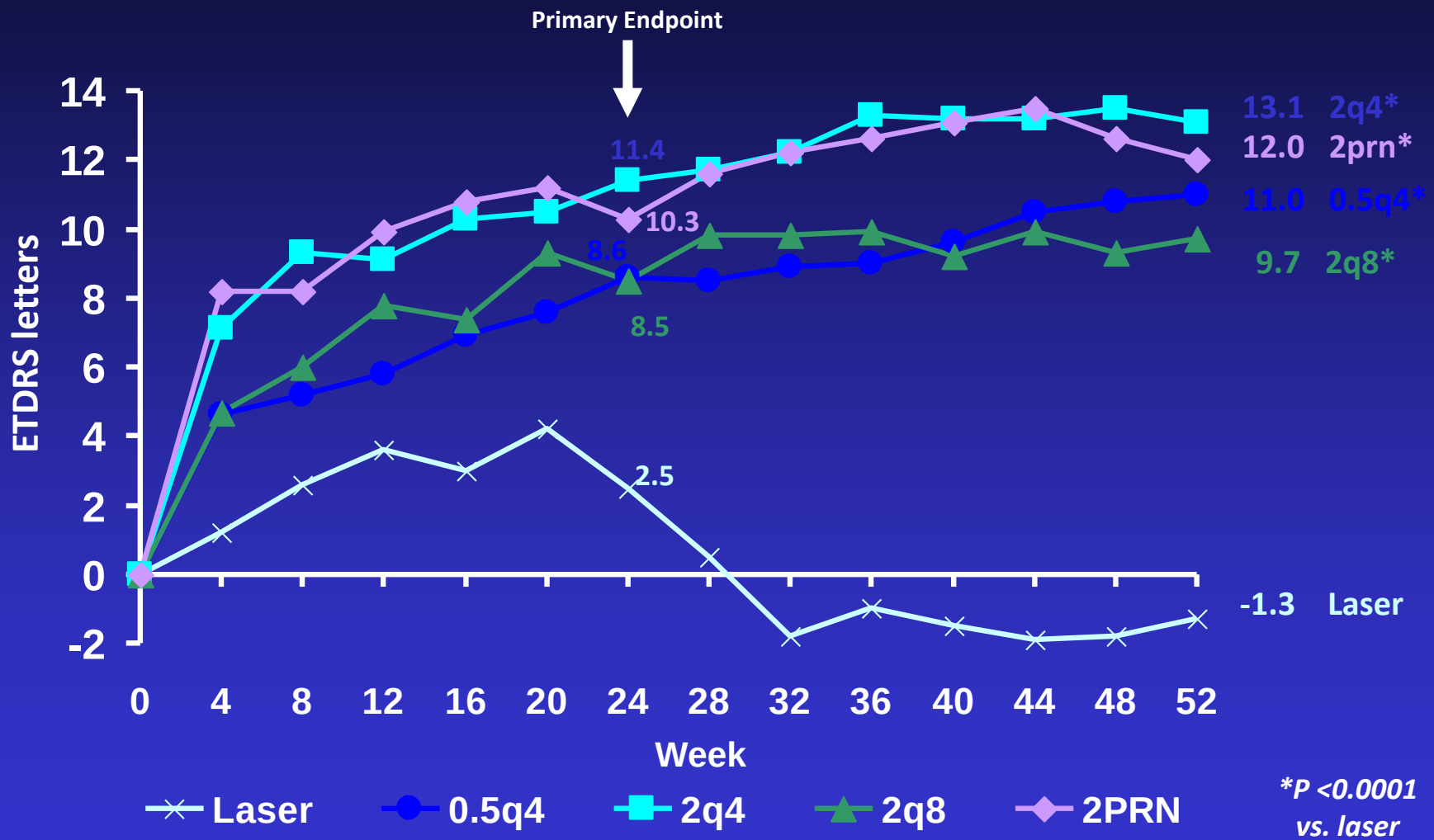
DA VINCI Study Design



*Following 3 monthly loading doses

Do DV. DA VINCI Study Group. Ophthalmology 2011

DA VINCI Study BCVA Changes



LOCF analysis; n=44 (laser, 0.5q4, 2q4); n=42 (2q8); n=45 (2prn)

**P <0.0001 vs. laser (ANCOVA)*
No statistical differences among VTE arms.

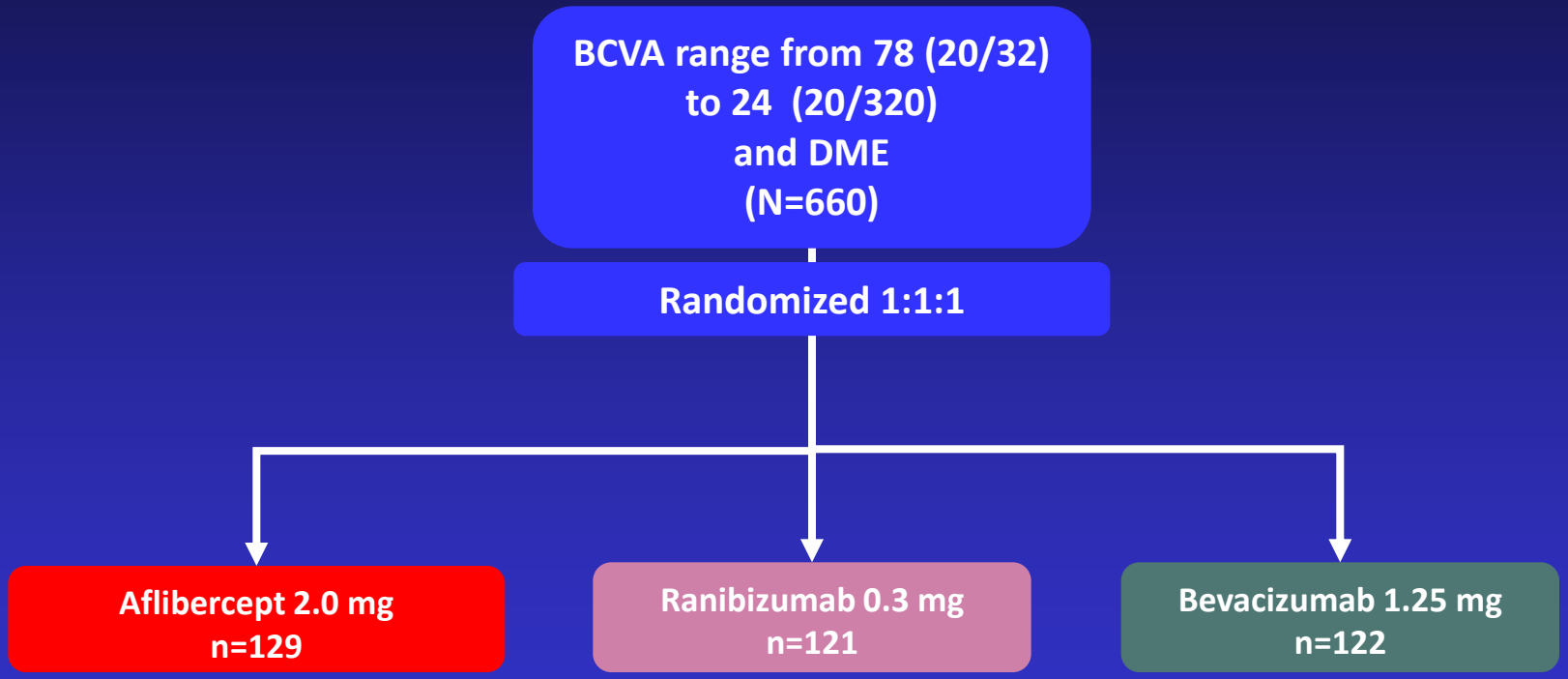
VISTA & VIVID Study

- RCT including 872 eyes from 2 different cohorts
- 12 months follow-up
- Randomization to:
  - IV Aflibercept 0.2 mg 4 weekly
  - IV Aflibercept 0.2 mg 8 weekly
  - Laser therapy

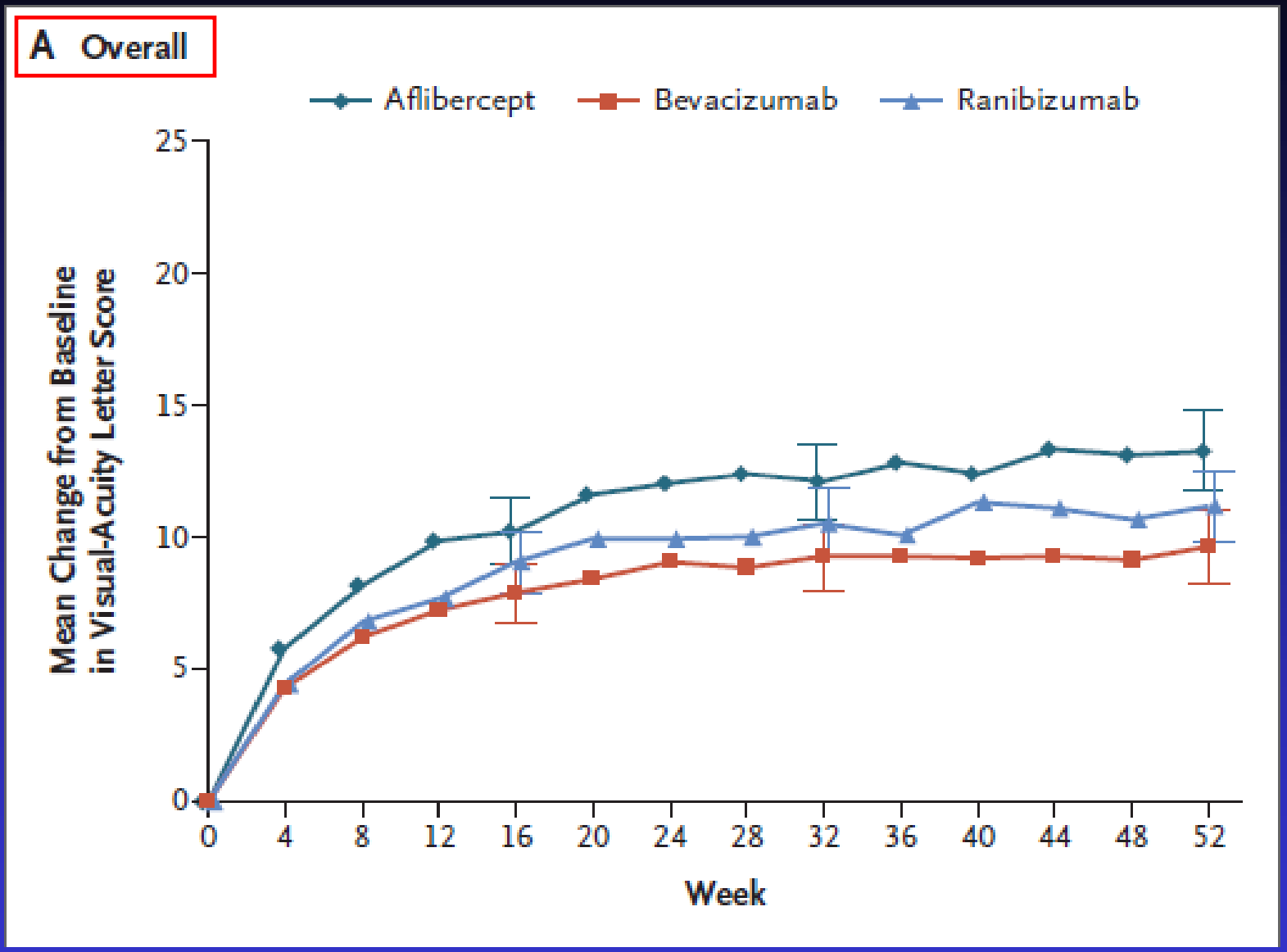
- Aflibercept superior to laser treatment in improving VA
- No difference of efficacy between 4 and 8 weekly
- Difference in terms on # of injections

Korobelnick JF. Ophthalmology 2014

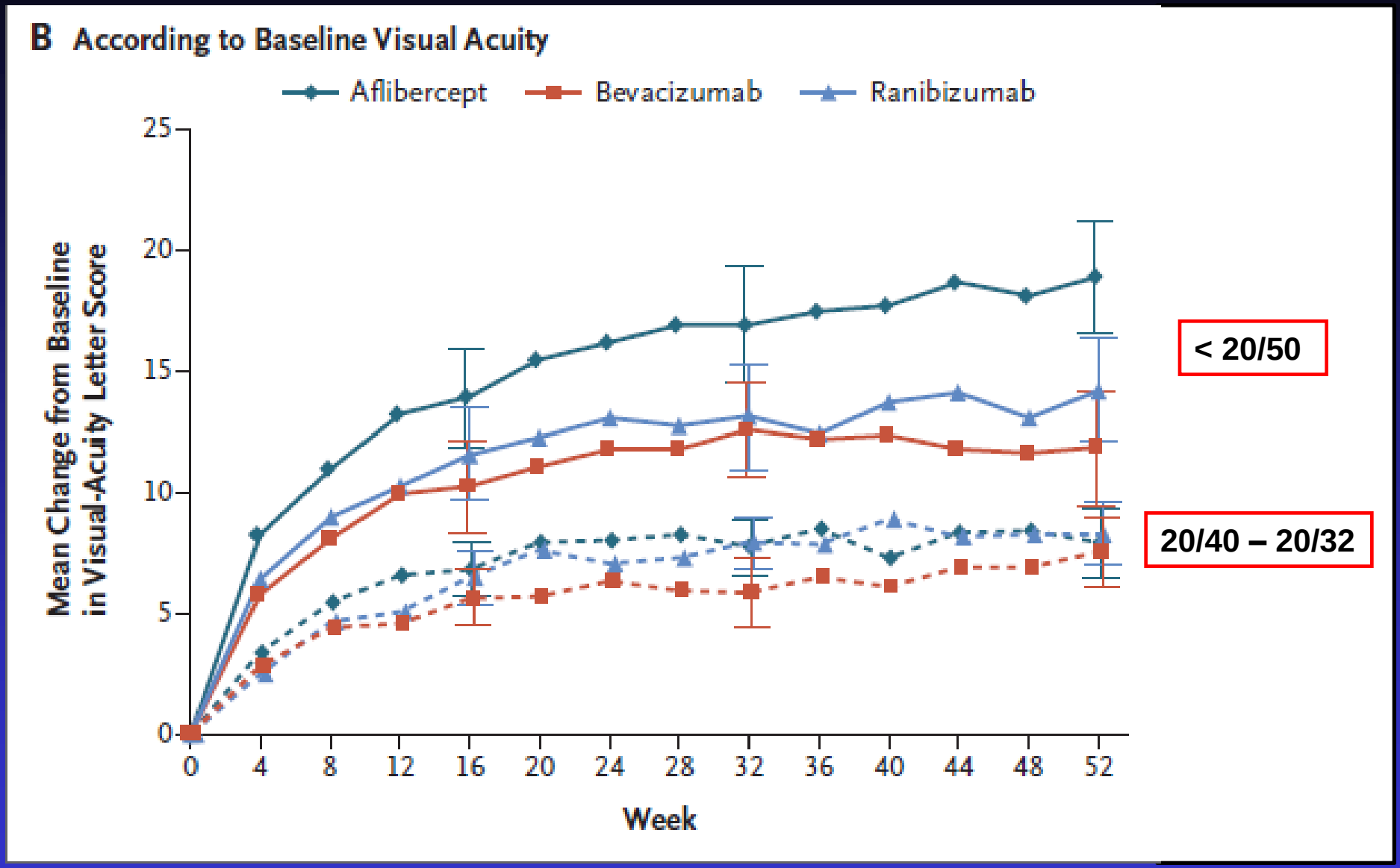
DME and anti-VEGF *DRCR.net* clinical *trial*



DRCRnet. NEJM 2015



DRCR net. NEJM 2015



DRCR net. NEJM 2015

Table 1. Visual-Acuity Outcomes.*

Visual-Acuity Letter Score and Snellen Equivalent	Aflibercept	Bevacizumab	Ranibizumab	Aflibercept vs. Bevacizumab		Aflibercept vs. Ranibizumab		Ranibizumab vs. Bevacizumab	
				Difference (95% CI)	P Value	Difference (95% CI)	P Value	Difference (95% CI)	P Value
Letter score of 78 to 69, equivalent to 20/32 to 20/40, at baseline									
No. of eyes	106	104	105						
Visual acuity at baseline									
Mean letter score	73.5±2.6	72.8±2.9	73.4±2.7						
Approximate Snellen equivalent	20/32	20/40	20/40						
Visual acuity at 1 yr									
Mean letter score	81.4±8.3	79.9±10.1	81.6±6.8						
Approximate Snellen equivalent	20/25	20/25	20/25						
Change from baseline in letter score									
Mean improvement	8.0±7.6	7.5±7.4	8.3±6.8	0.7 (−1.3 to 2.7)	0.69	−0.4 (−2.3 to 1.5)	0.69	1.1 (−0.9 to 3.1)	0.69
Improvement of ≥10 — no. (%)	53 (50)	47 (45)	52 (50)	6 (−9 to 21)	0.82	0 (−13 to 14)	0.95	6 (−10 to 21)	0.82
Worsening of ≥10 — no. (%)	4 (4)	2 (2)	1 (1)	2 (−3 to 6)	0.54	3 (−1 to 7)	0.54	−1 (−4 to 2)	0.54
Improvement of ≥15 — no. (%)	19 (18)	17 (16)	16 (15)	2 (−7 to 11)	0.73	4 (−5 to 12)	0.73	−2 (−10 to 7)	0.73
Worsening of ≥15 — no. (%)	2 (2)	1 (1)	1 (1)	1 (−2 to 4)	0.99	1 (−2 to 4)	0.99	0 (−3 to 3)	0.99

DRCR net. NEJM 2015

Table 1. Visual-Acuity Outcomes.*

Visual-Acuity Letter Score and Snellen Equivalent	Aflibercept	Bevacizumab	Ranibizumab	Aflibercept vs. Bevacizumab		Aflibercept vs. Ranibizumab		Ranibizumab vs. Bevacizumab	
				Difference (95% CI)	P Value	Difference (95% CI)	P Value	Difference (95% CI)	P Value
Letter score of <69, equivalent to 20/50 or worse, at baseline									
No. of eyes	102	102	101						
Visual acuity at baseline									
Mean letter score	56.2±11.1	56.6±10.6	56.5±9.9						
Approximate Snellen equivalent	20/80	20/80	20/80						
Visual acuity at 1 yr									
Mean letter score	75.2±10.9	68.5±13.6	70.7±12.0						
Approximate Snellen equivalent	20/32	20/40	20/40						
Change from baseline in letter score									
Mean improvement	18.9±11.5	11.8±12.0	14.2±10.6	6.5 (2.9 to 10.1)	<0.001	4.7 (1.4 to 8.0)	0.003	1.8 (−1.1 to 4.8)	0.21
Improvement of ≥10 — no. (%)	79 (77)	61 (60)	70 (69)	17 (2 to 31)	0.02	10 (−4 to 23)	0.20	7 (−6 to 20)	0.28
Worsening of ≥10 — no. (%)	1 (1)	4 (4)	2 (2)	−3 (−7 to 2)	0.56	−1 (−5 to 3)	0.56	−1 (−6 to 3)	0.56
Improvement of ≥15 — no. (%)	68 (67)	42 (41)	50 (50)	24 (9 to 39)	<0.001	18 (4 to 32)	0.008	6 (−7 to 19)	0.34
Worsening of ≥15 — no. (%)	1 (1)	2 (2)	2 (2)	0 (−3 to 3)	0.85	−1 (−4 to 2)	0.85	1 (−3 to 4)	0.85

DRCR net. NEJM 2015

Presentation Outline

- Epidemiologia
- Patogenesi
- Classificazione
- Imaging
- Terapia