Kocaeli-Mayıs 2015

DİABETİK RETİNOPATİ 'de DMÖ DIŞINDA Anti-VEGF'lerin ROLÜ VAR MI?

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DR'DE DMÖ DIŞI ANTİ-VEGF

- Dirençli NV'lerin tedavisinde
- Vitreus hemorajilerinin tedavisinde
- Ciddi NPDR ve PDR'nin tedavisinde kullanımı
- İris neovaskülerizasyonu ve neovasküler glokom tedavisinde

DRCR-Net'te DRP progresyonu

JAMA Ophthalmol. 2013 August ; 131(8): 1033–1040. doi:10.1001/jamaophthalmol.2013.4154.

Exploratory Analysis of Effect of Intravitreal Ranibizumab or Triamcinolone on Worsening of Diabetic Retinopathy in a Randomized Clinical Trial

Susan B. Bressler, MD[1], Haijing Qin, MS[2], Michele Melia, ScM[2], Neil M. Bressler, MD.[1], Roy W. Beck, MD, PhD[2], Clement K. Chan, MD[3], Sandeep Grover, MD[4], and David G. Miller, MD[5] for the Diabetic Retinopathy Clinical Research Network

[1]Wilmer Eye Institute, Johns Hopkins University School of Medicine

[2]Jaeb Center for Health Research

[3]Southern California Desert Retina Consultants

Kötüleşme kriterleri:

1. NPDR'den PDR'ye gidiş
2. Başlangıçta PDR yokken şiddet seviyesinde 2 veya> artış
3. Panretinal LASER uygulanması
4. Vitreus kanaması
5. Vitrektomi uygulanması

DR'de KÖTÜLEŞME (3 yıllık kümülatif olasılık)

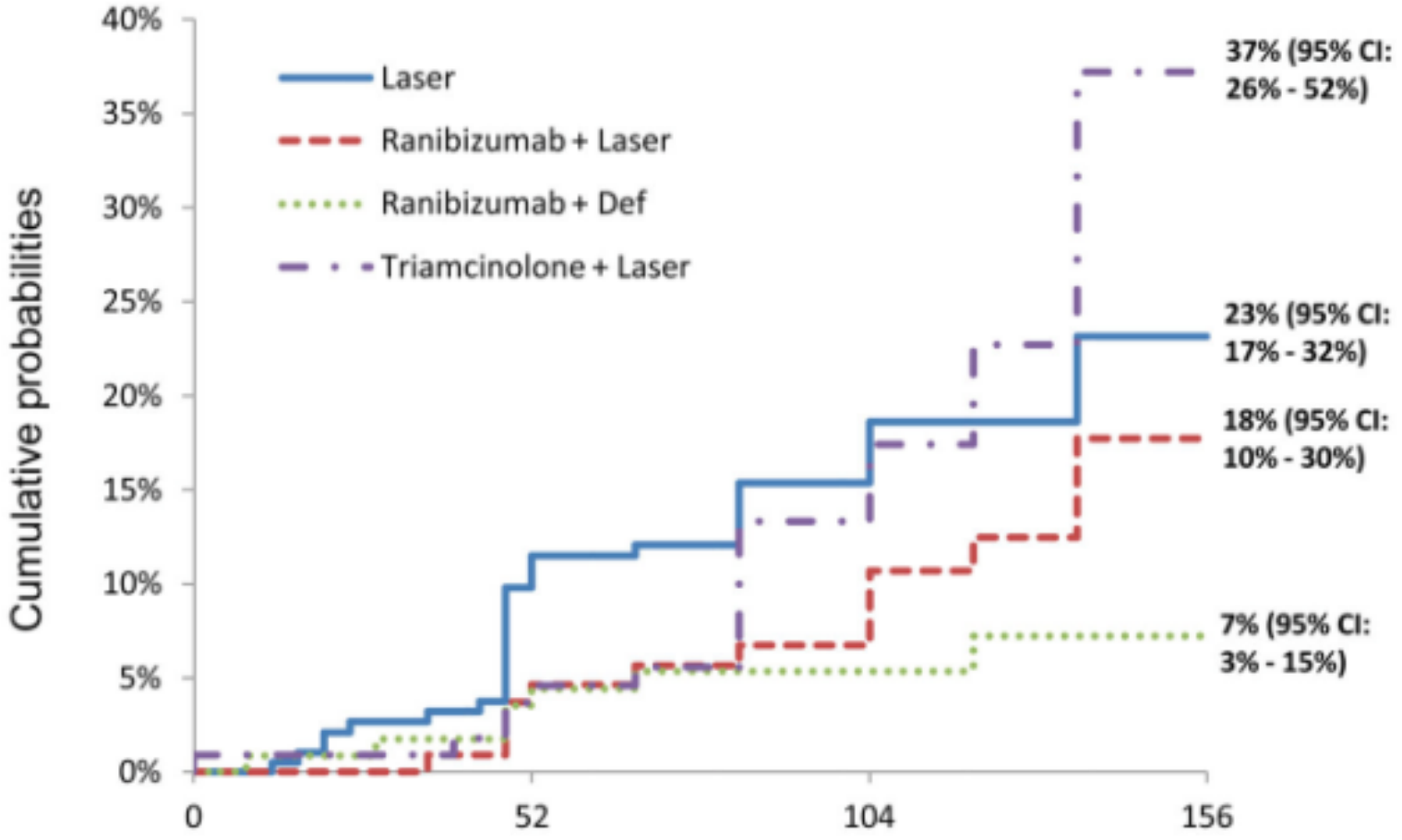
Başlangıçta PDR olmayanlarda

- Sham + laser grubunda % 23
- Ranibizumab + erken laser gr: % 18
- Ranibizumab + geç laser gr: % 7
- Triamsinolon + erken laser gr: % 37

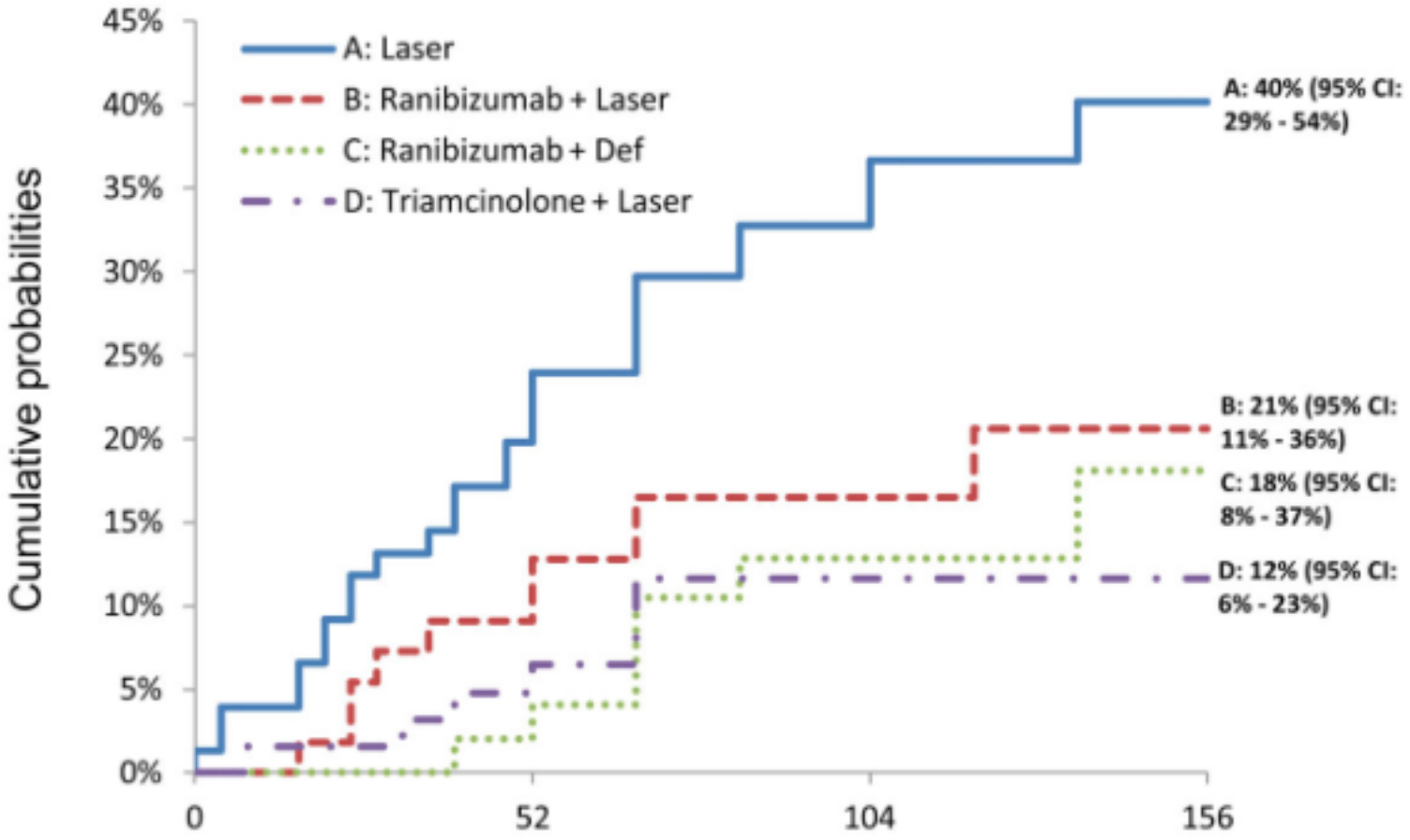
Başlangıçta PDR olanlarda

- Sham + laser grubunda % 40
- Ranibizumab + erken laser gr: % 21
- Ranibizumab + geç laser gr: % 18
- Triamsinolon + geç laser gr: % 12

Başlangıçta PDR olmayan gözlerde



Başlangıçta PDR olan gözlerde



DRCR-Net
Yeni Planlanan Çalışma

- NCT01489189

- Prompt PRP vs Ranibizumab+Deferred PRP for PDR

RISE/RIDE
DRP progresyonu

Arch Ophthalmol, 2012

CLINICAL SCIENCES

ONLINE FIRST

Long-term Effects of Ranibizumab on Diabetic Retinopathy Severity and Progression

Michael S. Ip, MD; Amitha Domalpally, MD; J. Jill Hopkins, MD; Pamela Wong, MPH; Jason S. Ehrlich, MD, PhD

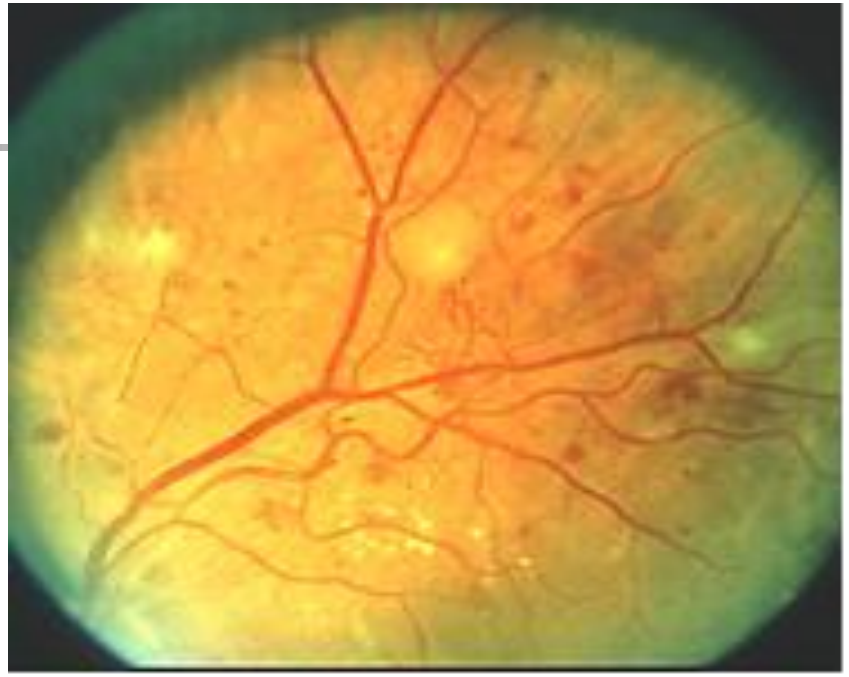
Objective: To evaluate effects of intravitreal ranibizumab on diabetic retinopathy (DR) severity over time in 2 phase 3 clinical trials (RIDE, NCT00473382; RISE, NCT00473330) of ranibizumab for diabetic macular edema.

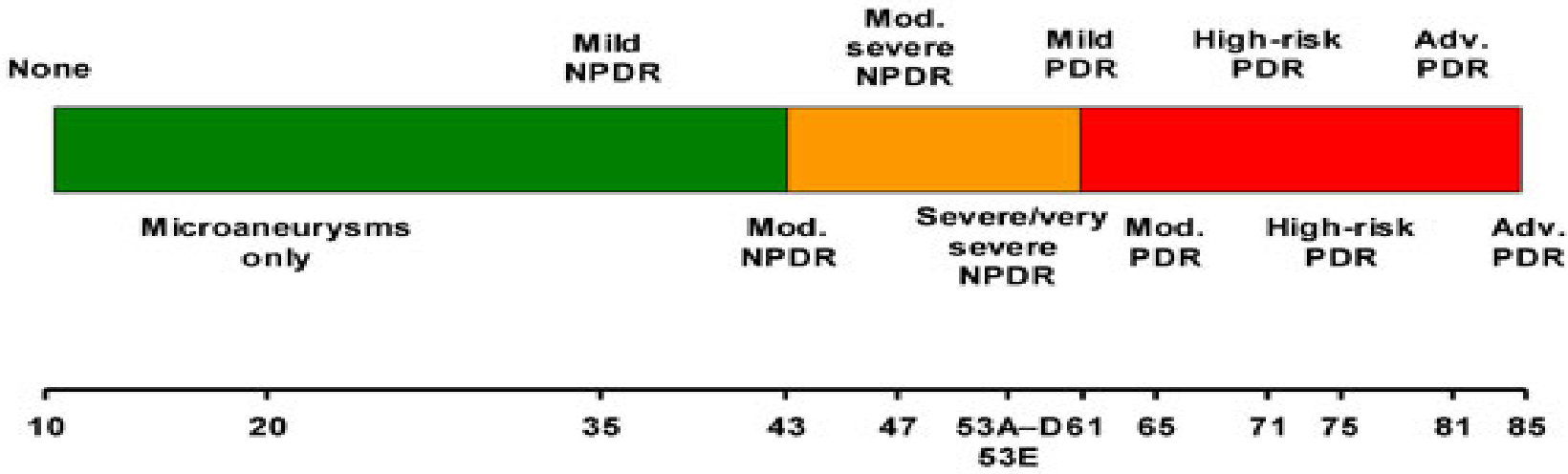
Results: At 2 years, the percentage of participants with DR progression (worsening by ≥2 or ≥3 steps) was significantly reduced in ranibizumab-treated eyes compared with sham-treated eyes, and DR regression (improving by ≥2 or ≥3 steps) was significantly more likely. The cumu-

9 step ETDRS severity scale

20. düzey

53. düzey

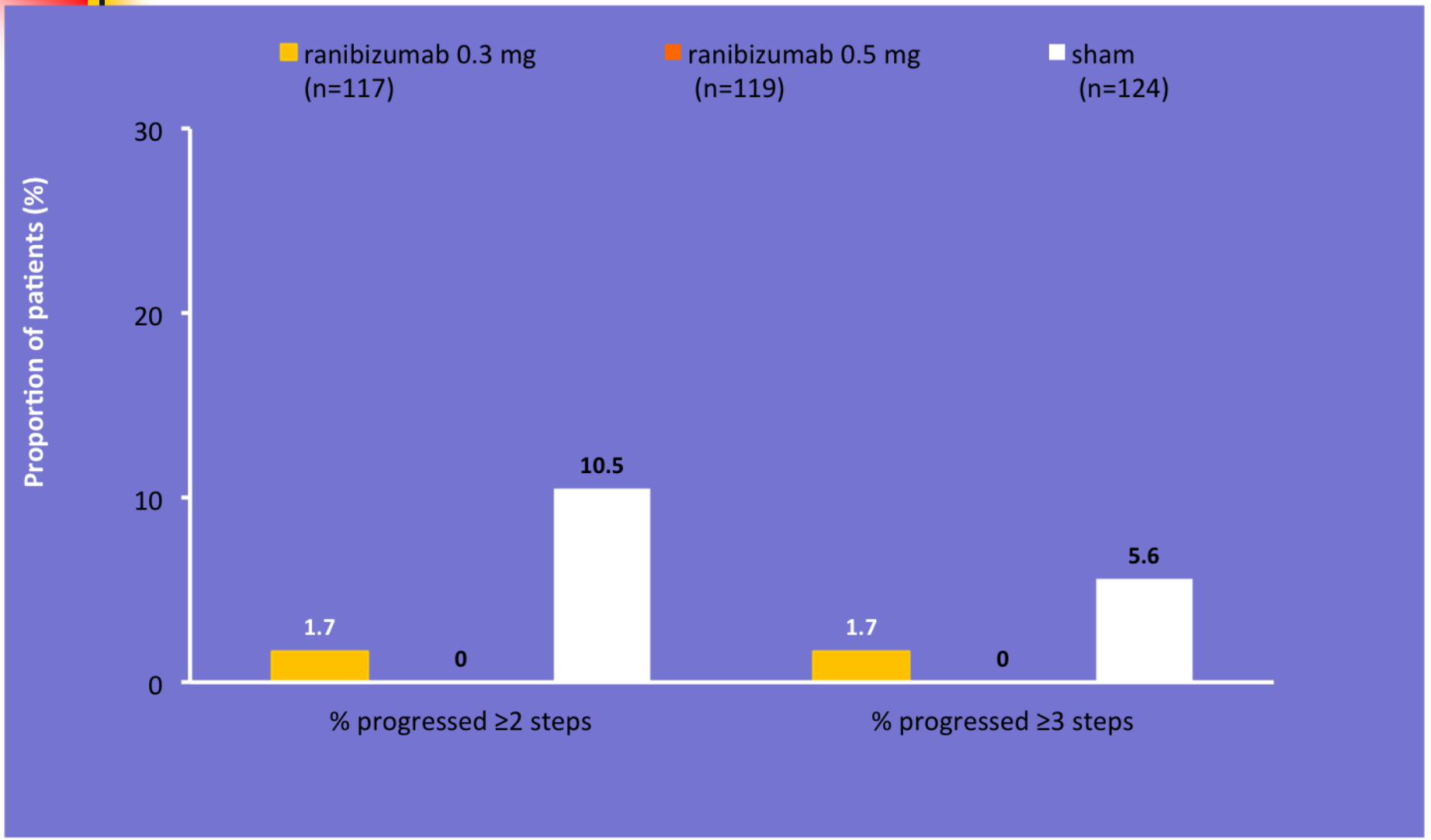




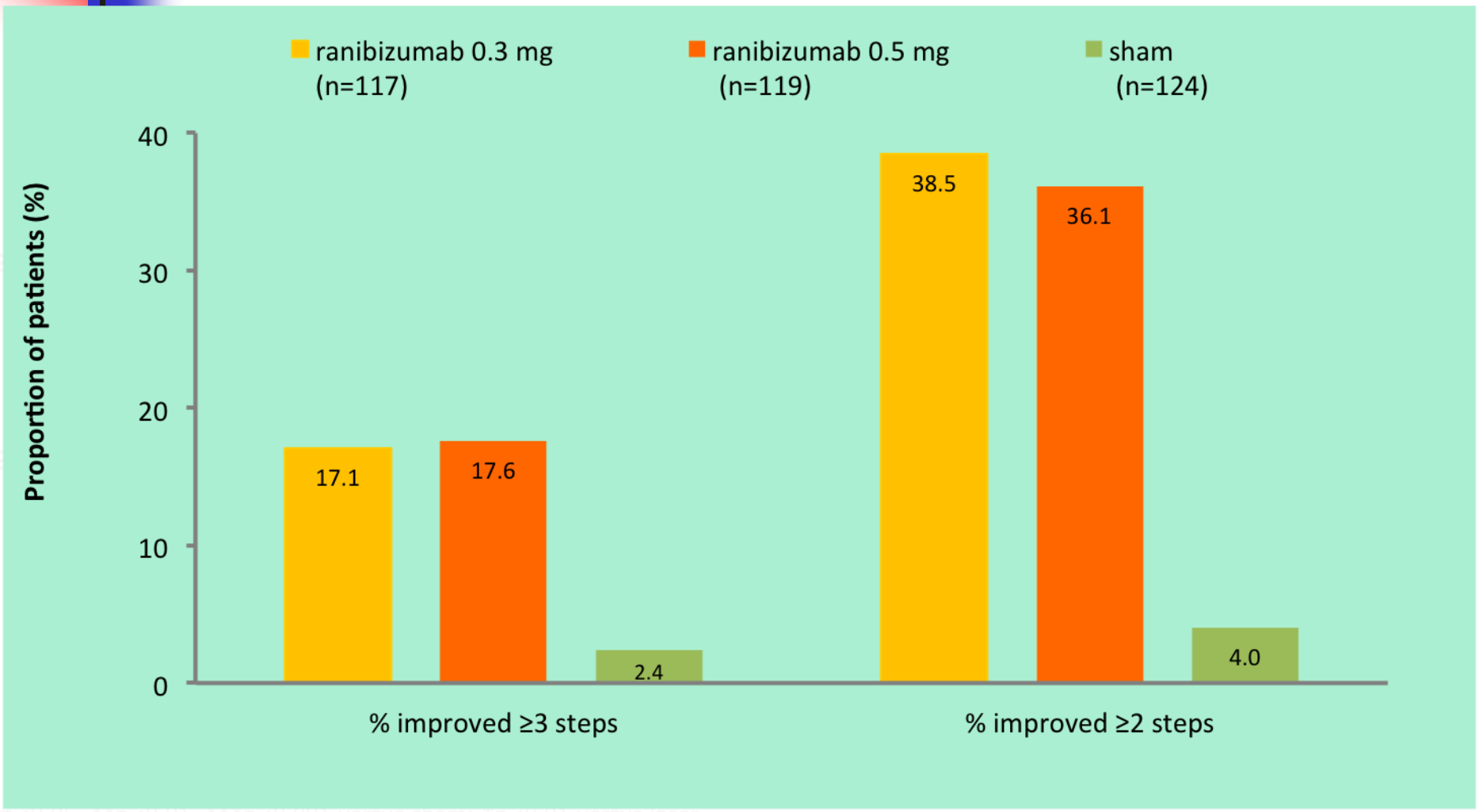
Klinik anlamlı kötüleşme

- RFF de NPDR'den PDR'ye ilerleme
- PRP uygulanması
- Vitreus kanaması görülmesi
- PPV yapılması
- RI gelişimi

24 ay sonunda median DR şiddet seviyesinde ilerleme



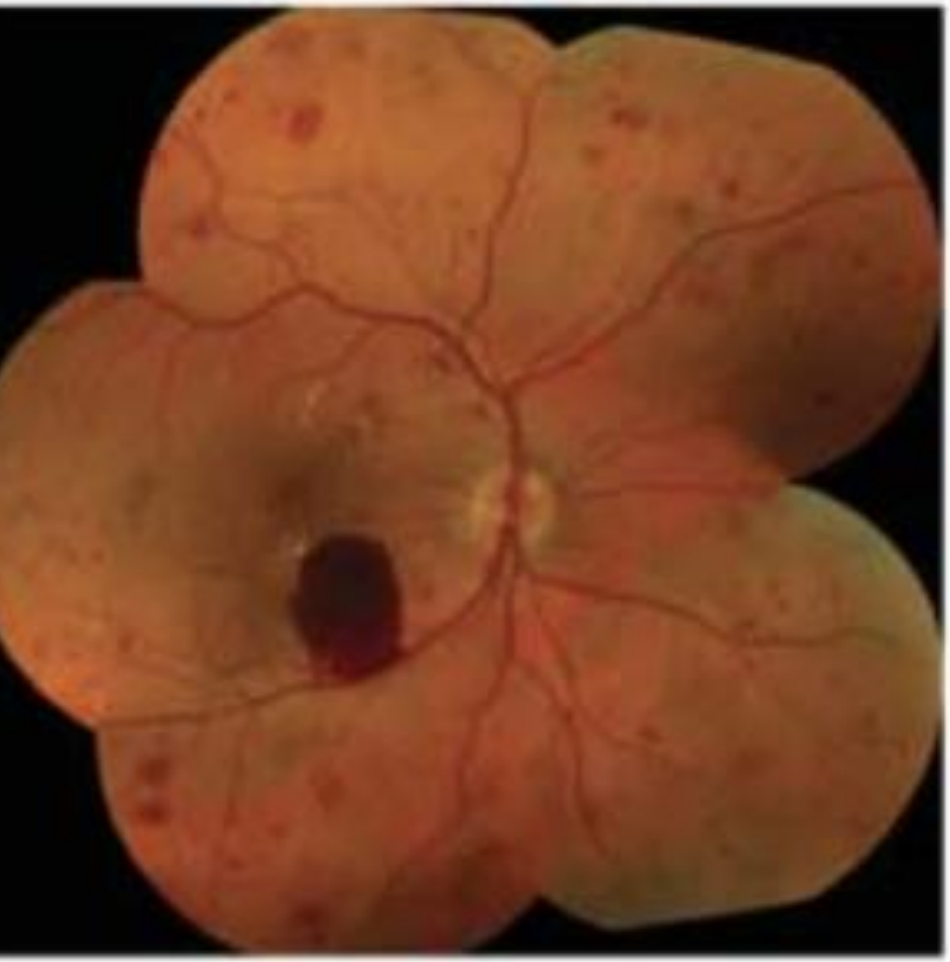
DMÖ'lü Hastalarda DR Şiddetinde Azalma

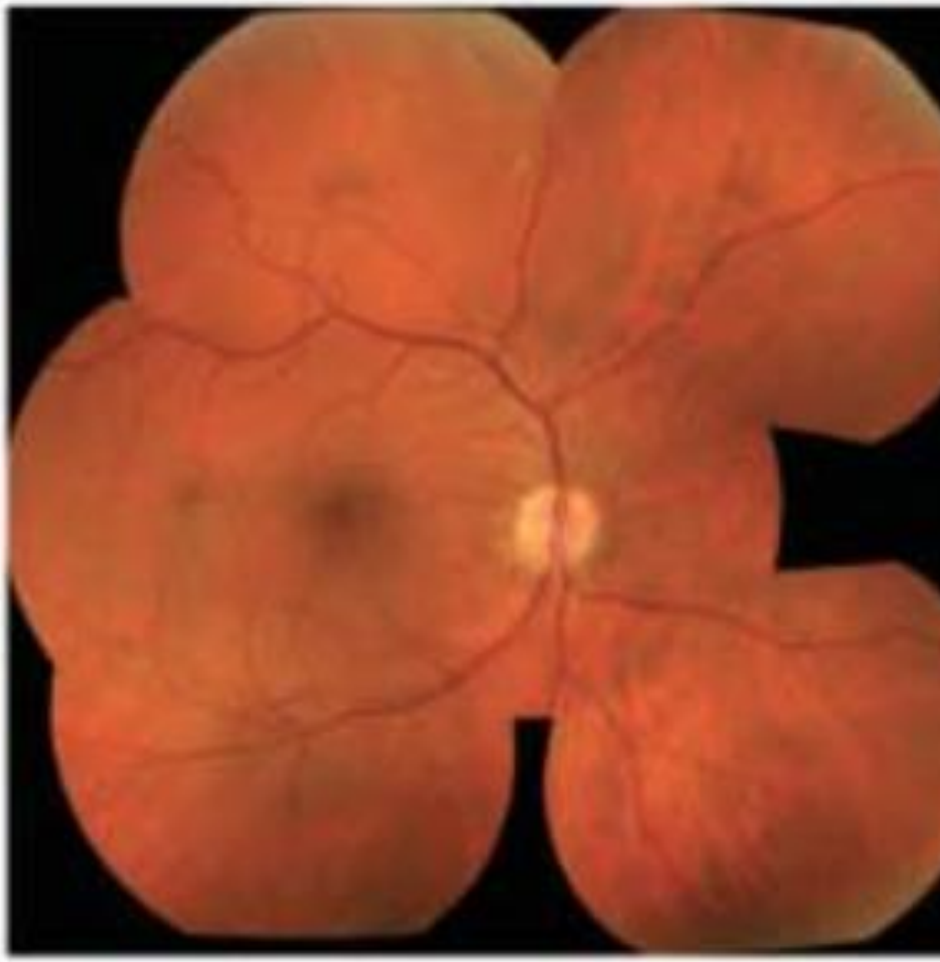


*p<0.05, **p<0.01, ***p<0.001 versus sham; †p<0.01 versus laser
DR, diyabetik retinopati; DRSS, diabetic retinopathy severity scale

Baseline

Month 24





High-risk PDR (level 71A)

Mild NPDR (level 35E)

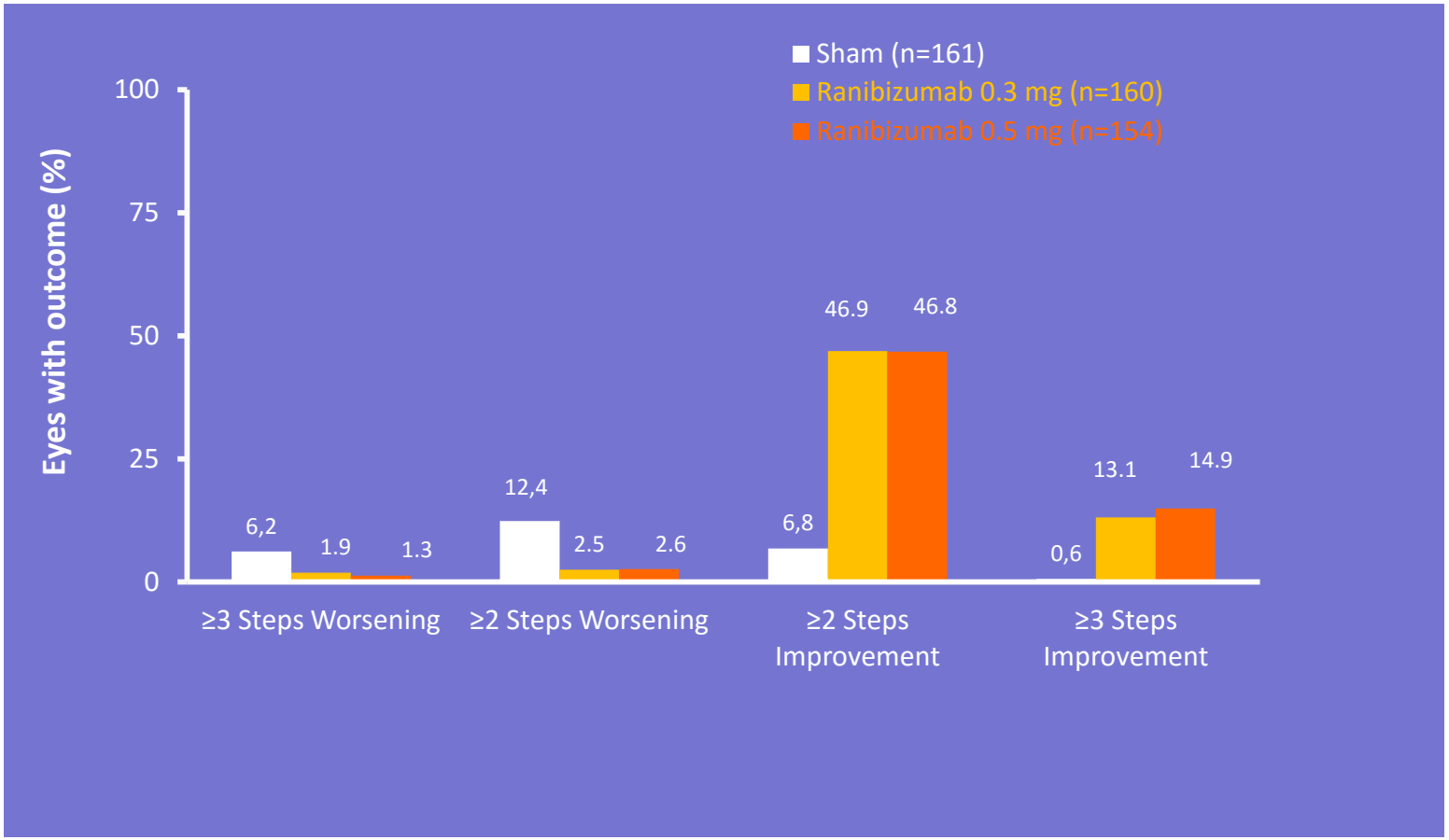
Başlangıç

24. ay

Mild PDR (level 61B)

Mild NPDR (level 35F)

Non-PDR olanlarda daha da iyi! (≤53E) RISE-RIDE-24 ay



AMERICAN ACADEMY OF OPHTHALMOLOGY
The Eye M.D. Association

Long-term Effects of Therapy with Ranibizumab on Diabetic Retinopathy Severity and Baseline Risk Factors for Worsening Retinopathy

Michael S. Ip, MD,[1] Amitha Domalpally, MD,[1] Jennifer K. Sun, MD, MPH,[2] Jason S. Ehrlich, MD, PhD[3]

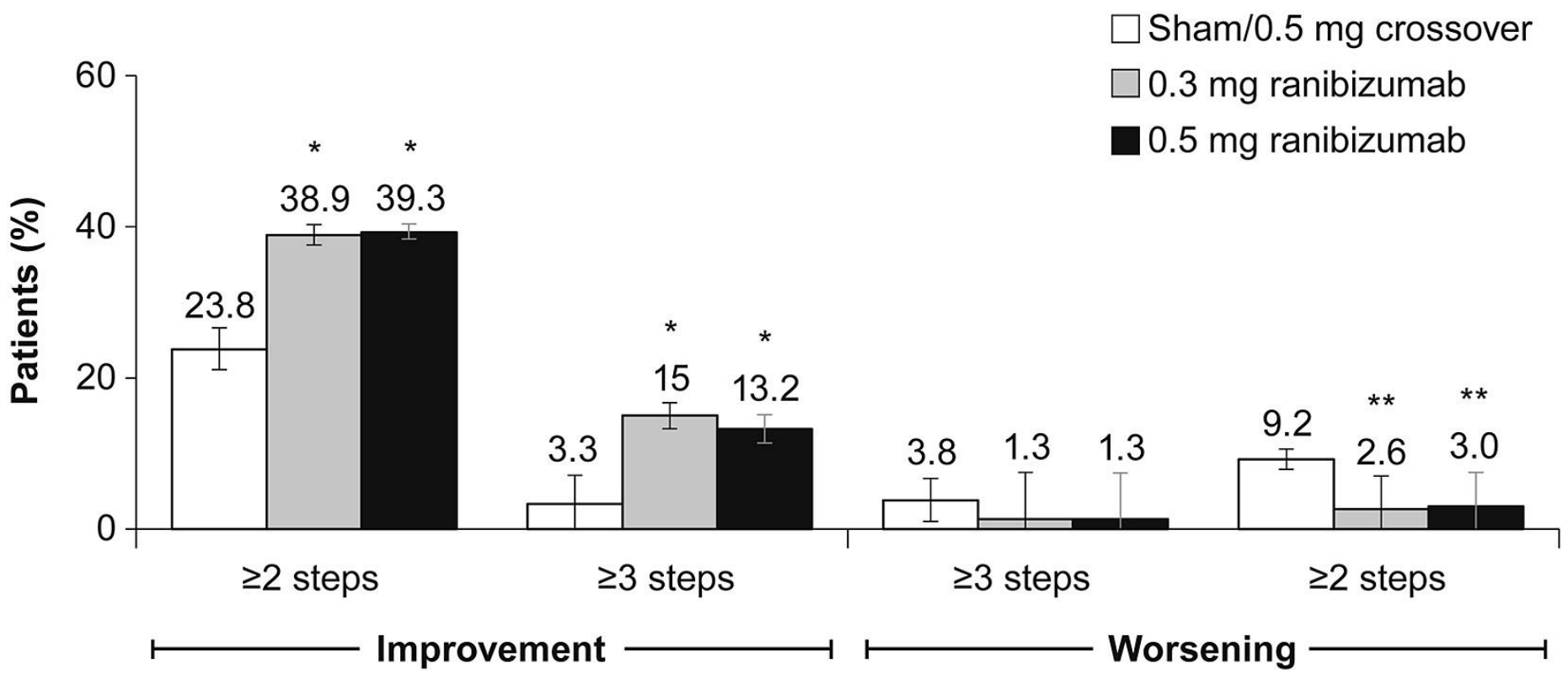
Purpose: To assess the effects of intravitreal ranibizumab on diabetic retinopathy (DR) severity when administered for up to 3 years, evaluate the effect of delayed initiation of ranibizumab therapy on DR severity, and identify baseline patient characteristics associated with the development of proliferative DR (PDR).

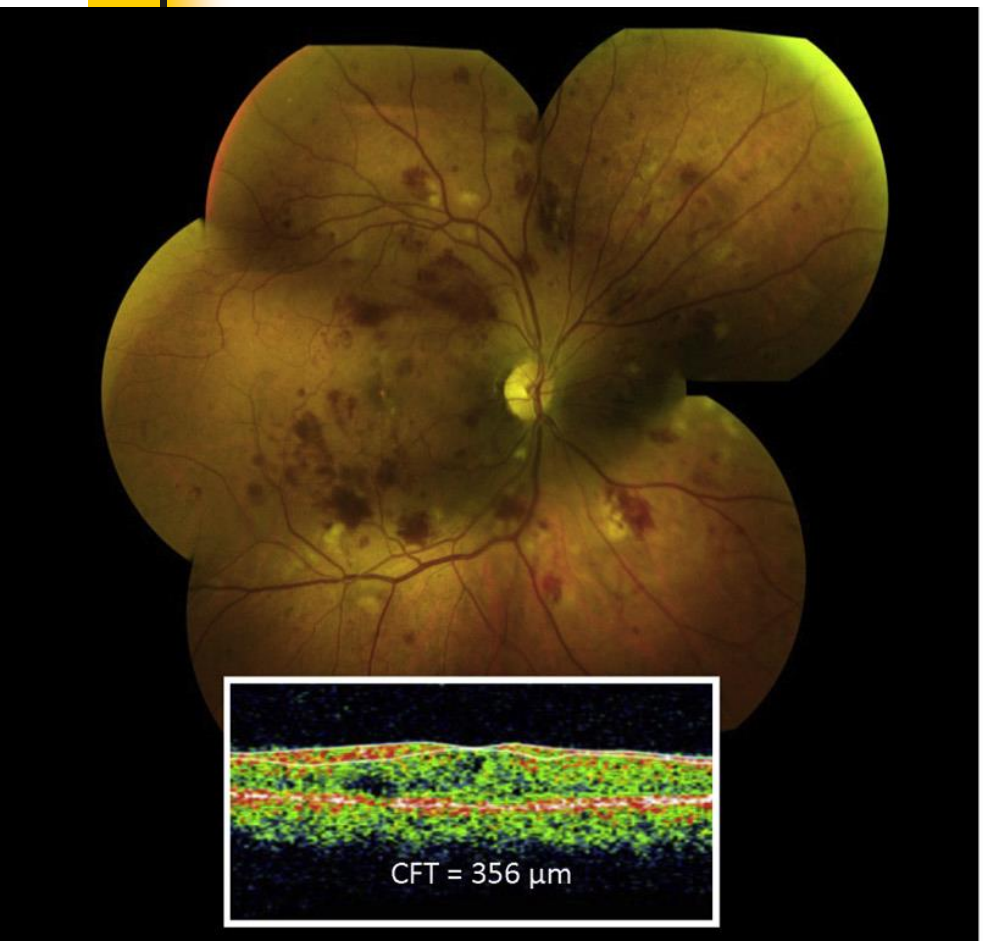
Design: Exploratory analyses of phase III, randomized, double-masked, sham-controlled multicenter clinical trials.

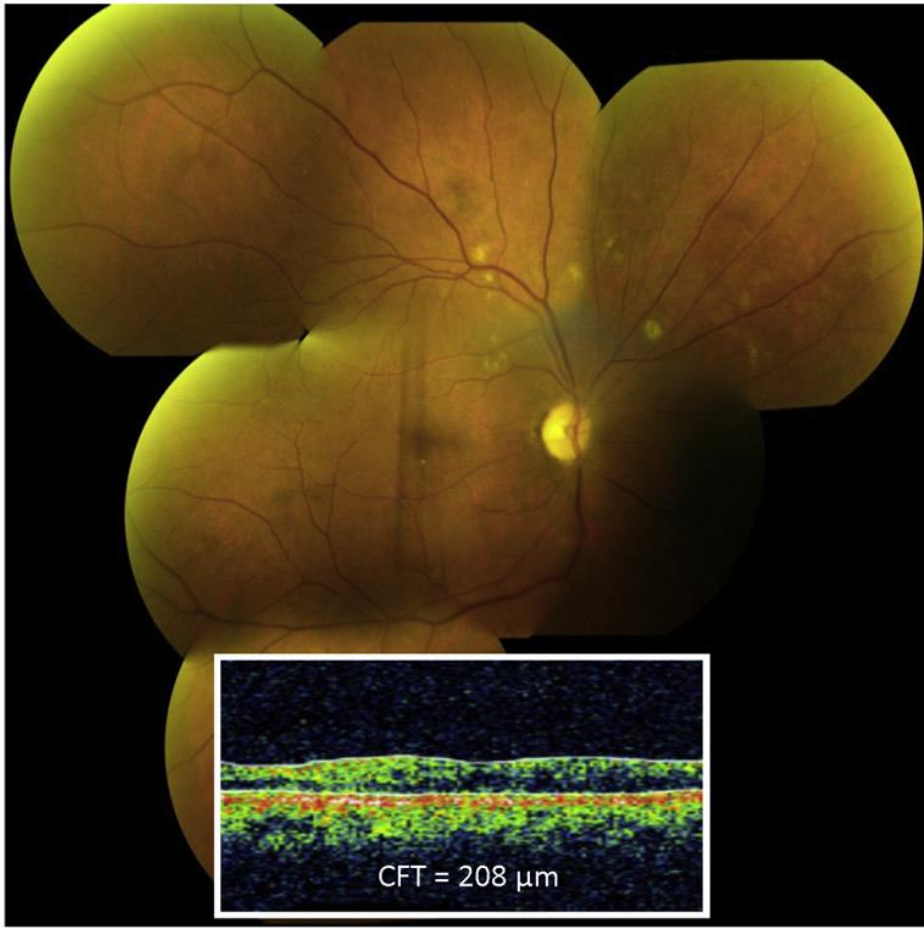
Ophthalmology Volume 122, Issue 2, Pages 367-374 (February 2015)

RISE-RIDE: 3.YIL

- 3. yılda sham → 0.5mg Ranibizumab




CFT = 356 µm


CFT = 208 µm

DR TEDAVİSİ İÇİN RANİBİZUMAB FDA ONAYI!

FDA News Release

FDA approves Lucentis to treat diabetic retinopathy in patients with diabetic macular edema

For Immediate Release February 6, 2015

Release

Español

The U.S. Food and Drug Administration today expanded the approved use for Lucentis (ranibizumab injection) 0.3 mg to treat diabetic retinopathy (DR) in patients with diabetic macular edema (DME).

VIVID – VISTA çalışmalarında DRP progresyonu

OF OPHTHALMOLOGY
The Eye M.D. Association

Intravitreal Aflibercept for Diabetic Macular Edema

Jean-François Korobelnik, MD,[1,2,3] Diana V. Do, MD,[4] Ursula Schmidt-Erfurth, MD,[5] David S. Boyer, MD,[6] Frank G. Holz, MD,[7] Jeffrey S. Heier, MD,[8] Edoardo Midena, MD,[9] Peter K. Kaiser, MD,[10] Hiroko Terasaki, MD,[11] Dennis M. Marcus, MD,[12] Quan D. Nguyen, MD,[4] Glenn J. Jaffe, MD,[13] Jason S. Slakter, MD,[14] Christian Simader, MD,[5] Yuhwen Soo, PhD,[15] Thomas Schmelter, PhD,[16] George D. Yancopoulos, MD, PhD,[15] Neil Stahl, PhD,[15] Robert Vitti, MD,[15] Alyson J. Berliner, MD, PhD,[15] Oliver Zeitz, MD,[16,17] Carola Metzig, MD,[16] David M. Brown, MD[18]

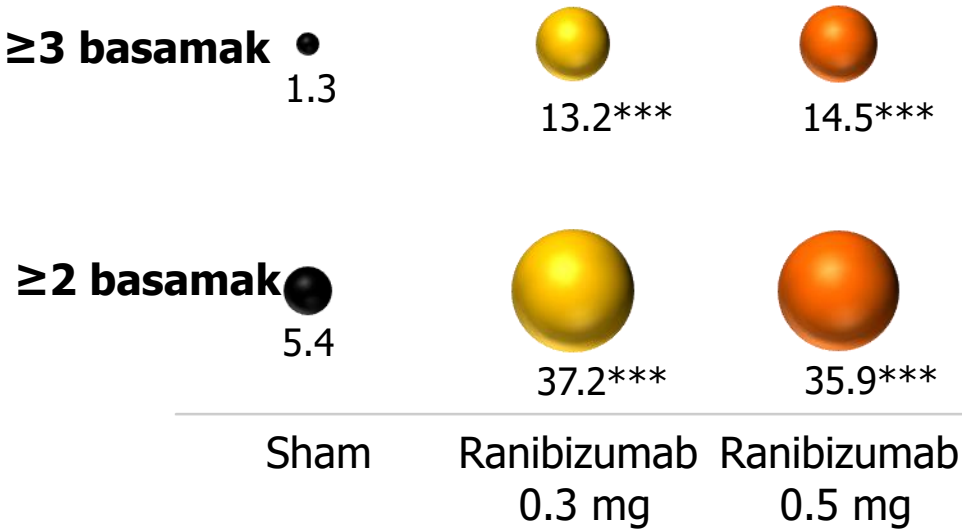
Purpose: A head-to-head comparison was performed between vascular endothelial growth factor blockade and laser for treatment of diabetic macular edema (DME).
Design: Two similarly designed, double-masked, randomized, phase 3 trials, VISTA^{DME} and VIVID^{DME}.
Participants: We included 872 patients (eyes) with type 1 or 2 diabetes mellitus who presented with DME with central involvement.

- Laser, 4 haftada bir aflibercept, 8 haftada bir aflibercept gruplarının karşılaştırılması
- 52 hafta sonunda 2 ve daha fazla step düzelme
- 2q4: % 33,8 - % 33,3
- 2q8: % 29,1 - % 27,7
- Laser: % 14,3 - % 7,5

Anti-VEGF'ler ile DMÖ'lü Hastalarda DR Şiddetinde Azalma

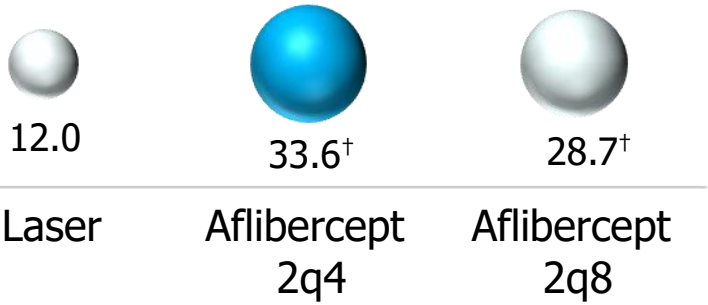
RISE & RIDE: improvement at Year 2

2. yılda ETDRS skorunda ≥2 veya ≥3 basamak iyileşme (%)



VIVID & VISTA: improvement at Year 1

52. Haftada DRSS Skorunda ≥2 basamak iyileşme



Aflibercept ile ≥3 basamak iyileşen veya kötüleşen hasta oranları ile ilgili veri yoktur.

Ip MS et al. Arch Ophthalmol 2012;130:1145-52;
Korobelnik JF, et al. Ophthalmology 2014 epub ahead of print

Dirençli NV'lerin tedavisinde Anti-VEGF

- Pegaptanib (Macugen): 1 olgu 15 ay

  Mendrinos E, et al. Rapid and persistent regression of severe new vessels on the disc in proliferative diabetic retinopathy after a single intravitreal injection of pegaptanib. *Acta Ophthalmol.* 2008

- Macugen diabetik retinopati çalışma grubu:
- 13 PDR'li göz
- 0, 6, 12hf ve gerektikçe 6 enjeksiyona kadar
- Gözlerin 8'inde (%62) NV'de gerileme
- 3/8'ünde tedavinin kesilmesinden sonra geç dönemde (5.ay) tekrar NV'de ilerleme

(Adamis et al. (MDRSG). Changes in retinal neovascularization after pegaptanib (Macugen) therapy in diabetic individuals. Ophthalmology 2006)

PDR li gözlerde PRP + Bevacizumab

- İris veya retinal NV' li 44 gözde-IVB
- Tümünde FFA sızıntı↓
- %87: PRP(+)
- NV'de tam rezolüsyon:
  - RI: %82 NVE: %59, NVD: %73
  - Hızlı etki, düşük doz (1.25mg)

Avery RL, Pearlman J, Pieramici DJ, et al. Intravitreal bevacizumab (Avastin) in the treatment of proliferative diabetic retinopathy. Ophthalmology. 2006

PDR li gözlerde PRP + Bevacizumab

Mirshahi et al (2008)

- Prospektif, 40 hasta 80 göz
- 1,25 mg IVB + PRP ..... sham + PRP
- NV tamamen düzelen
- 6. hafta..... %87,5 ..... %25
- 16. hafta..... %70 ..... %65

Mirshahi A1, Roohipoor R, Lashay A et al. Bevacizumab-augmented retinal laser photocoagulation in proliferative diabetic retinopathy: a randomized double-masked clinical trial. Eur J Ophthalmol 2008 Mar-Apr;18(2):263-9.

PDR-Dirençli NV-IVB

- 11 göz, 6 ay takip
- %73 tam regresyon
- 6. ayda %36 rekürrens
- Ort 2.9 ayda tekrar tedavi ihtiyacı
- Ort 1.9 enjeksiyon / 6 ay
- 3 ayda 1 enjek.

Schmidinger G, Maar N, BolzM et al. Repeated intravitreal bevacizumab treatment of persistent new vessels in proliferative diabetic retinopathy after complete panretinal photocoagulation. Acta Ophthalmol. 2011

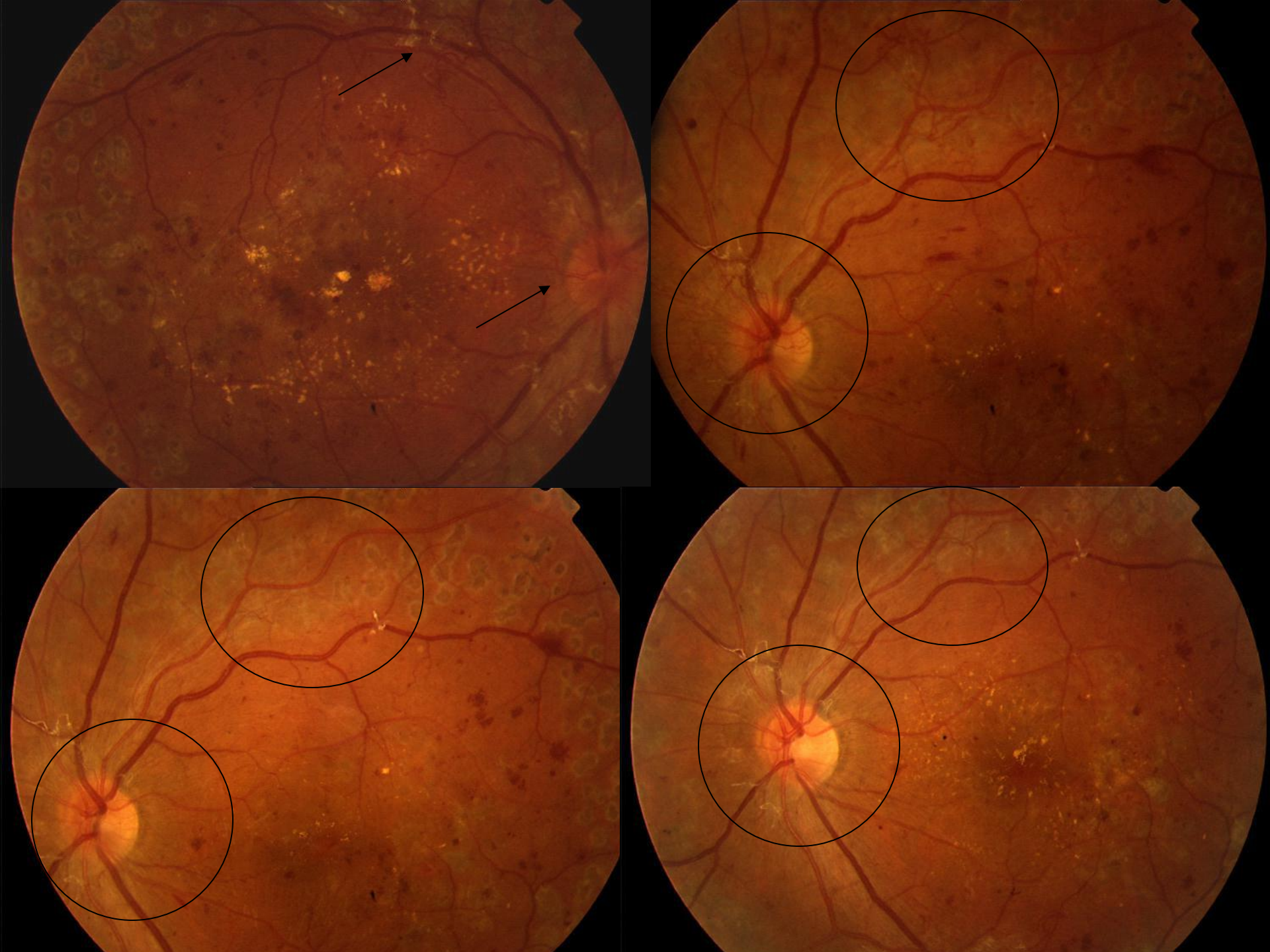
PDR-Dirençli NV-IVB

- 39 hastanın 43 gözü, dirençli NV + DMÖ
- 1,25 veya 2,5 mg bevacizumab

NV'de gerileme:

- 6 ay sonunda
- % 61.4 tam, % 34.1 kısmi, % 4.5 gerileme yok
- 2 yıl sonunda
- % 39.5 tam, % 34.9 kısmi, % 25.6 gerileme yok
- Etki geçici, direnç gelişiyor!

J. Fernando Arevalo, MD, FACS Intravitreal Bevacizumab as Anti-Vascular Endothelial Growth Factor in the Management of Complications of Proliferative Diabetic Retinopathy MEHDI Ophthalmology Journal 2013.



PDR li gözlerde PRP + Bevacizumab

- PDR'li 40 göz, prospektif
- IVB + PRP alanlarda:
  - SFK ve GK daha iyi
  - Vitreus hemorajisi daha az (p = 0.023)

Cho WB, , Oh SB , Moon JW et al. Panretinal photocoagulation combined with intravitreal bevacizumab in high-risk proliferative diabetic retinopathy Retina. 2009 Apr;29(4):516-22.

Anti-VEGF + PRP: Sonuç

- PRP'yi güçlendirici, tamamlayıcı
- NV'ların daha hızlı gerilemesi,
  - Vit Hem riski↓
- Görsel sonuçların daha iyi
  - PRP'ye bağlı maküla ödemi↓

Vitreus hemorajisi & Anti-VEGF

- NV'ler geriler
- Yeni hemorajiyi önler
- Mevcut hemoraji kendiliğinden çekilir
- PRP tamamlanır
- Postop hemorajilerde!

GÜTF: VİTREUS HEM-AVASTİN 20 Olgu

Enjeksiyon öncesi hemoraji derecesi ve oranları

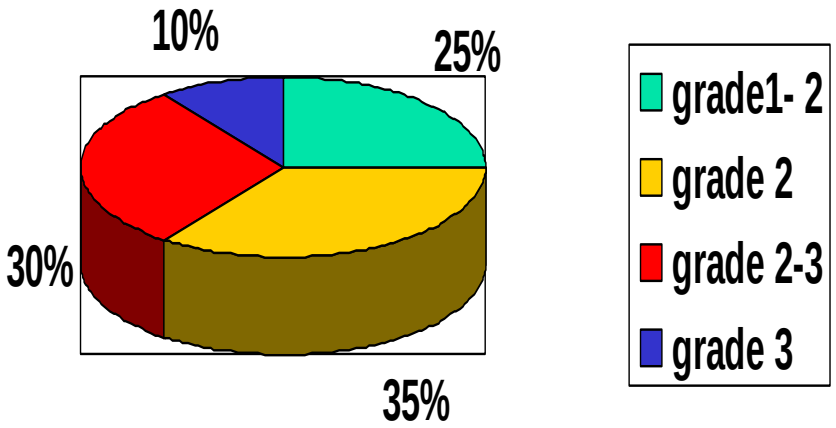
Grade 0: hemoraji yok

Grade 1: Retina detayları seçilebilecek derecede vitreus hemorajisi PRP tx mümkün

Grade 2: Flue ama ana damarlar seçilebiliyor, perifer seçilebiliyor ve perifer aydınlatılabilen alanlara PRP tx mümkün

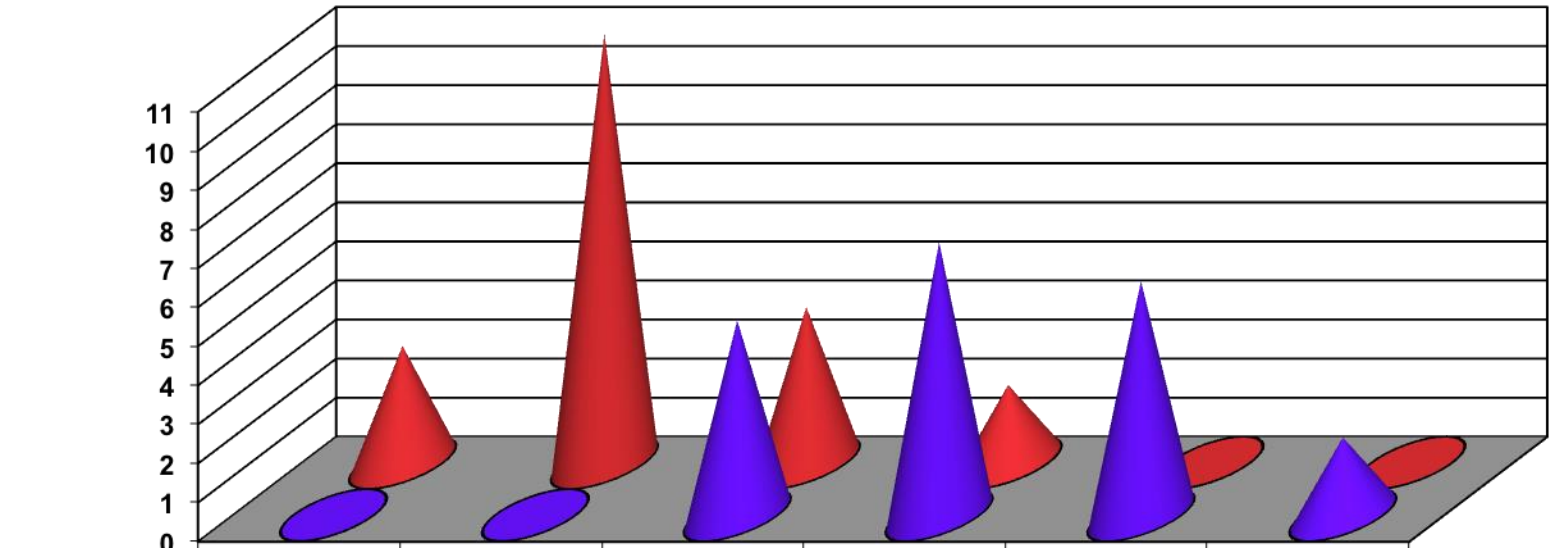
Grade 3: Kırmızı refle var ama ana damarlar seçilmiyor ve tx mümkün değil

Grade 4: Kırmızı refle yok



Gün Kantarcı FA, Yolcu D, Özdek Ş. Diabetik vitreus hemorajisinde İVB etkinliği. 45. Ulusal Oftalmoloji Kongresi. Ekim 2011.

Vitreus hemorajisi & Anti-VEGF-GÜTF



	grade 0	grade 1	grade 1-2	grade2	grade2-3	grade3
enj önce	0	0	5	7	6	2
enj 1 ay sonra	3	11	4	2	0	0

Vitreus hemorajisi & Anti-VEGF-GÜTF

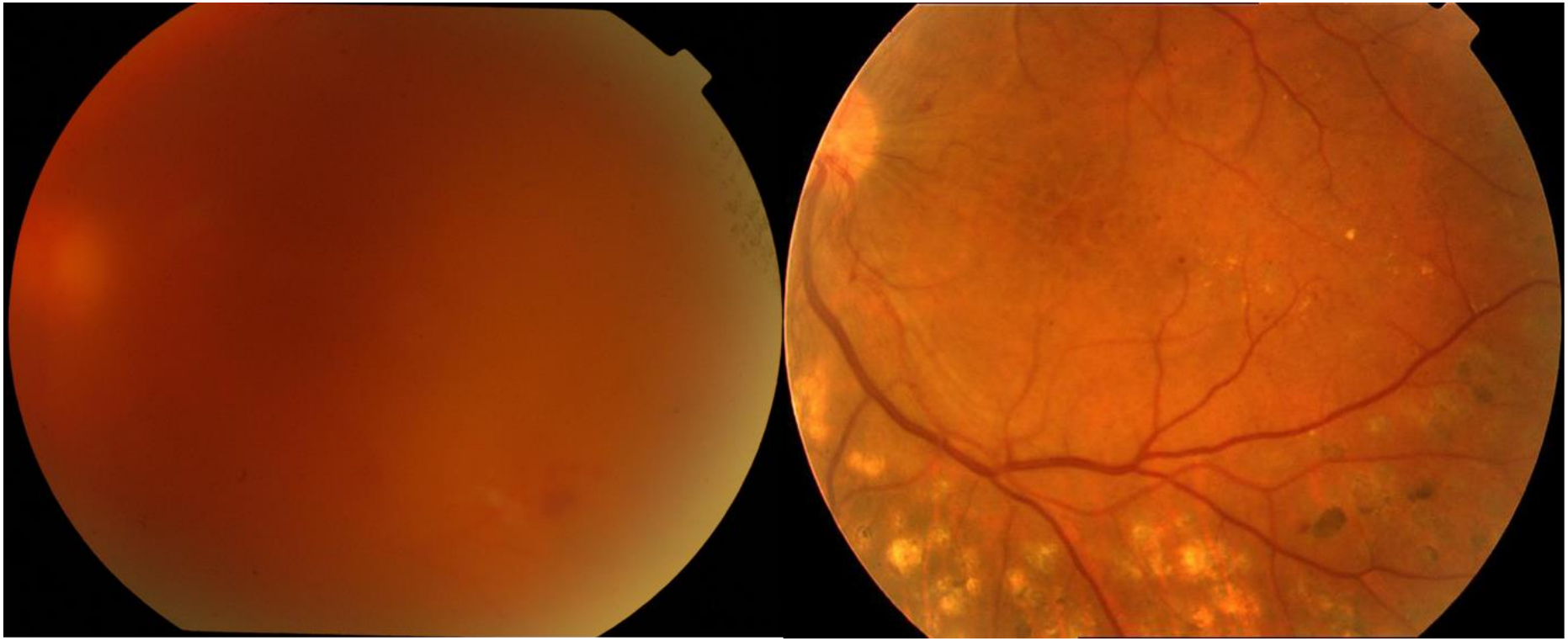
- Avastin öncesi Vit. hem süresi: 2,5 ±0,7ay
- Enjeksiyon öncesi ort GK: 0,24 ± 0,12
- Enj sonrası 1. ay ort. GK: 0,45 ± 0,15
- 17 aylık takip sonrası GK: 0,6 ± 0,21

Vitreus hemorajisi & Anti-VEGF-GÜTF

- Ortalama takip süresi 17,3 ± 4,8 ay
- 6 olgu (%30): PPV gerekti.
- 14 olgu (%70): Vitrektomi gerekmedi.

PRP (+) Hemoraji (-)

65y, tip 2 DM, GK: 0.7/2mps, USG: ERM(-) VM(-) SOL: IVB sonrası 20. gün GK: 0.2…0.4 (PRP tamamlandı)



Vitreus Hemorajisi-IVB

Spaide et al:

- PDR + VH: 2 olgu, 1,25 mg VH
- 1. ayda 2 sıra ve 5 sıra görme artışı
- 1. ve 3. ayda tekrar enjeksiyon
- NV gerilemiş, VH çekilmiş, PRP yapılabilmiş

Spaide RF, Fisher YL. Intravitreal bevacizumab (Avastin) treatment of proliferative diabetic retinopathy complicated by vitreous hemorrhage. Retina 2006 Mar;26(3):275-8.

PPV öncesi anti-VEGF

- NV'ler geriler
- NV'lerin retinaya tutunma sıkılıkları↓
- Vasküler membranlar retinadan daha kolay ayrılır.
- İntraoperatif kanama azalır.

- 2-5 gün önce

PPV öncesi Anti-VEGF

Zhang ZH et al., PPV öncesi Bevacizumab, **Meta-analiz** :

- Daha kısa cerrahi süresi
- Daha az endodiatermi
- Daha az perop kanama
- Daha seyrek erken tekrar kanama (1 ay)
- İatrojenik yırtık sıklığı aynı

Zhang ZH et al., Vitrectomy with or without preoperative intravitreal bevacizumab for proliferative diabetic retinopathy: a meta-analysis of randomized controlled trials. Am J Ophthalmol. 2013 Jul;156(1):106-115.

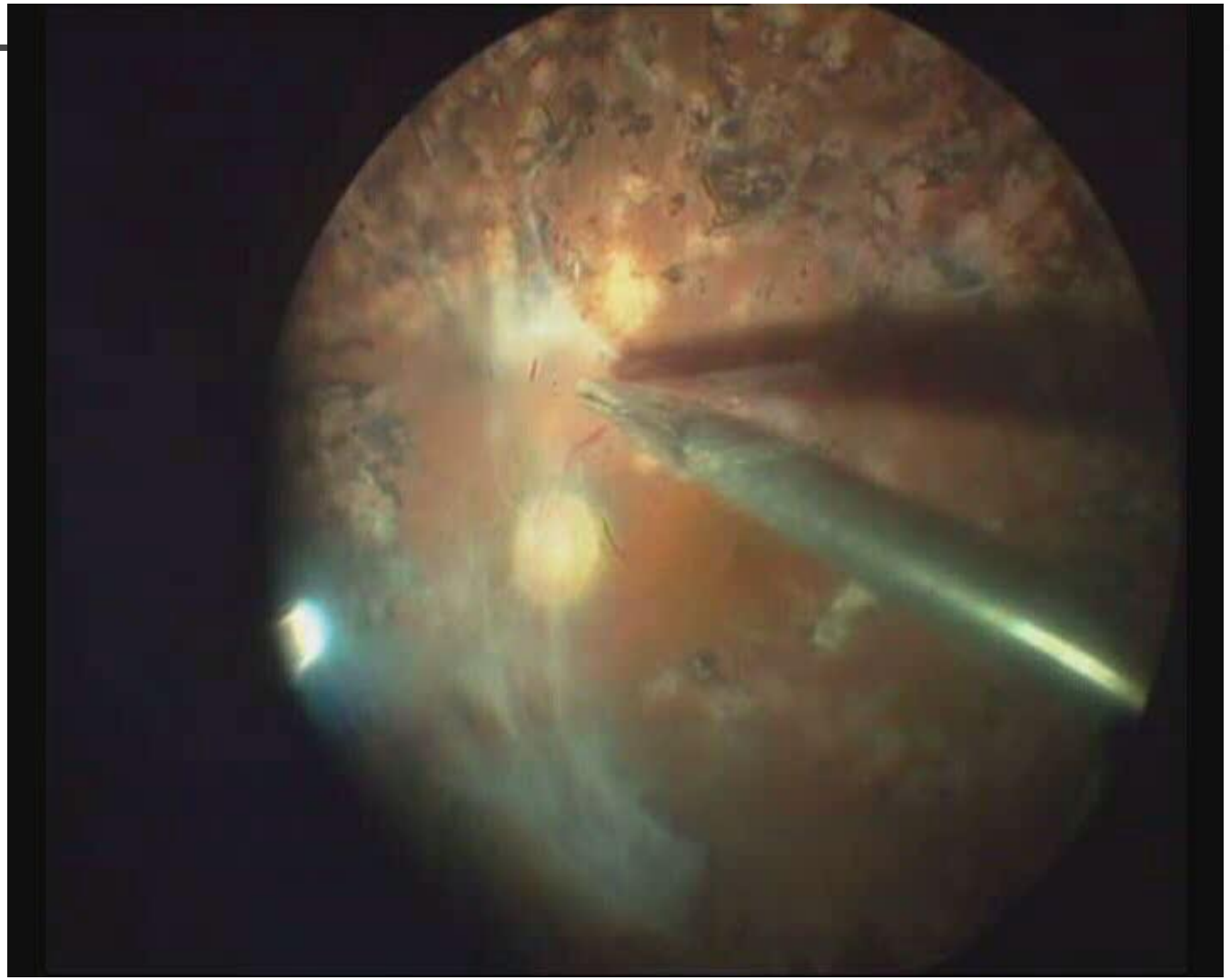
PPV öncesi Bevacizumab vs Ranibizumab

Pakzad-Vaezi Ket al. :

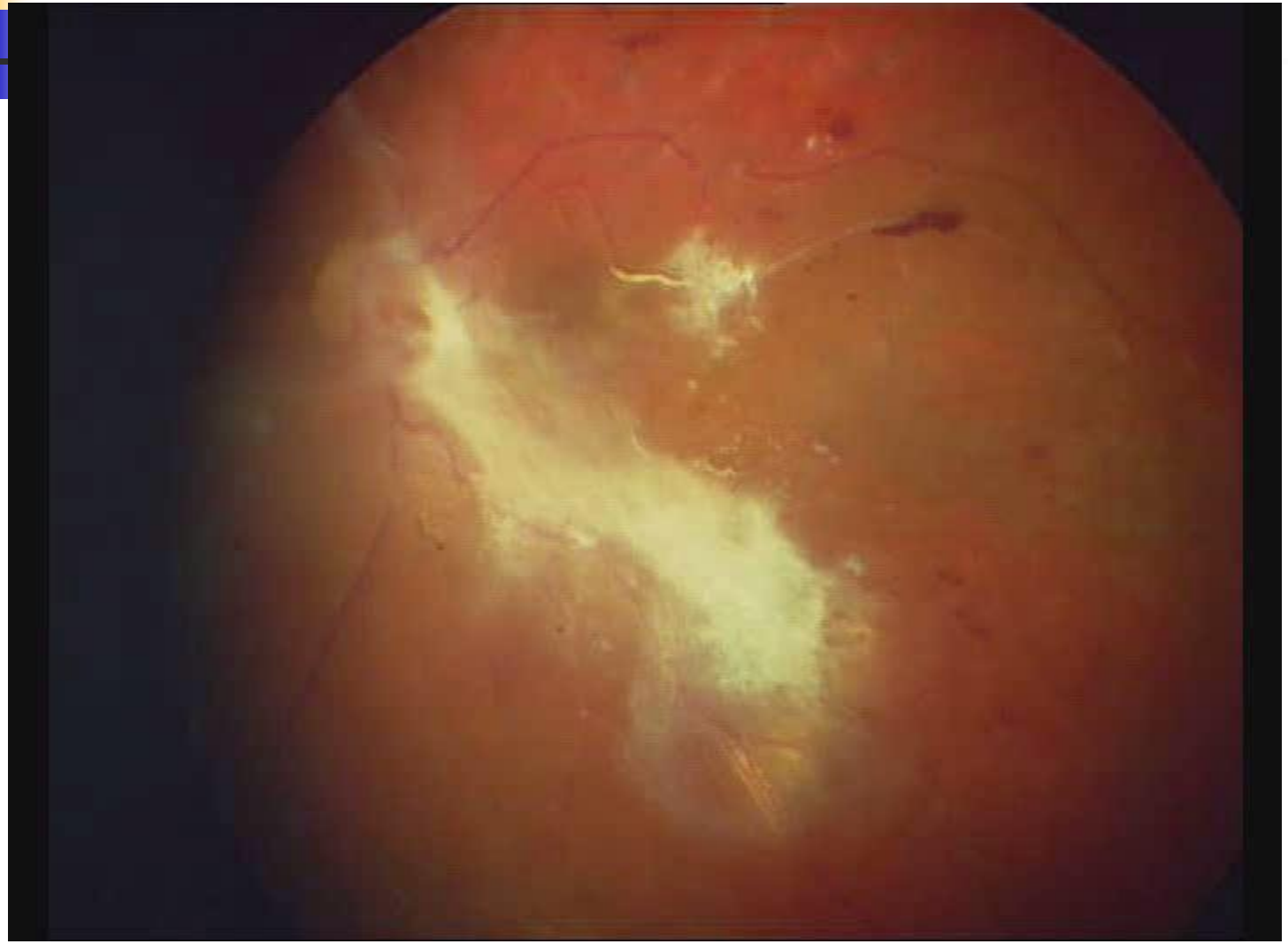
- 29 TRD veya VH'lı PDR olgusu, prospektif, randomize
- 1 hafta önce IVB veya IVR
- Toplam ameliyat süresi, İatrojenik yırtık, TRD varlığı, perop kanama, endodiatermi kullanımı, silikon kullanımı
- Gruplar arasında fark yok

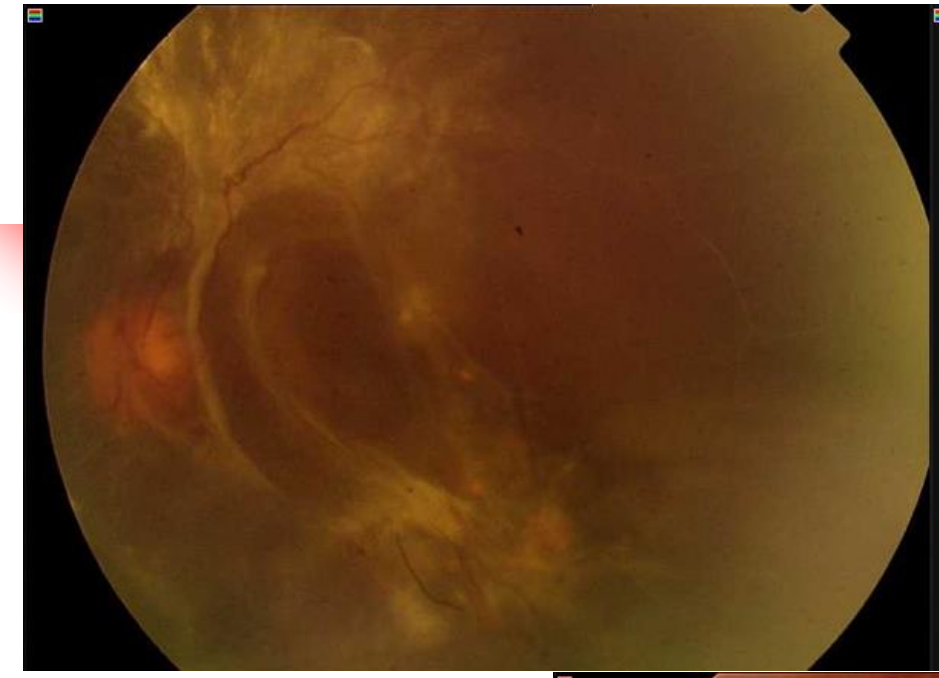
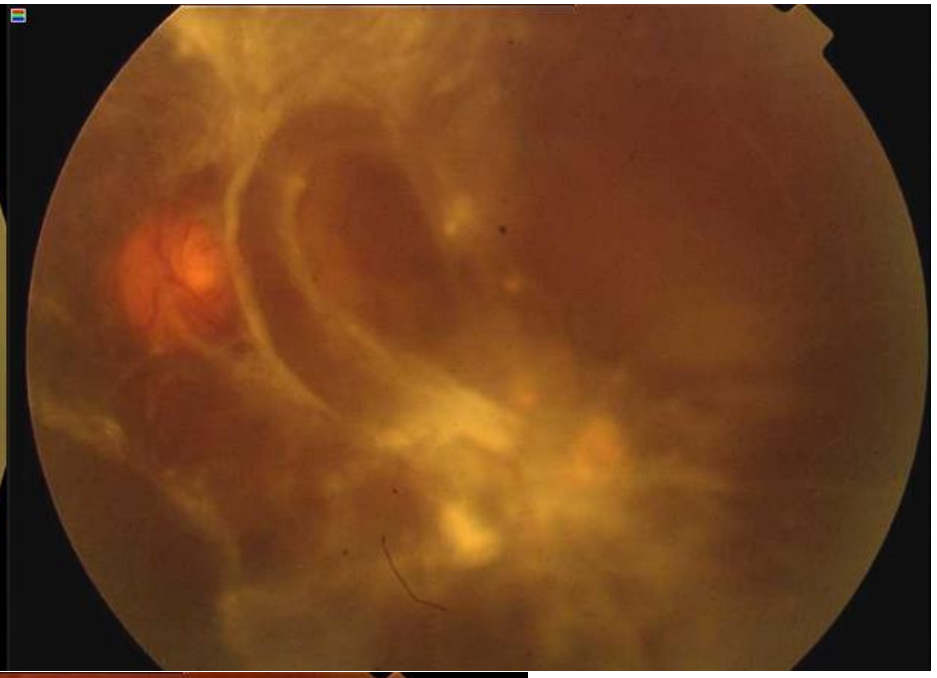
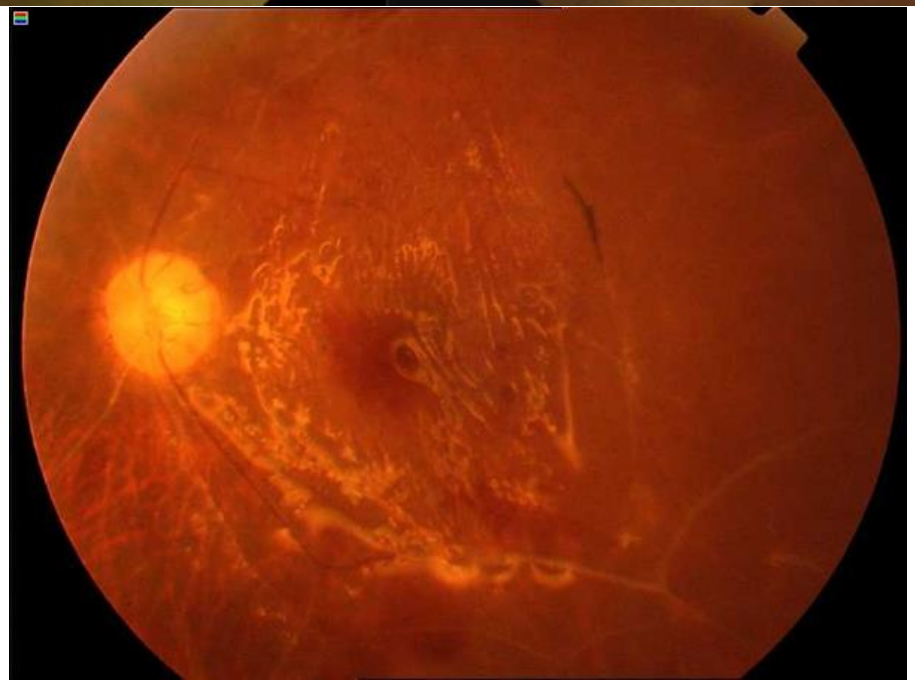
Pakzad-Vaezi K, Albiani DA, Kirker AW et al. A randomized study comparing the efficacy of bevacizumab and ranibizumab as pre-treatment for pars plana vitrectomy in proliferative diabetic retinopathy. Ophthalmic Surg Lasers Imaging Retina. 2014 Nov-Dec;45(6):521-4.

Preop Avastin (+) (4 gün önce)



Preop Avastin (-)



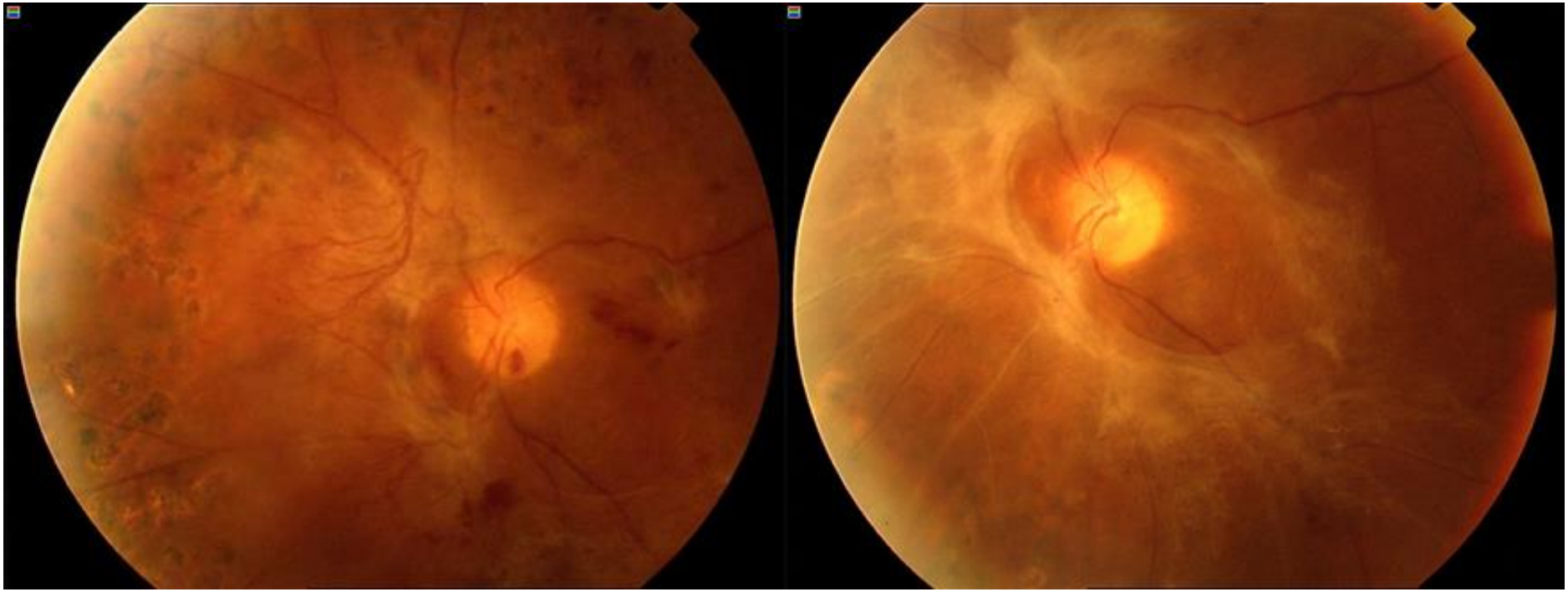
Cerrahi öncesi zamanlama!

- Fibrovasküler doku kontraksiyonu
- Traksiyonlar↑ …. RD↑ (11/215 göz: %5)
- Ort 13 günde

Wu L, et al. Twelve-month safety of intravitreal injections of bevacizumab (Avastin): results of the Pan-American Collaborative Retina Study Group (PACORES). Graefes Arch Clin Exp Ophthalmol 2008; 246: 81-7.

Arevalo JF, et al. Tractional retinal detachment following intravitreal bevacizumab (Avastin) in patients with severe proliferative diabetic retinopathy. Br J Ophthalmol 2008;92:213-6

Fibrovasküler doku kontraksiyonu



Kurtulmuşoğlu MÖ, Özdek Ş, ve ark. Ciddi proliferatif diabetik retinopati olgularında vitrektomi öncesi intravitreal bevacizumab enjeksiyonu. 41. Ulusal oftalmoloji kongresi, Antalya, 2007.

PPV'nin sonunda anti-VEGF kullanımı

- PPV sonrası rehemoraji: %75
- %4-38'inde reop gerekebilir.
- Rehemorajiyi azaltmak.

GÜTF: PDR - Vit. hem (72 göz)

- 34'üne cerrahinin sonunda IVB
- 38'i kontrol grubu
- 1. gün gözlerin %44 hafif-orta hemoraji
- Hemoraji:
  - %.8.8 IVB, %13.1 kontrol grubu (p>0.05)
- 1 er vaka PPV gerektirdi.

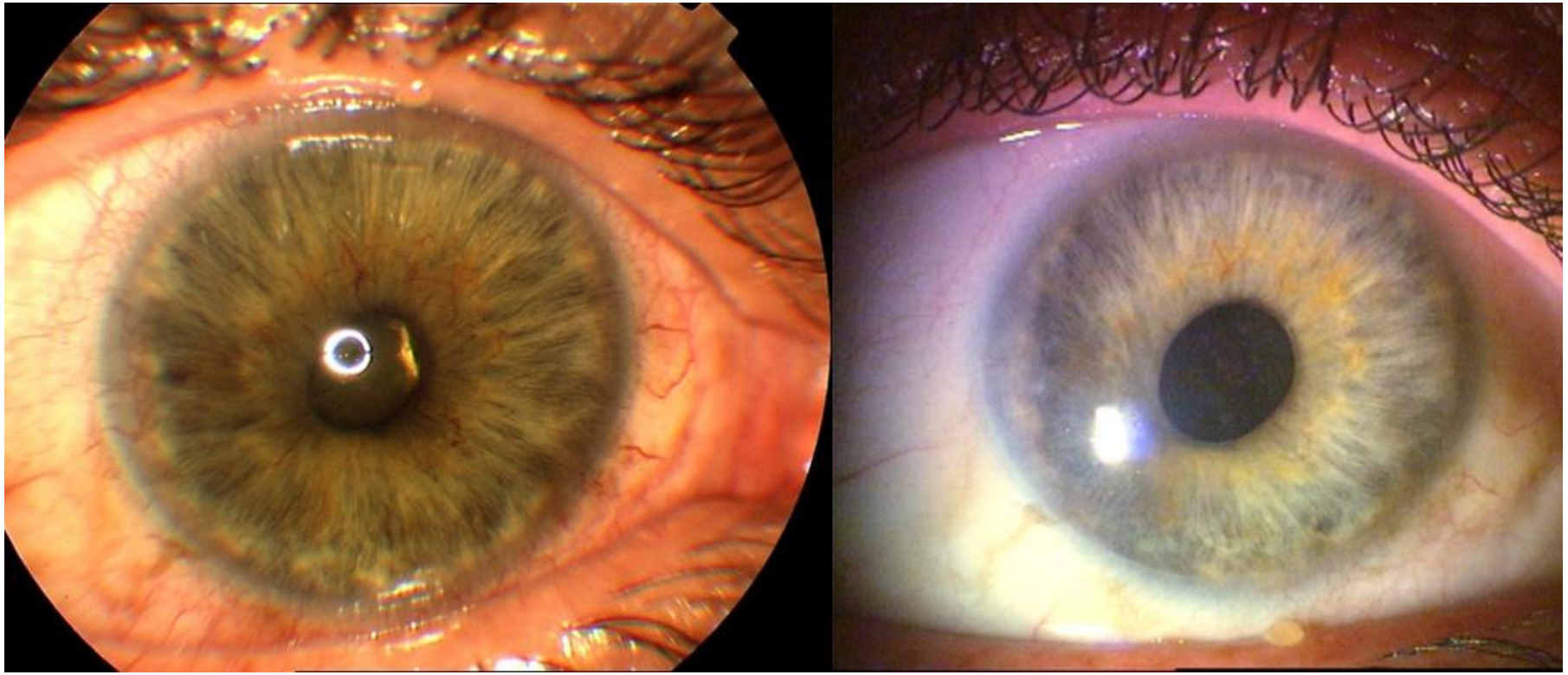
- *Göncü T, Ozdek S, Unlü M. The role of intraoperative bevacizumab for prevention of postoperative vitreous hemorrhage in diabetic vitreous hemorrhage. Eur J Ophthalmol. 2014.*

RI ve NVG tedavisinde anti-VEGF

- RI ve Açı NV:
  - %15'i PRP ye rağmen gerilemez.
- IVB: 1-7 günde tam çekilme!
- Laser'e yardımcı!

Fernandez-Vigo J, et al. Diabetic iris neovascularization. Natural history and treatment. Acta Ophthalmol Scand 1997

RI ve NVG tedavisinde anti-VEGF



NVG tedavisinde Avastin

- İntravitreal, subkonjonktival, intrakameral veya subtenon
- Preop bevacizumab
- Amaç:
  - Cerrahi kanamaları azaltmak,
  - Glokom cerrahisinin başarısını arttırmak
  - Kalıcı tedavi değil!

SONUÇLAR

- İleri NPDR ve PDR tedavisinde altın standart: PRP
- İleri NPDR ve PDR'li DMÖ'lü olgularda DR tedavisi için aylık 0,3 mg. ranibizumab FDA onayı aldı.
- PRP endikasyonu olan hastalarda, başlamadan veya ilk seanstan hemen sonra intravitreal anti – VEGF faydalı
- Vitreus hemorajili seçilmiş hastalarda IV anti – VEGF PRP yapılmasını, PPV ye gerek kalmamasını sağlayabilir
- Dirençli NV, iris NV ve NV glokom cerrahisi öncesi faydalı
- PDR nedeniyle yapılacak PPV öncesinde intravitreal anti – VEGF faydalı

TEŞEKKÜRLER...