Venöse retinale Gefäßverschlüsse:

Diagnostik, Risikofaktoren, Therapie

Lars-Olof Hattenbach

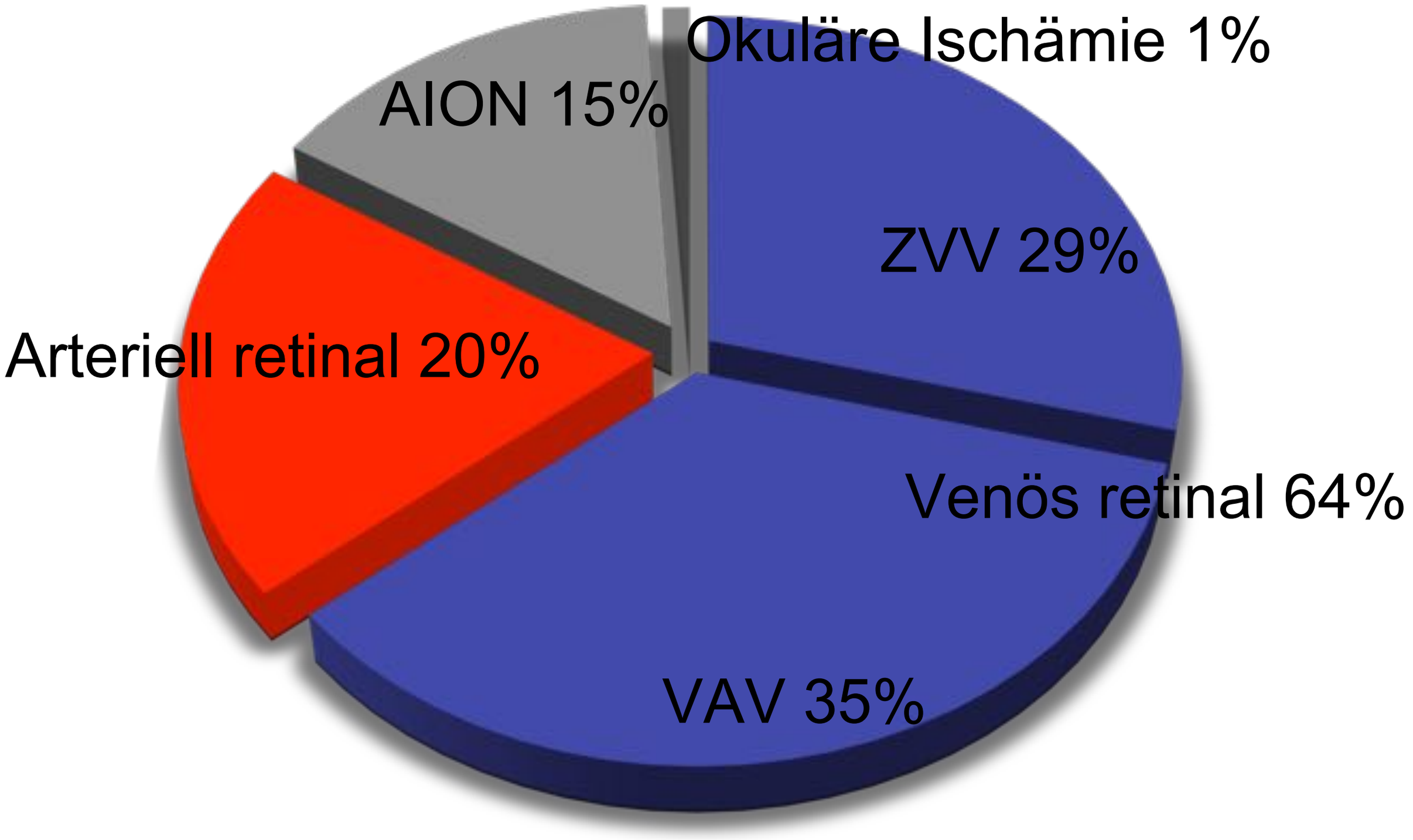
Augenklinik des
Klinikums Ludwigshafen

AAD 2018

Die “Basics“

Diagnostik & Risikofaktorabklärung

„Durchblutungsstörungen“ des Auges



Warum welche Diagnostik bei RVO?

- Visus
- Tensio, ggf. Tagesprofil
- VAA
- Funduskopie
- OCT
- Fluoreszenzangiografie (ggf. im Verlauf)
- Abklärung systemischer Risikofaktoren

Differentialdiagnose ZVV: Okuläre Ischämie !

Kein (rascher) Visusverlust
Fleckige Blutungen

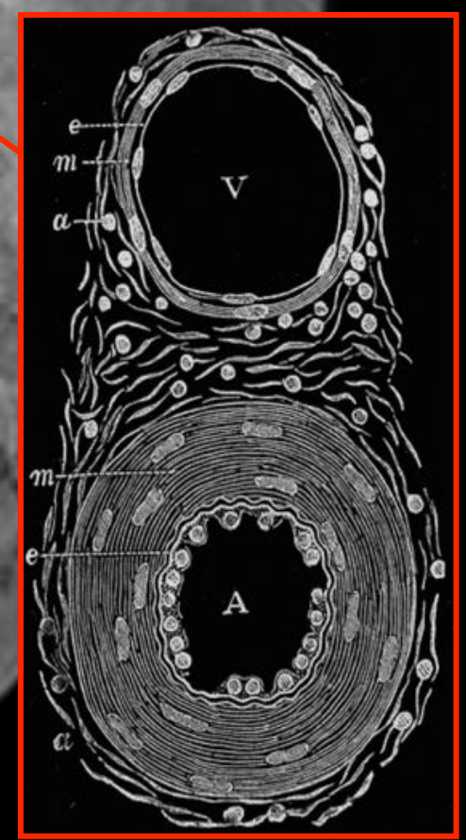
Differentialdiagnose ZVV:
„Bild ZVV“ bei systemischen Erkrankungen

DD: Infektiöse Genese (Borreliose!), Anämien

Insbesondere junge Patienten
ohne erkennbare Risikofaktoren !

Prädilektionsstelle VAV: AV-Kreuzungen (>99%)

Blutströmungsverlangsamung
Endothelschädigung
Gerinnungsneigung



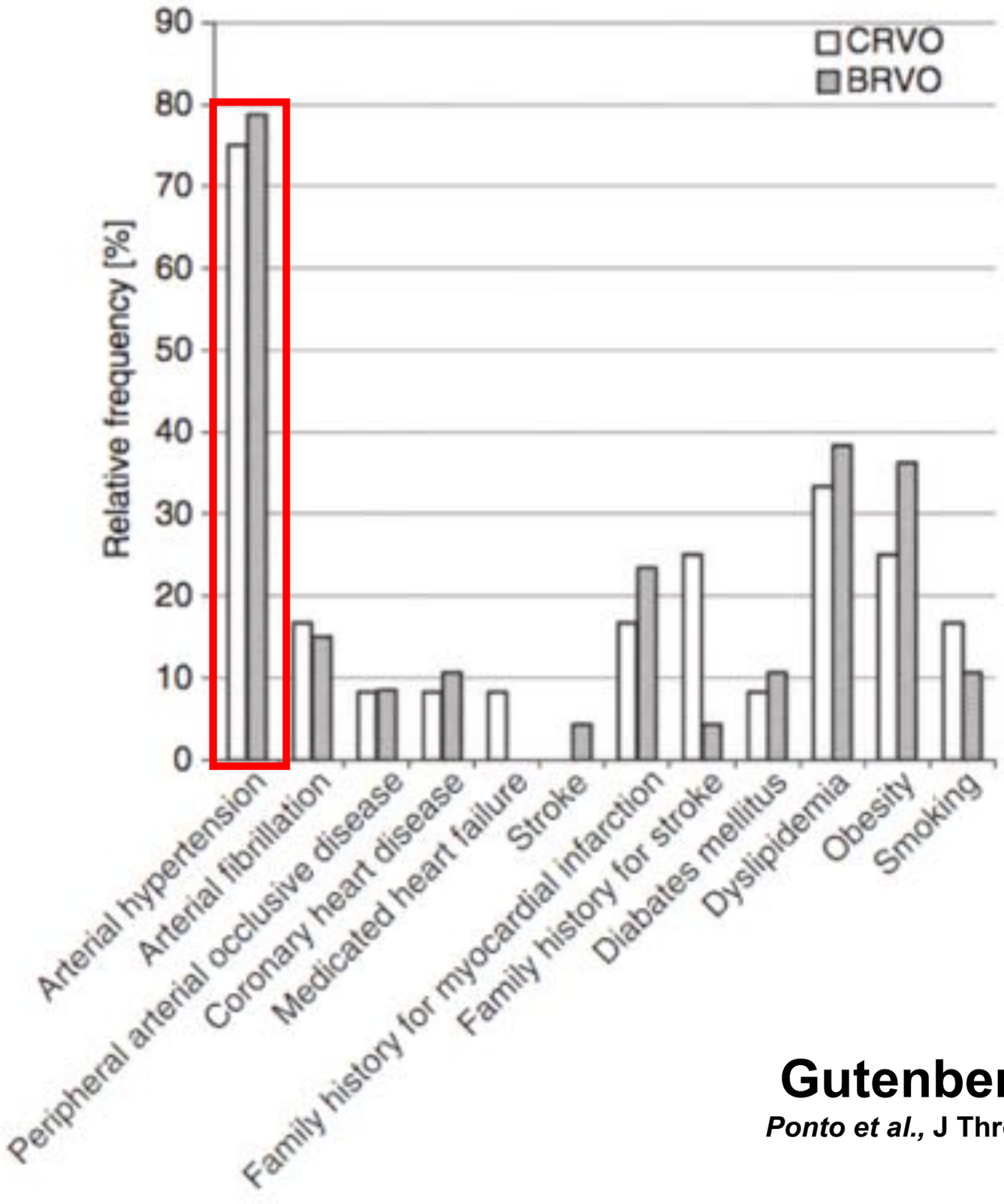
1'34''

	ZAV/AAV	ZVV/VAV	AION
Arterielle Hypertonie >70%	+++	+++	+++
Rauchen 40-50%	+++	++	++
Diabetes mellitus 14-34%	+	+	+
Sonstige	Embolien 20%	Glaukom Trauma	Embolie Blutverlust

Risikofaktor Nr. 1: Arterielle Hypertonie

ZVV: 75%

VAV: 78,7%



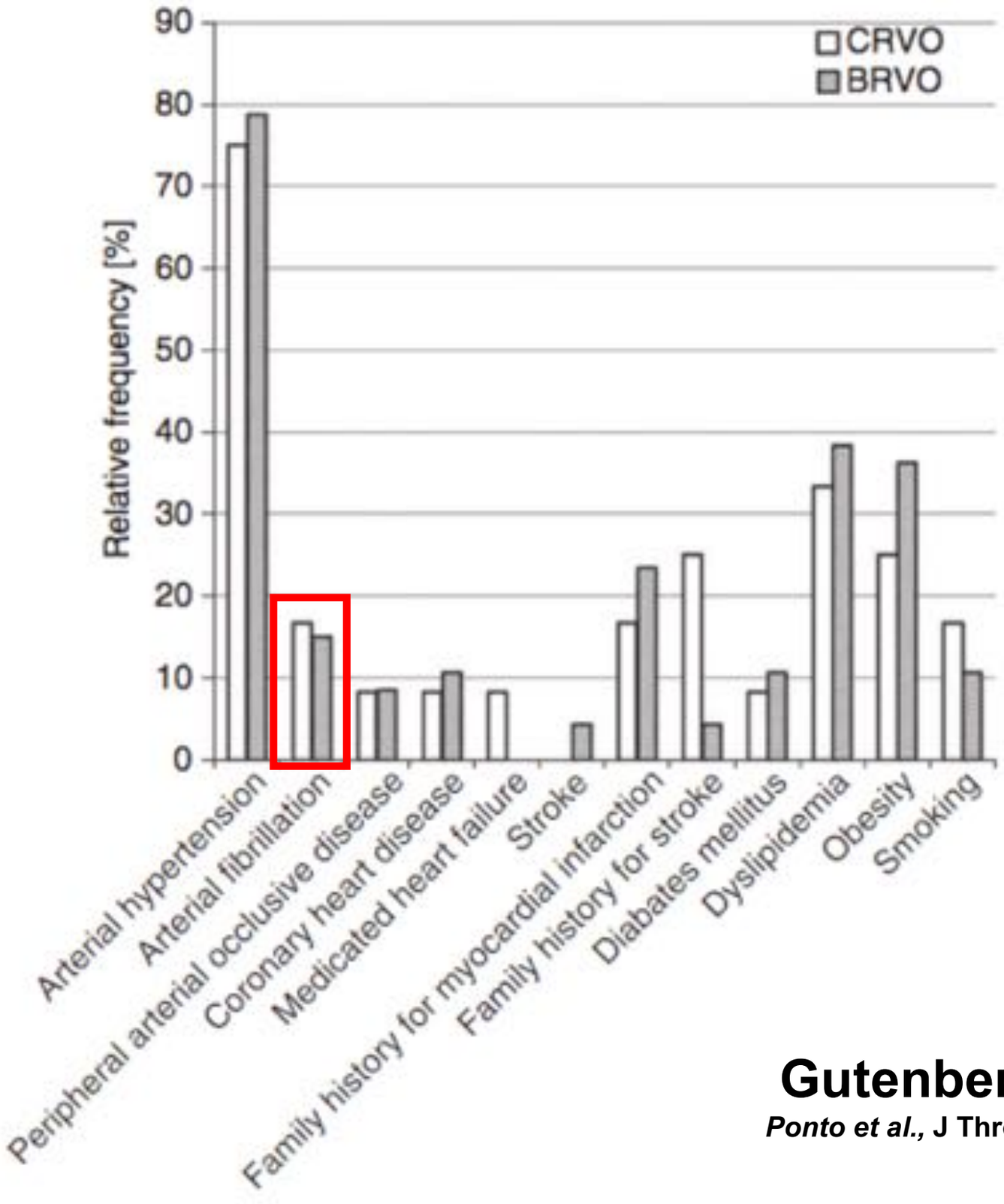
Gutenberg Health Study

Ponto et al., **J Thromb. Haemost. 2015;13:1254-1263**

Nicht nur bei RAO: Vorhofflimmern bei RVV (!)

ZVV: 16,7%

VAV 14,9%



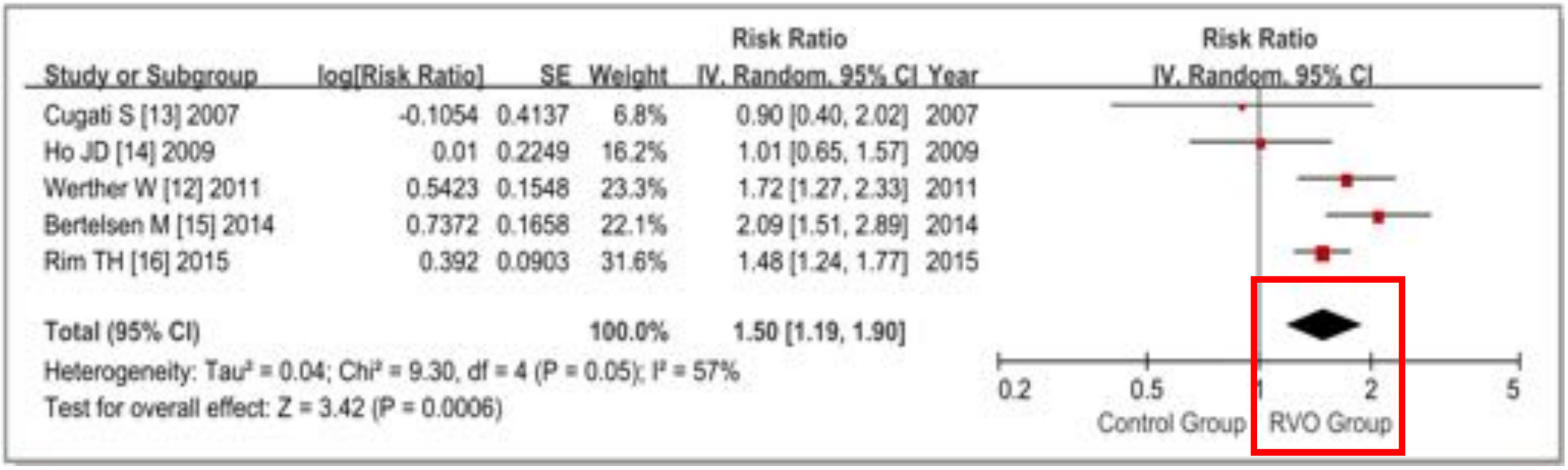
Gutenberg Health Study

Ponto et al., **J Thromb. Haemost. 2015;13:1254-1263**

Erhöhtes Schlaganfallrisiko nach RVV

***Li et al.*, J Am Heart Assoc. 2016**

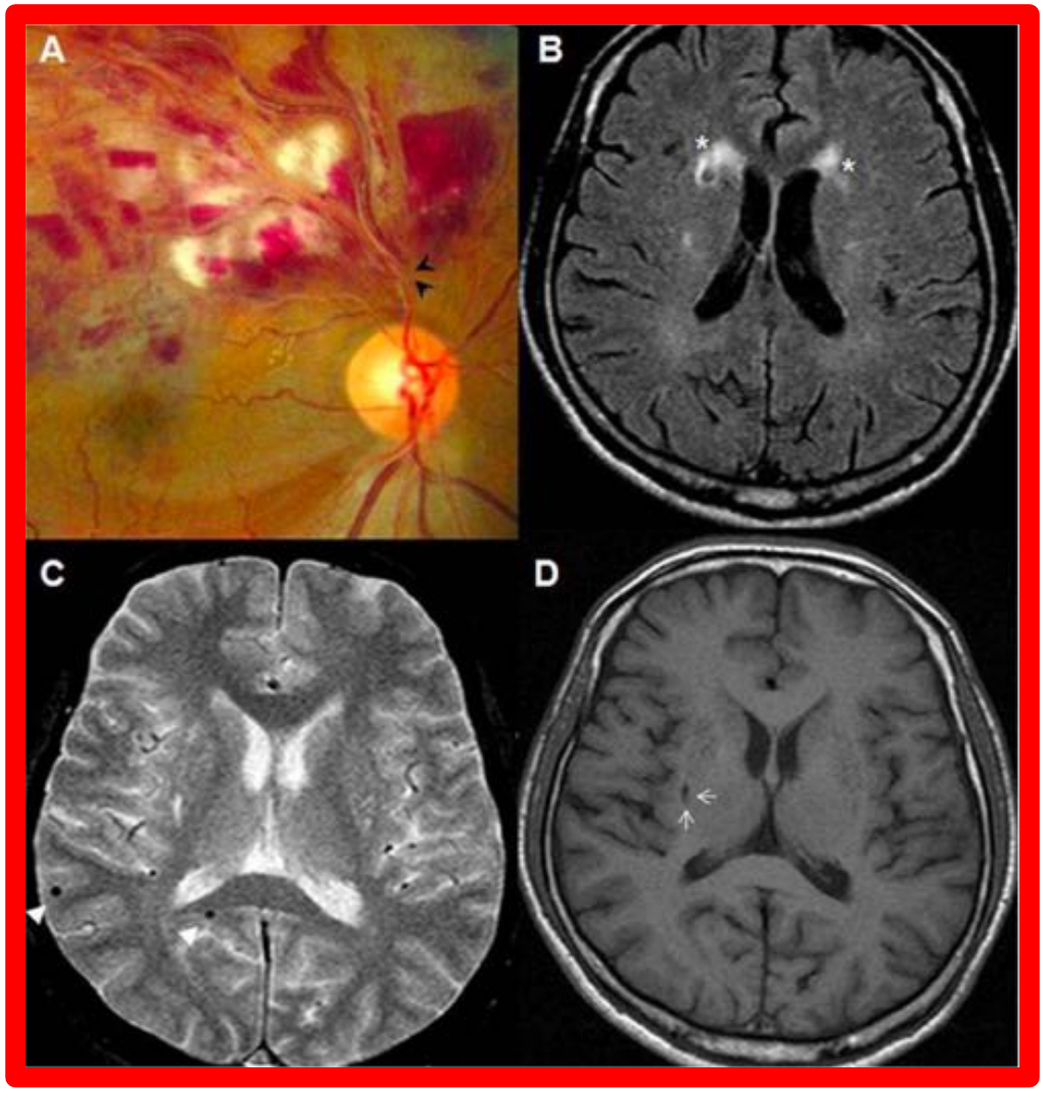
- **Metaanalyse, 5 Studien**
- **37.471 RVV-Patienten -> 431x Schlaganfall**
- **Relatives Risiko: 1,5**



RVV korreliert mit cerebralen Gefäßveränderungen ("Small Vessel Disease")

Cho et al., IOVS 2017;58(6):BIO82-BIO87

< 60 Jahre



Characteristics	< 60 Years, *n* = 39	Controls, *n* = 1105	*P* Value
Age, mean, y	50.5 ± 9.4	48.3 ± 7.7	0.486†
Sex, male, *n* (%)	25 (64%)	649 (59%)	0.502
Cardiovascular risk factors, *n* (%)			
Hypertension	18 (46%)	476 (43%)	0.703
Diabetes	6 (15%)	93 (8%)	0.128
Dyslipidemia	12 (31%)	441 (40%)	0.251
Smoking	15 (38%)	463 (42%)	0.668
Cerebral SVD	15 (38%)	47 (4%)	<0.001*
WMH, *n* (%)†			
Grade 0	17 (44%)	973 (88%)	<0.001*
Grade 1	15 (38%)	130 (12%)	<0.001*
Grade 2	12 (31%)	2 (0%)	<0.001*
Grade 3	1 (3%)	0 (0%)	0.034*
CMB, *n* (%)	5 (13%)	38 (3%)	0.002*
Silent lacunar infarct, *n* (%)	9 (23%)	34 (3%)	<0.001*

Vorhofflimmern: Frühzeitige Diagnostik wichtig für Schlaganfallprophylaxe!

- Rivaroxaban *Xarelto*
- Apixaban *Eliquis*
- Edoxaban *Lixiana*

50% Reduktion hämorrhagischer Schlaganfall durch Direkte Orale Antikoagulanzien (DOAC)

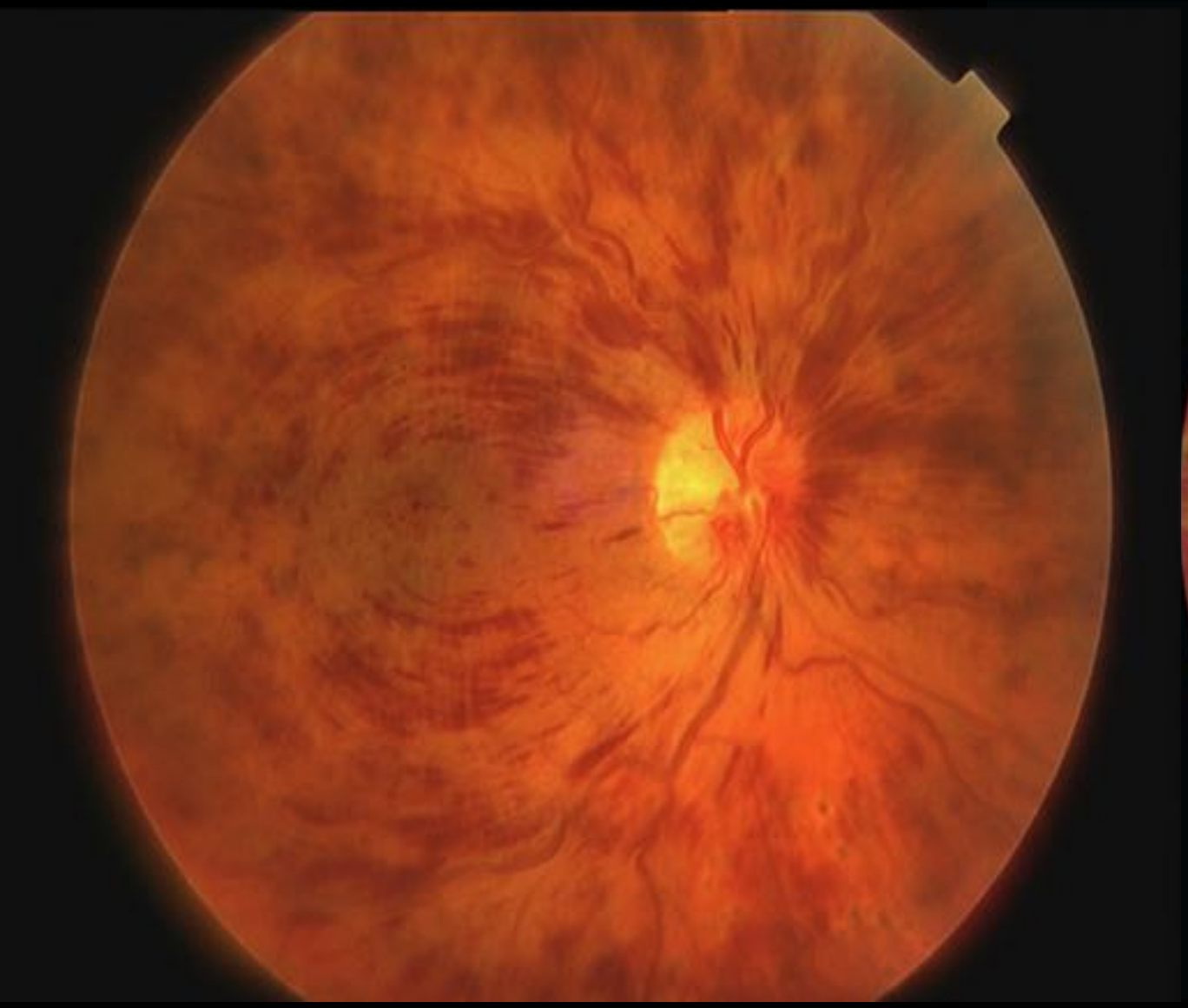
DOAC: 10% weniger Gesamtletalität

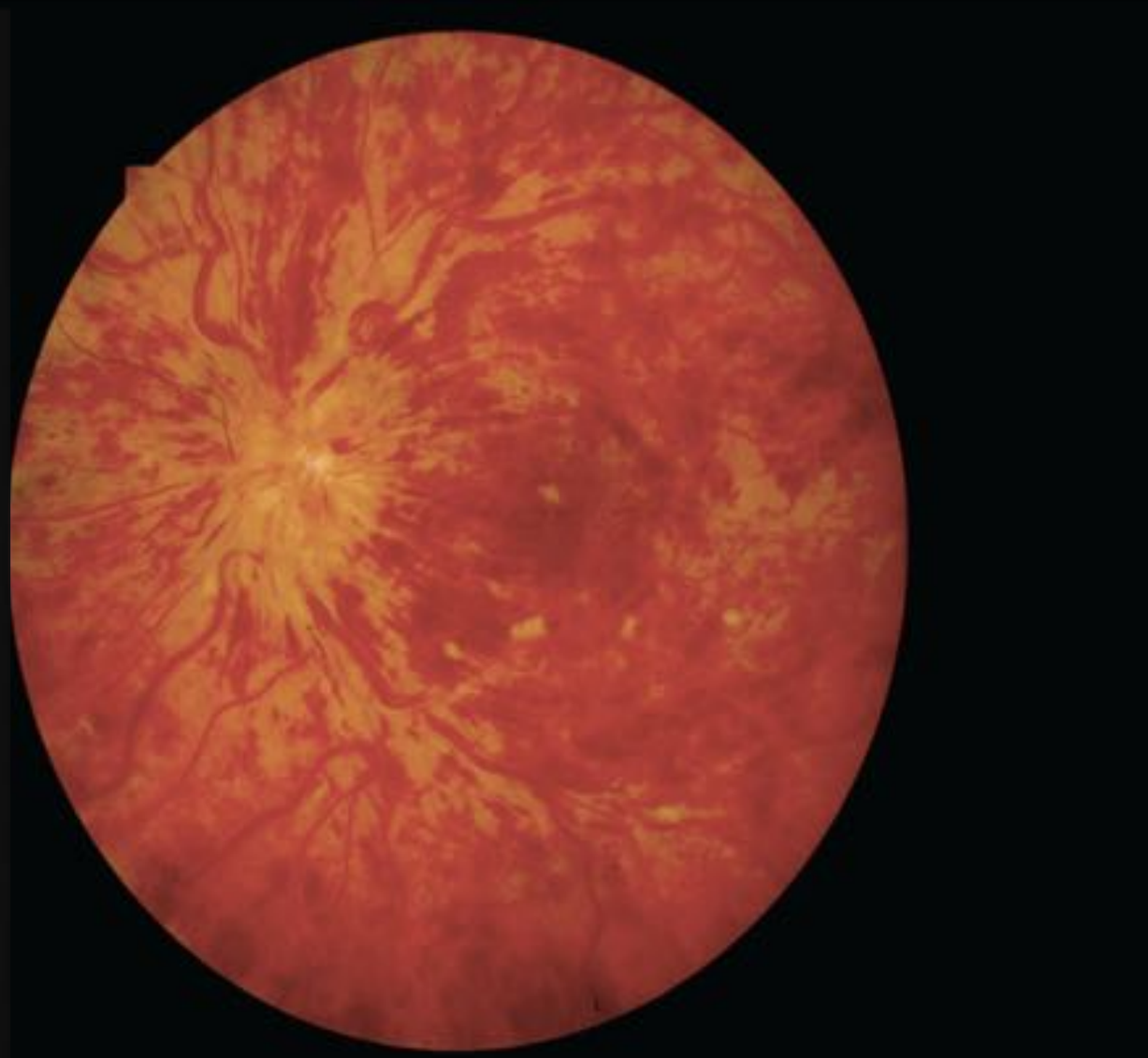
Meta-Analyse Ruff CT et al. Lancet 2014;383:955-62

ktor Hämatologische Erkrankungen (“Rheologischer A

♀ , 72 J., Thrombozytose (>800.000), Leukozytose

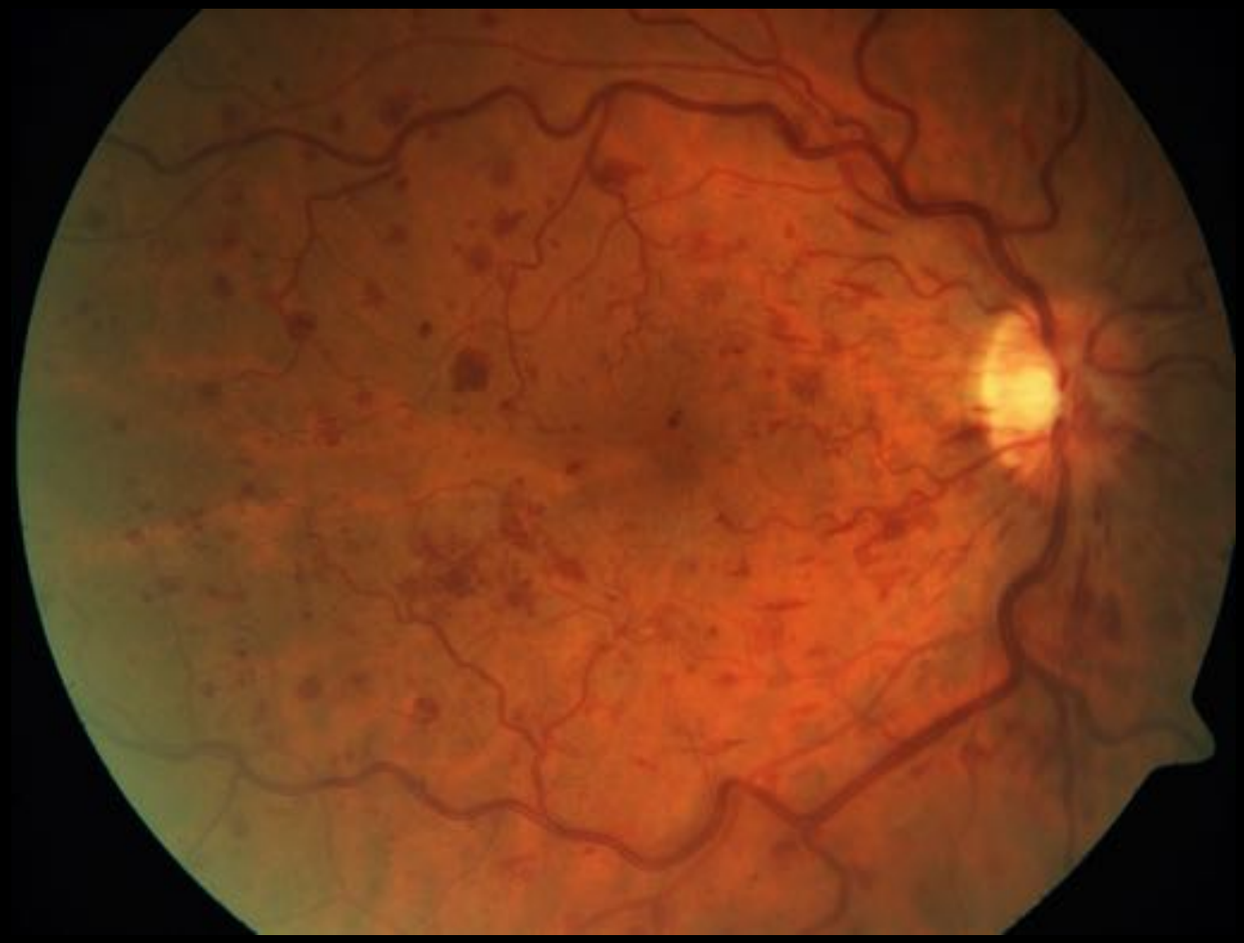
„Thrombophilie“

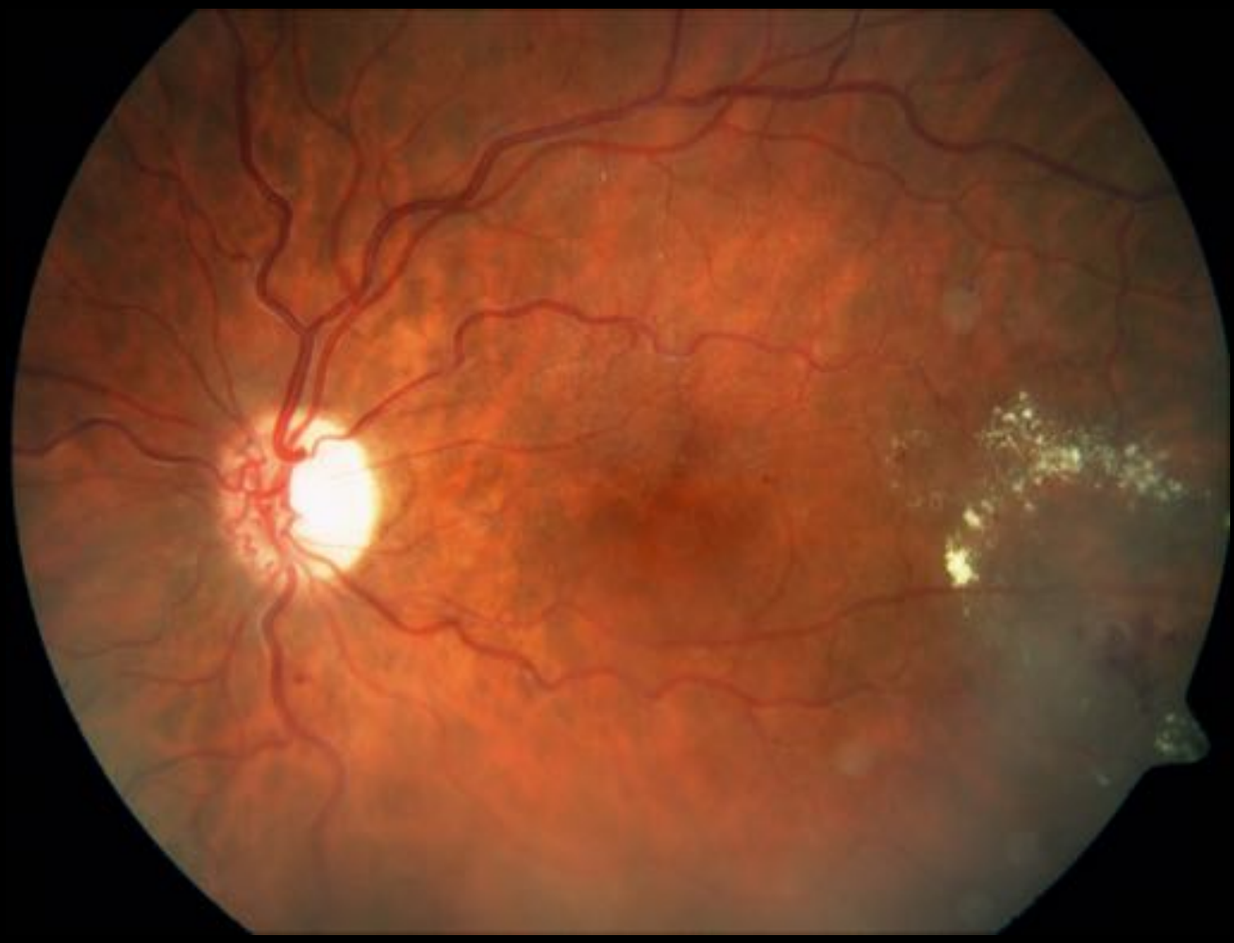




♂, 47 J., beidseitiger ZVV innerhalb von 2 Jahren,
Z.n. BVT im Alter von 33 Jahren: *Homozygote **APC-Resistenz***
(50fach erhöhtes Thromboserisiko !)

„Thrombophilie“





♂, 71 J., m., rezidivierende ZVV seit 2007
Erhöhte Lipoprotein(a)-Spiegel und heterozygote Mutation im Gen für Apolipoprotein A = Risikofaktor Arteriosklerose (KHK, Apoplex)

Klinische Studie

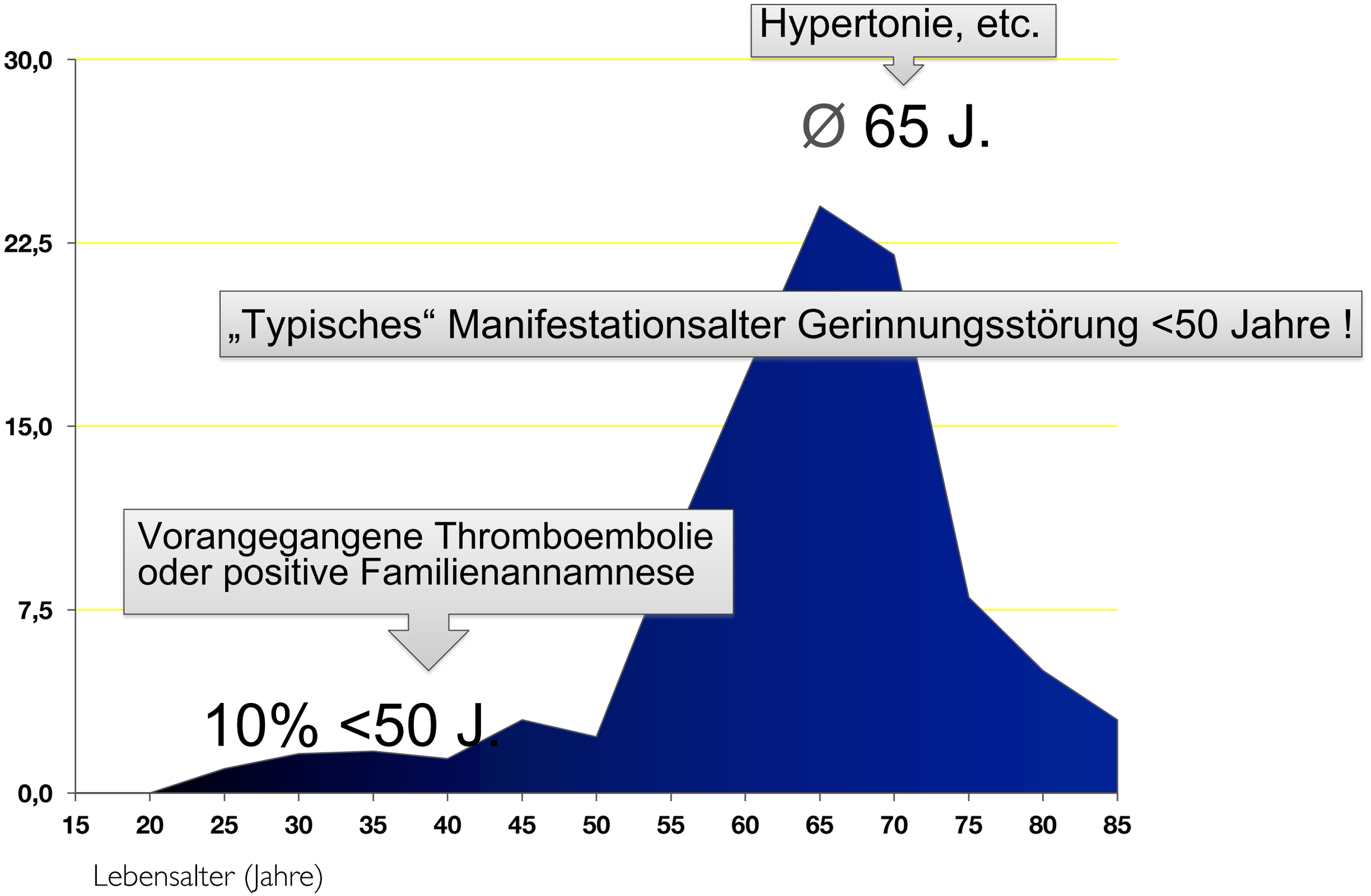
Prävalenz erhöhter Lipoprotein(a)-Spiegel bei unter 60-jährigen Patienten mit venösen retinalen Gefäßverschlüssen

Prevalence of Elevated Lipoprotein (a) Levels in Patients < 60 Years of Age with Retinal Vein Occlusion

Autoren: C. Kuhli-Hattenbach[1], P. Hellstern[2], W. Miesbach[3], T. Kohnen[1], L.-O. Hattenbach[4]

Institute:
[1] Klinik für Augenheilkunde, Klinikum der Johann Wolfgang Goethe-Universität Frankfurt
[2] Institut für Hämostaseologie und Transfusionsmedizin, Klinikum der Stadt Ludwigshafen gGmbH
[3] Medizinische Klinik II/Institut für Transfusionsmedizin und Immunhämatologie, Klinikum der Johann Wolfgang Goethe-Universität Frankfurt
[4] Augenklinik, Klinikum der Stadt Ludwigshafen gGmbH

RVO und Lebensalter



Kuhli-Hattenbach C, Scharrer I, Lüchtenberg M, Hattenbach LO. Coagulation disorders and the risk of retinal vein occlusion. ***Thromb Haemost*** 2010;103:299-305.

Allgemeindiagnostische Abklärung bei RVO

Obligat:

- Ausschluß / Einstellung Arterielle Hypertonie (RR, Langzeit-RR)
- Auschluß Diabetes mellitus

Bei begründetem Verdacht:

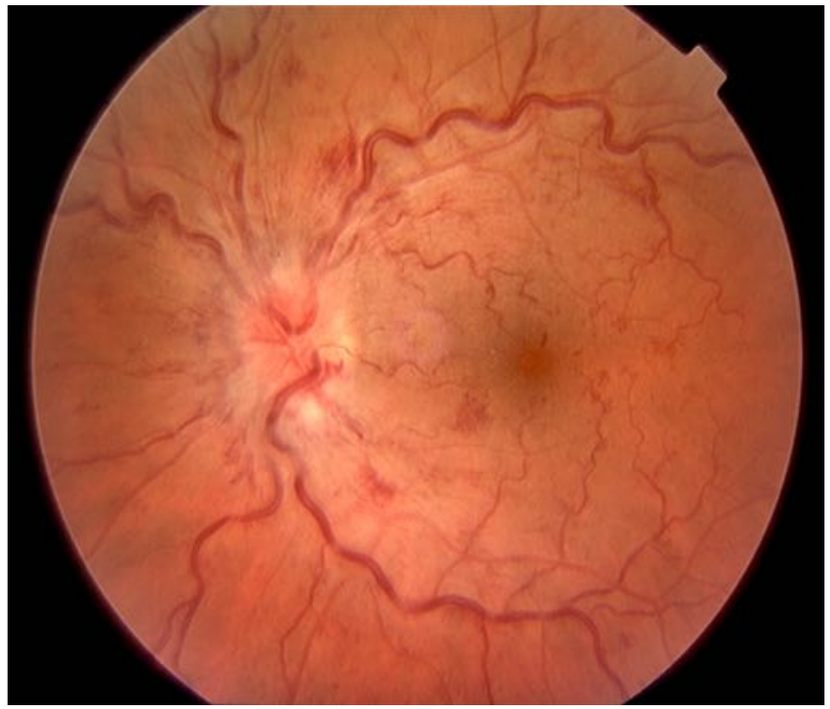
Farbduplex-Sonografie hirnversorgende Gefäße (DD Ischämiesyndrom)

Echokardiografie

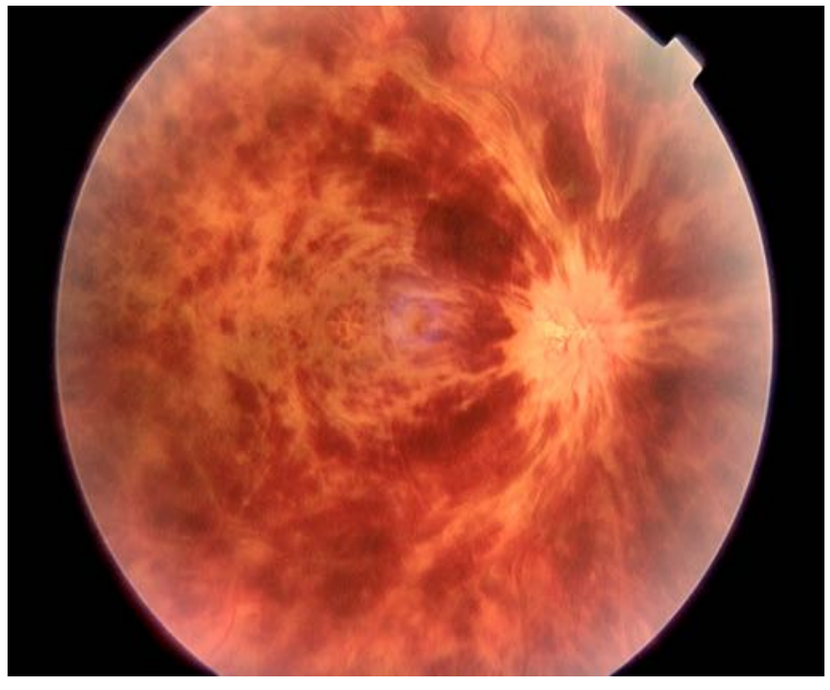
Spezielle Diagnostik, z.B. BB, Diff.-BB, Thrombophilie-Screening, Ausschluß entzündlicher Ursachen (Serologie), etc.

Diagnostik RVO:
Einteilung nach Schweregrad (Hayreh 1983)

Nicht-ischämischer ZVV
(„Venöse-Stase Retinopathie“)



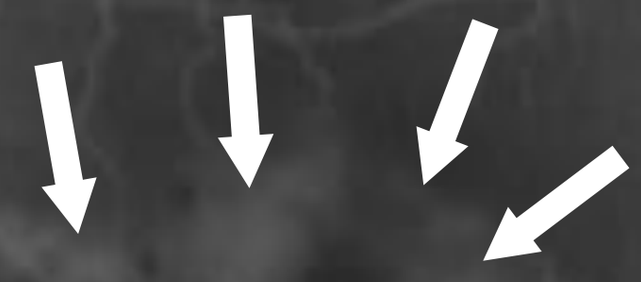
Ischämischer ZVV
(„Hämorrhagische Retinopathie“)



05:11.42

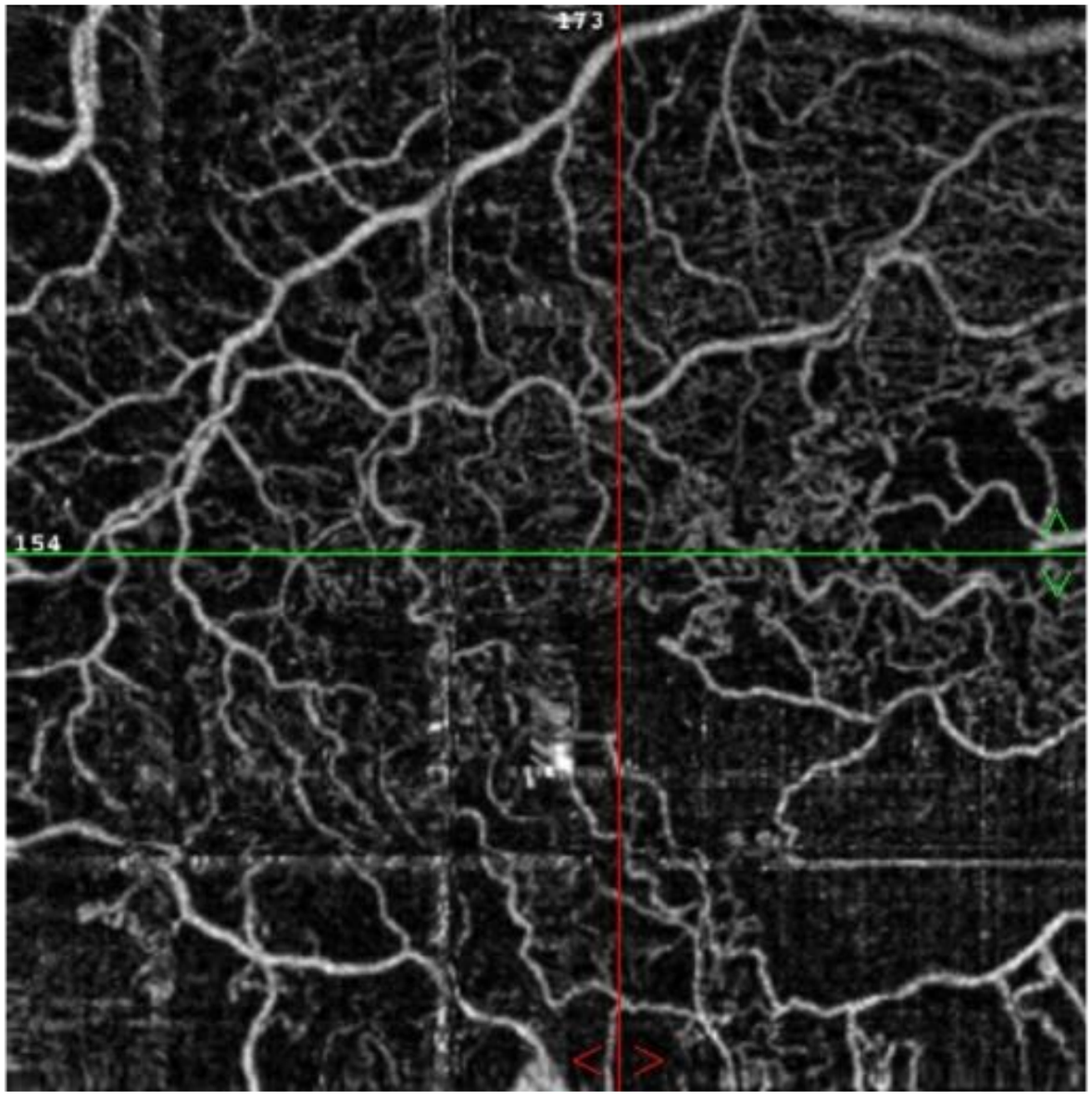
OD

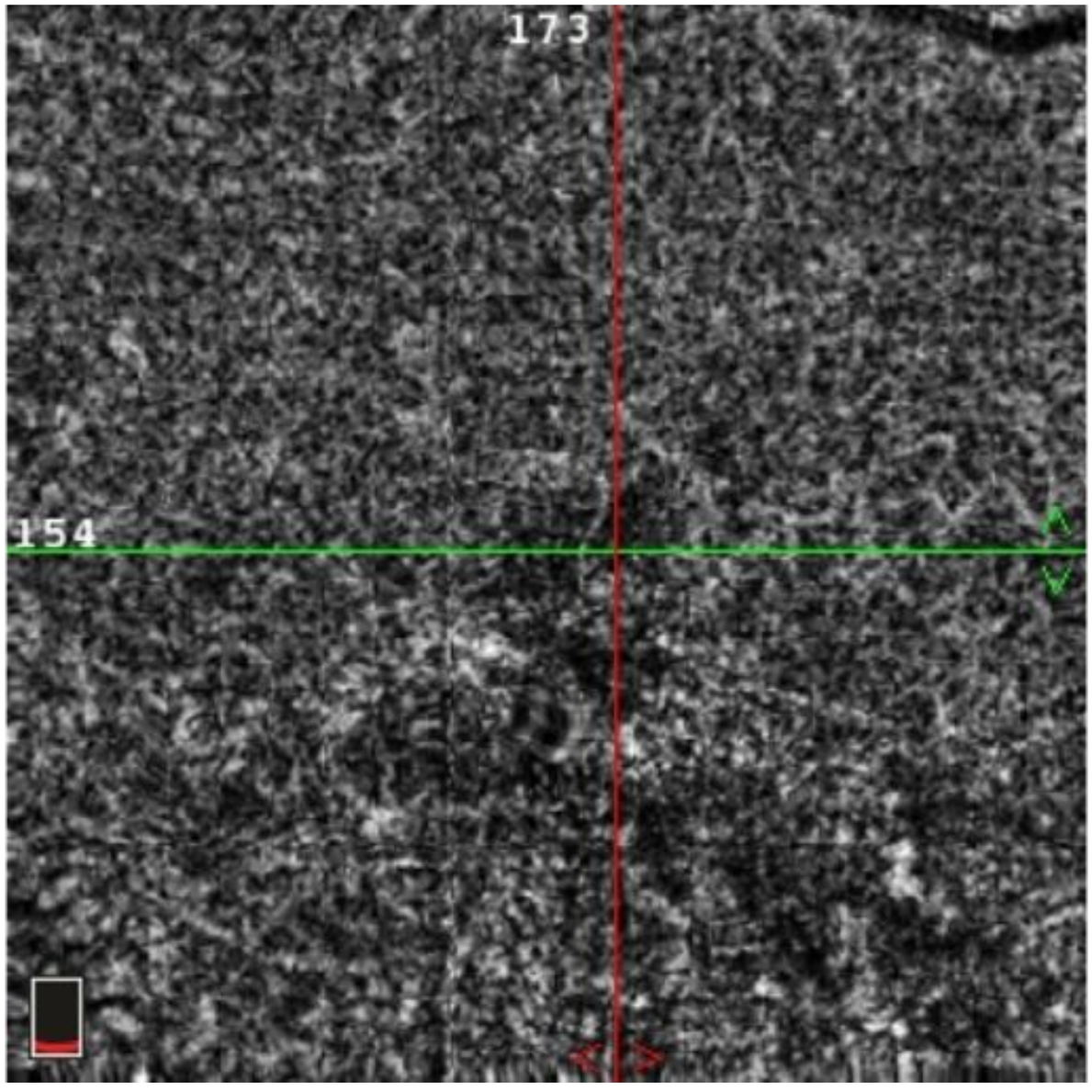
Kapilläre Perfusionsstörung bei RVO



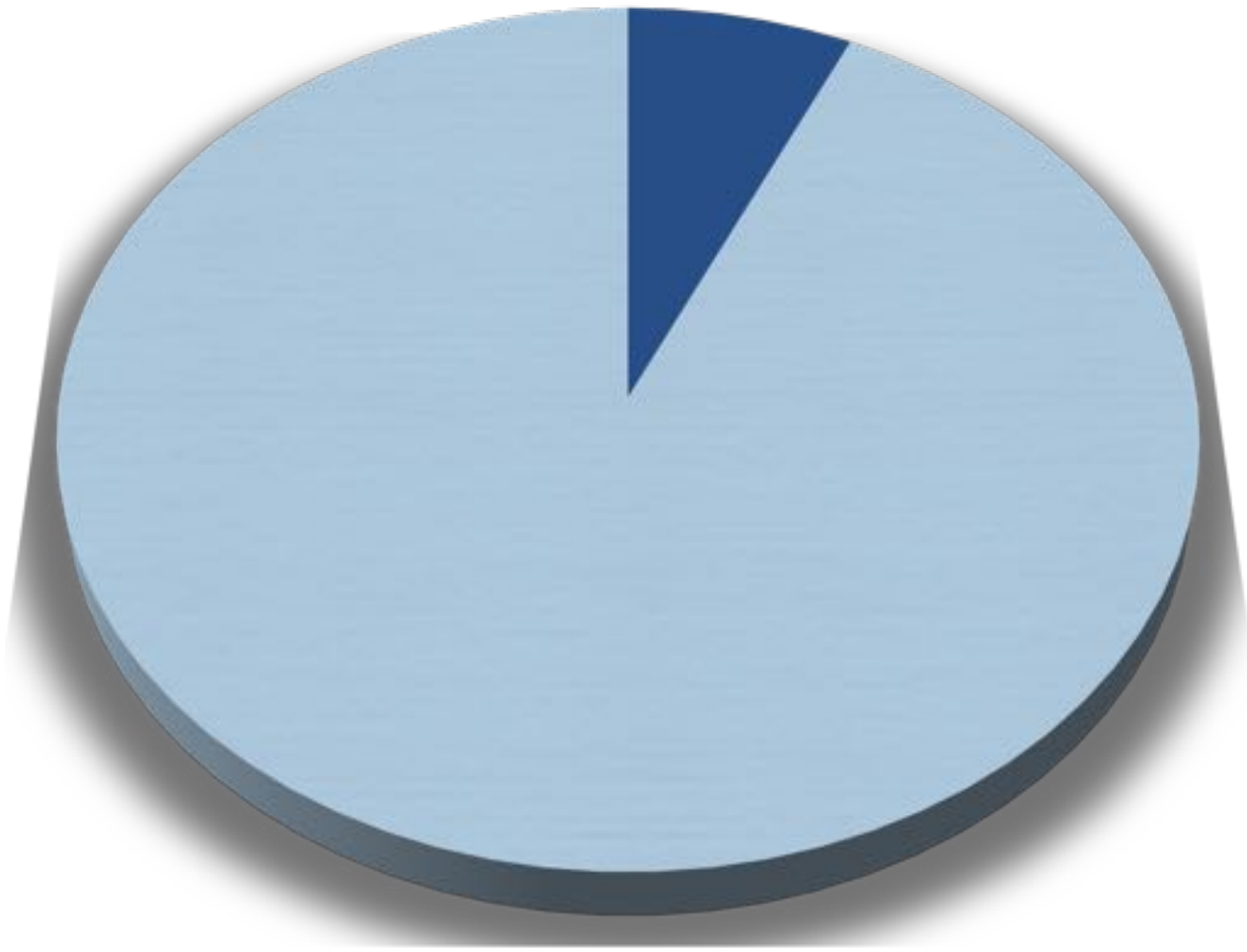
Kapillarischämie

OCT-Angiografie: Perfusionsausfall bei VAV

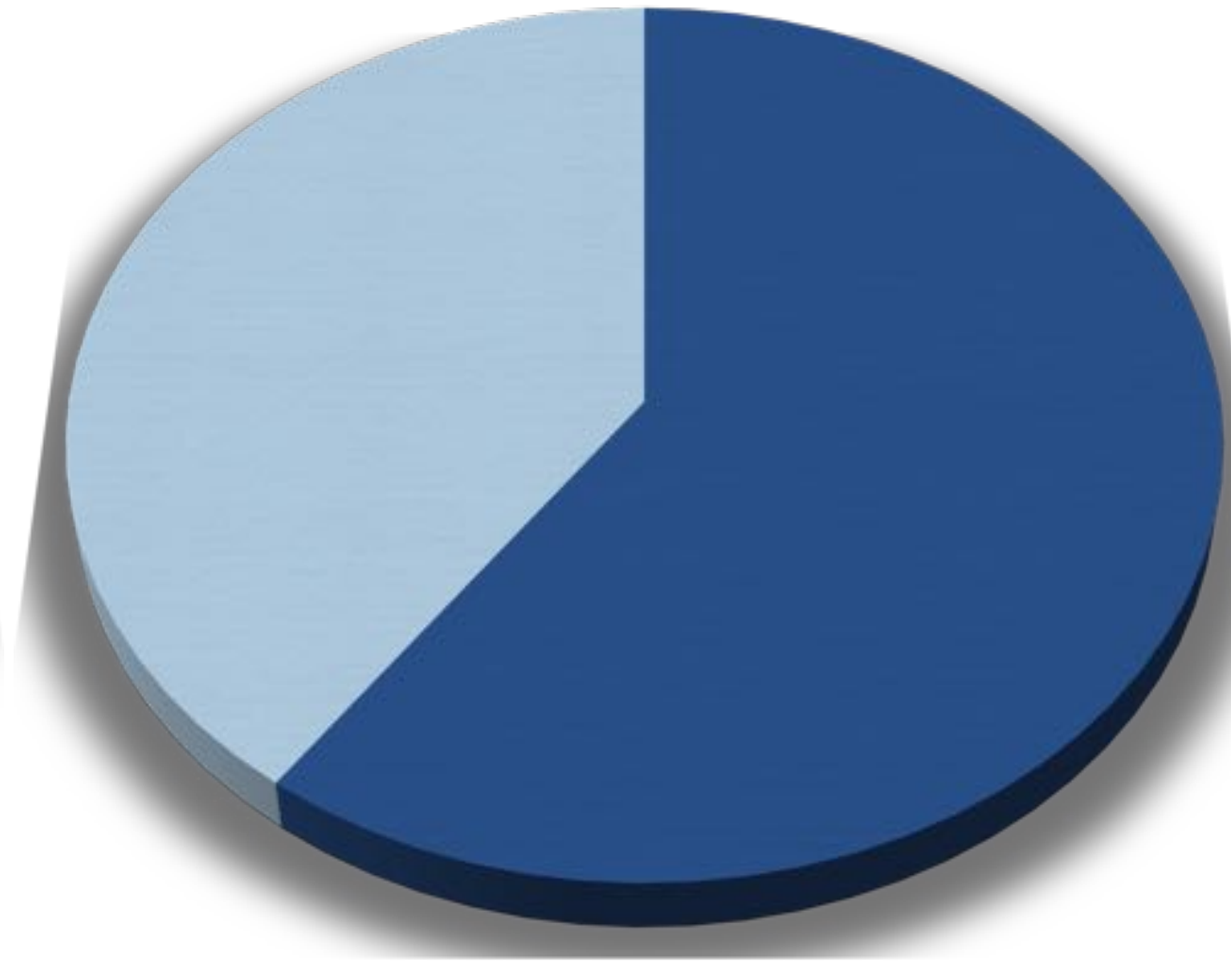




RVV: Zusammenhang Ischämiegrad und Visusprognose

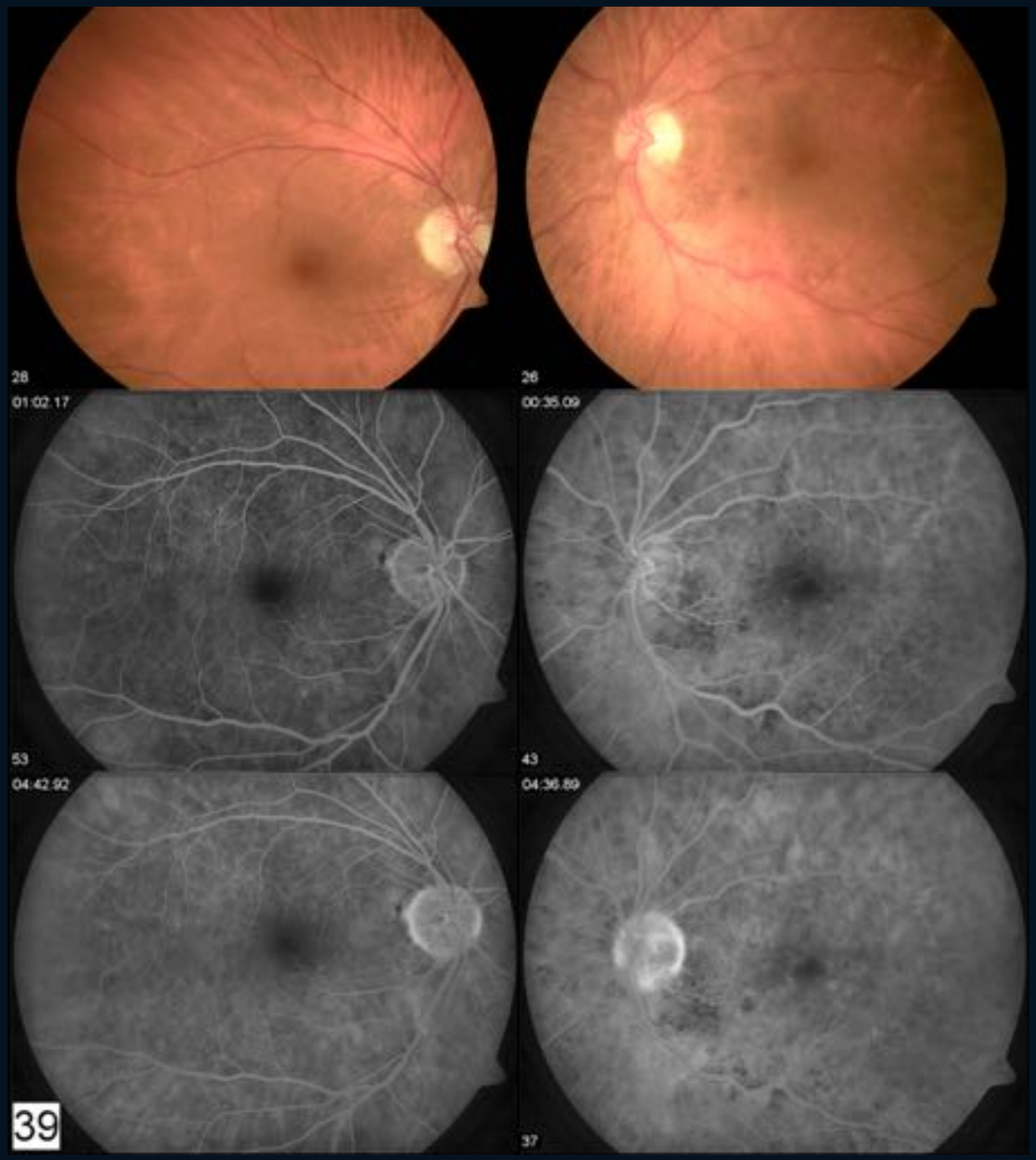


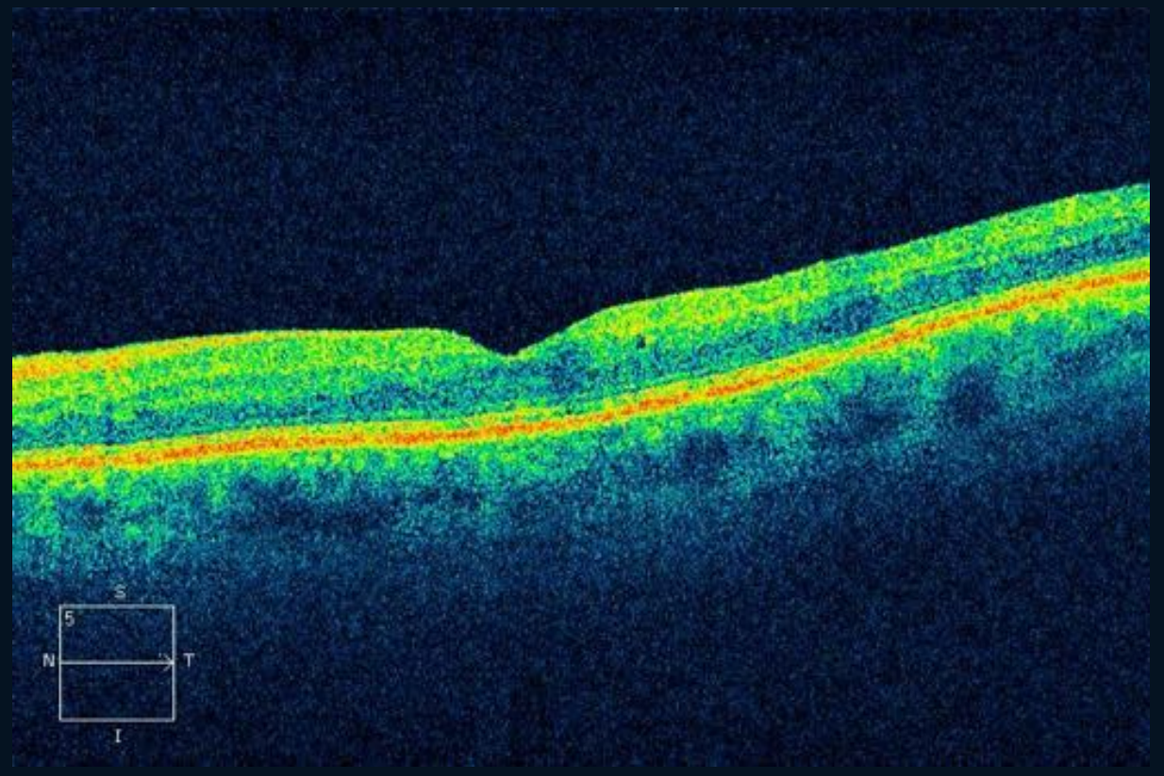
Ischämischer ZVV: 93% <0,1



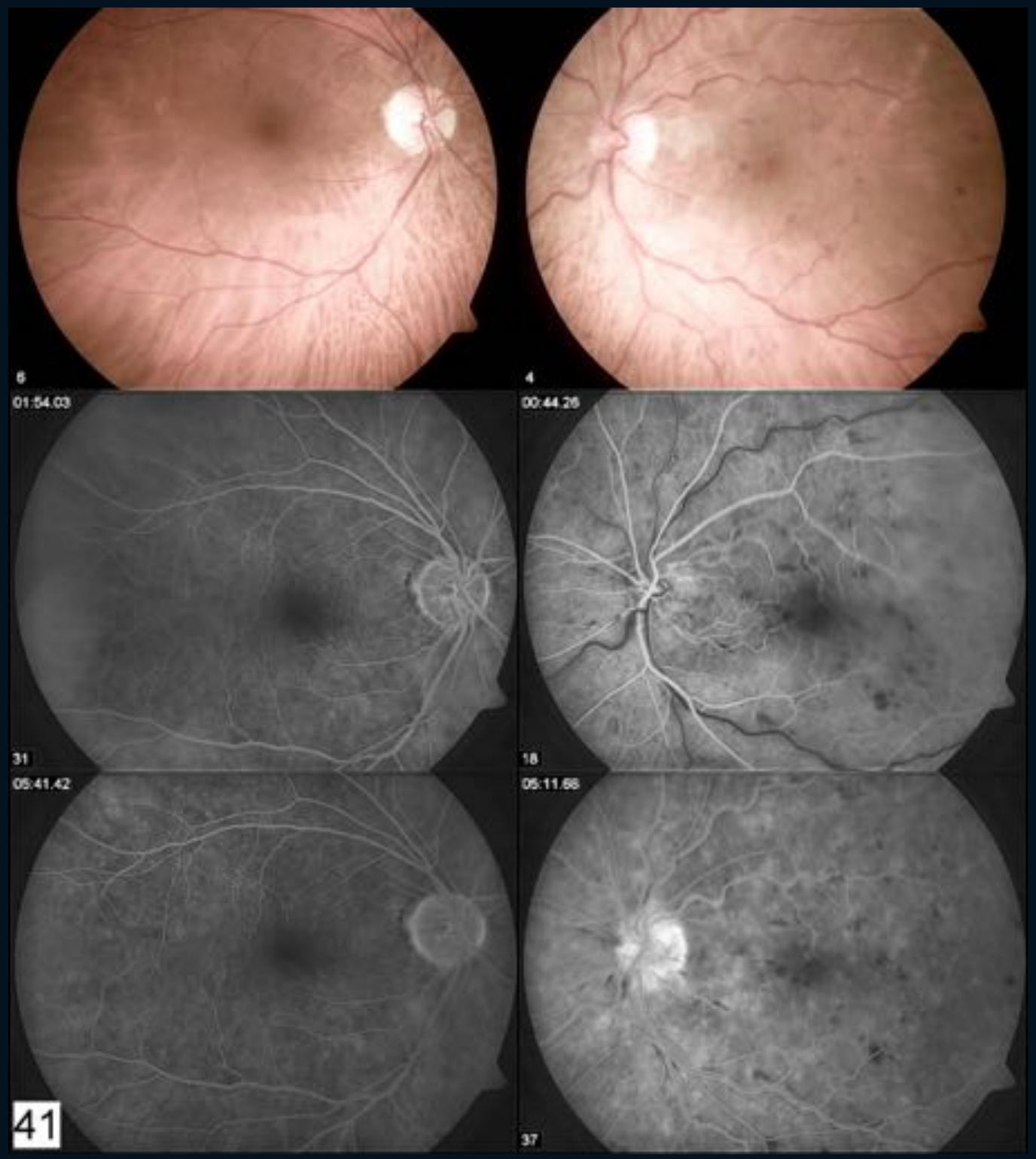
VAV: 50-60% ≥0,5

Initialer Befund ZVV LA, Visus 1,0, Therapie: Beobachtung

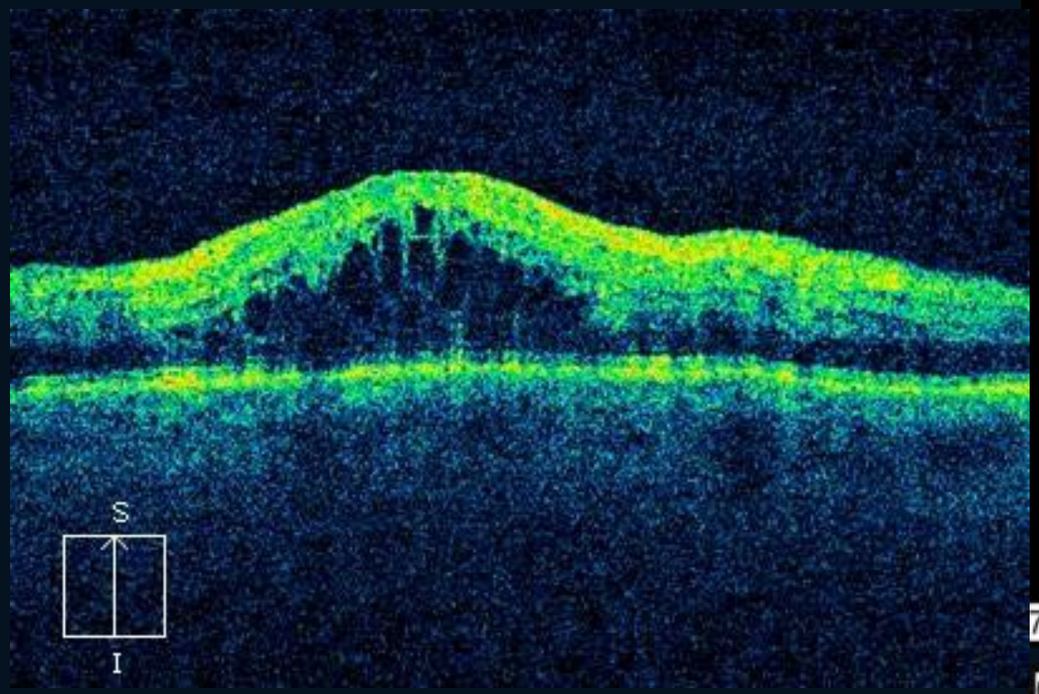


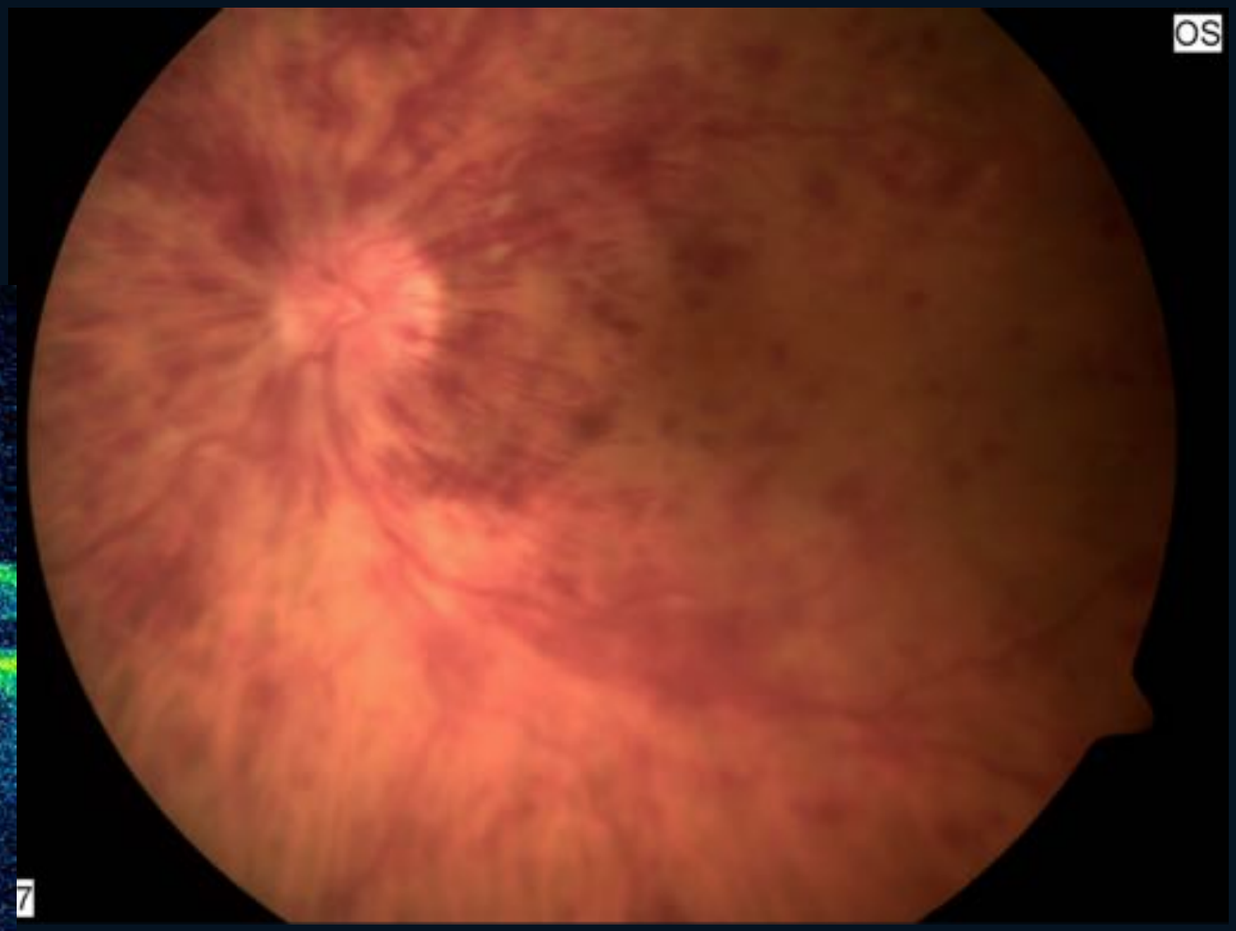


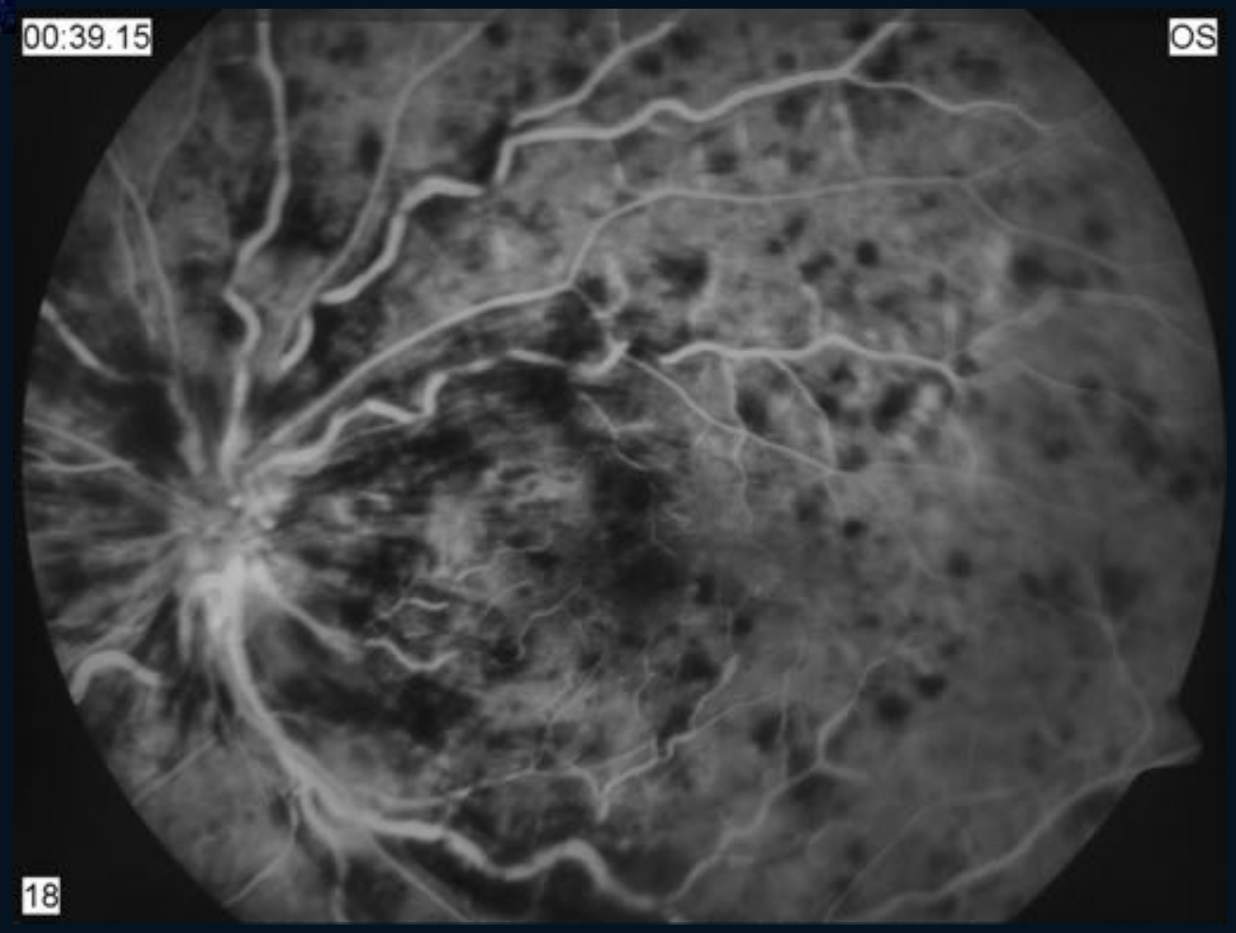
Befund nach 5 Monaten



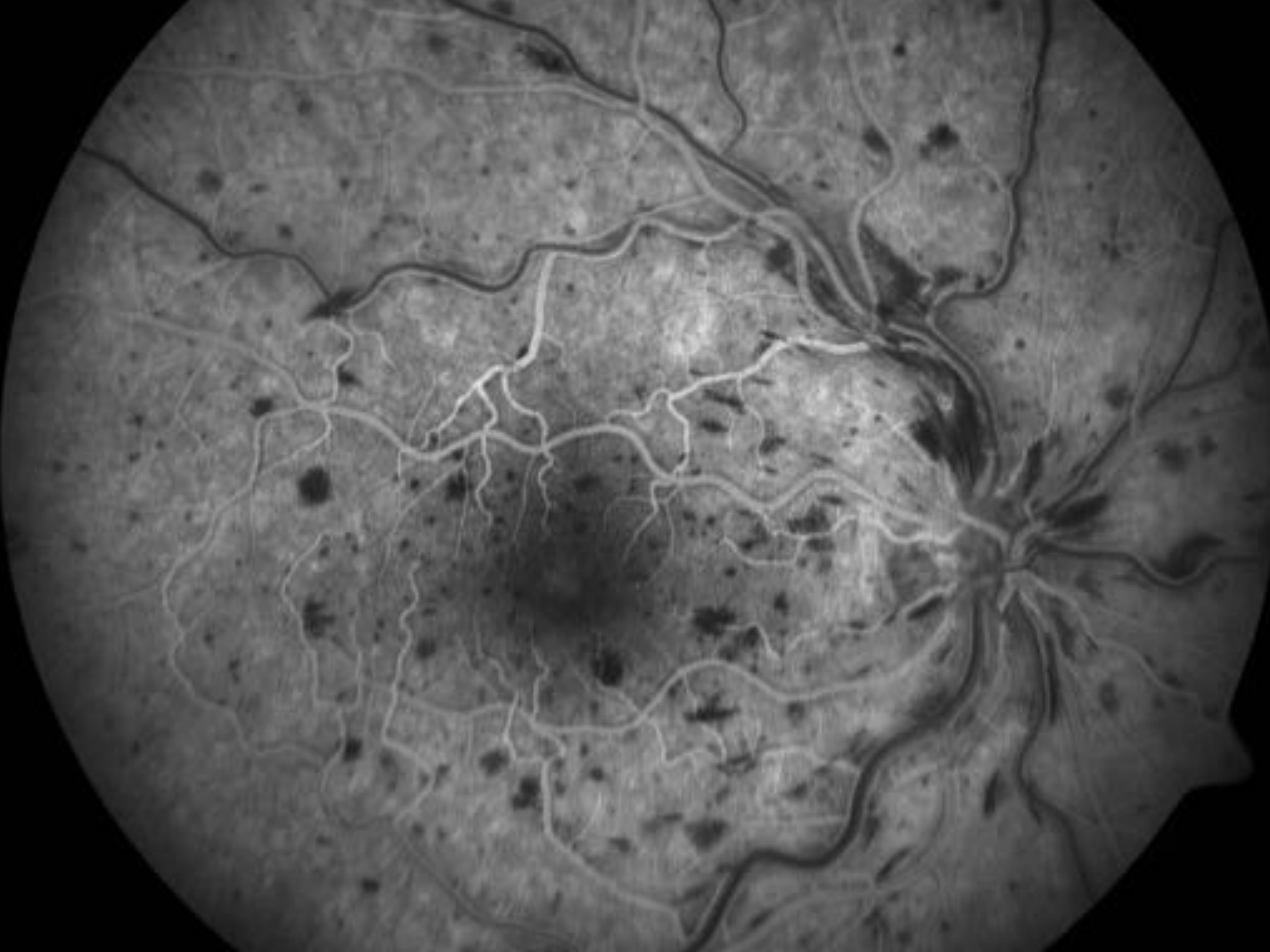
Befund nach 8 Monaten



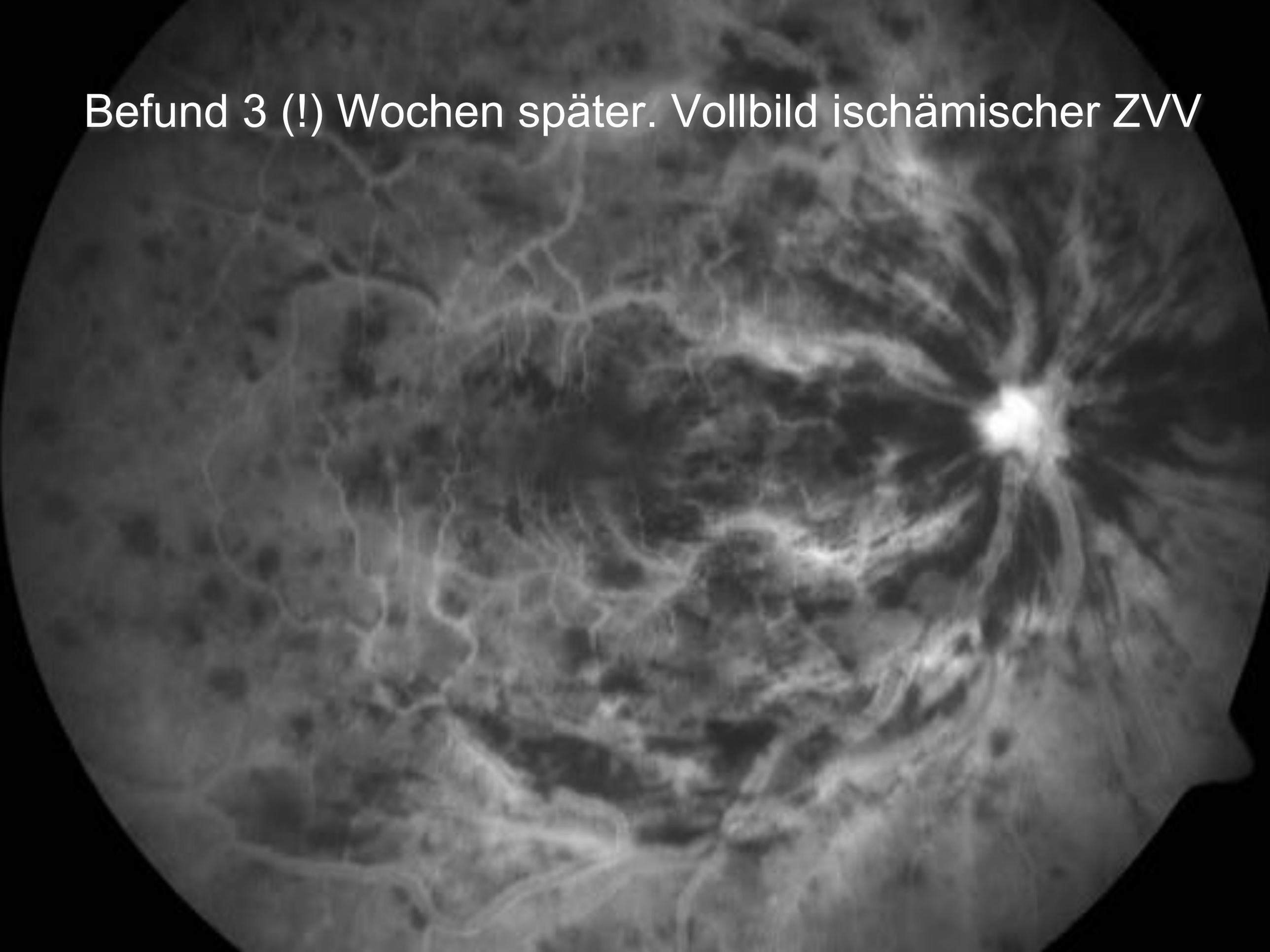




Nicht-ischämischer ZVV



Befund 3 (!) Wochen später. Vollbild ischämischer ZVV



Nicht-ISCHÄMISCHER
ZVV

20-30%

ISCHÄMISCHER
ZVV

ASSOCIATION BETWEEN RETINAL HEMORRHAGIC PATTERNS AND PERFUSION STATUS IN EYES WITH ACUTE CENTRAL RETINAL VEIN OCCLUSION

YUKI MURAOKA, MD, PhD,* AKIHITO UJI, MD, PhD,* AKITAKA TSUJIKAWA, MD, PhD,† TOMOAKI MURAKAMI, MD, PhD,* SOTARO OOTO, MD, PhD,* KIYOSHI SUZUMA, MD, PhD,* AYAKO TAKAHASHI, MD,* YUTO IIDA, MD,* YUKO MIWA, MD,* MASAYUKI HATA, MD,* NAGAHISA YOSHIMURA, MD, PhD*

Purpose: To evaluate peripheral retinal hemorrhagic patterns in eyes with acute central retinal vein occlusion, and to explore their clinical relevance in differentiating for the retinal perfusion status, through a prospective, and cross-sectional study.

Methods: Fifty eyes with acute central retinal vein occlusion were included. Retinal hemorrhagic patterns at the equator and retinal perfusion status were evaluated by ultra-wide field fundus photography and fluorescein angiography.

Results: Retinal perfusion was categorized as nonischemic in 29 eyes, ischemic in 18 eyes, and undeterminable in 3 eyes. None of the examined eyes had flame-shaped retinal hemorrhages in the periphery. All hemorrhages were rounded-dot or blot and were variable in size. Particle analysis was performed to quantify hemorrhage size, and showed higher values in eyes having larger blot hemorrhages, and lower values in eyes having dot or smaller blot hemorrhages. Mean size of maximum peripheral dot or blot hemorrhage was larger in eyes classified as ischemic (10,763.0 ± 5,946.3 pixels) than as nonischemic (2,839.9 ± 1,153.6 pixels, $P < 0.001$). The authors calculated area under the curve to investigate the ability of continuous variables to discriminate retinal perfusion status, which was 0.963 ($P < 0.001$) for mean size of maximum peripheral blot hemorrhages.

Conclusion: The authors objectively evaluated retinal hemorrhagic patterns at the equator in eyes with acute central retinal vein occlusion using particle analysis. The resulting hemorrhage size measurement was considered to be often useful in determining retinal perfusion status. Because they can be noninvasively evaluated with readily available equipment, peripheral hemorrhagic patterns might be good clinical markers of retinal perfusion.

RETINA 0:1–9, 2016

Nicht-ischämisches peripheres Hämorrhagie-Muster

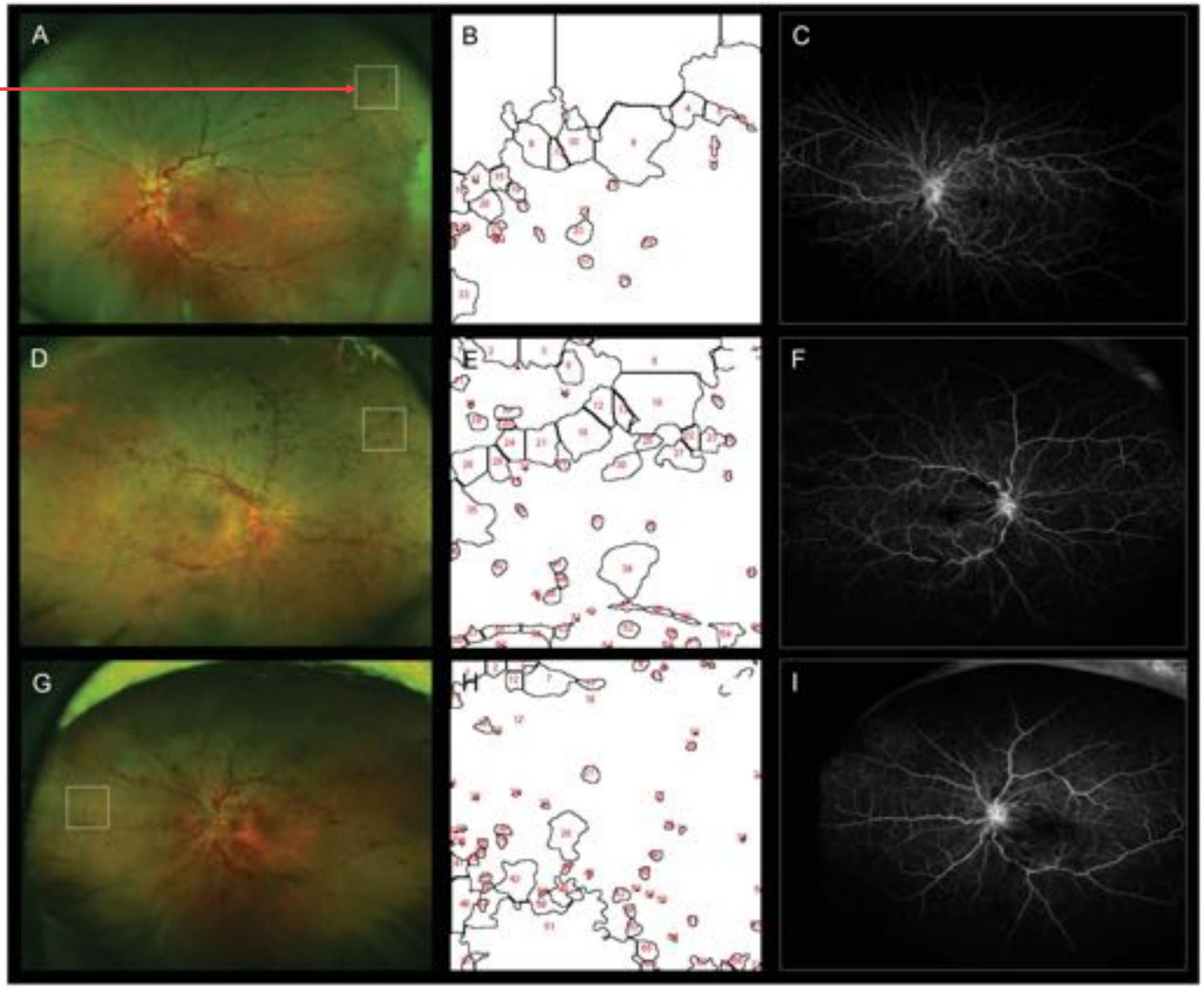


Fig. 2. Small blot hemorrhages are visible in the periphery of 3 eyes with nonischemic CRVO. Ultra-wide field color fundus photographs show small blot hemorrhages, predominantly in the retinal periphery (**A**, **D**, and **G**). **B**, **E**, and **H.** Results of particle analysis performed to determine the size of peripheral blot hemorrhages at the equatorial retina. The resulting mean sizes of maximum peripheral retinal hemorrhages were 1,879 (**B**), 3,100 (**E**), and 2,466 (**H**) pixels. **C**, **F**, and **I.** Images from UWF fluorescein angiograms showing that the eyes had no definitive areas of retinal nonperfusion.

Ischämisches peripheres Hämorrhagie-Muster

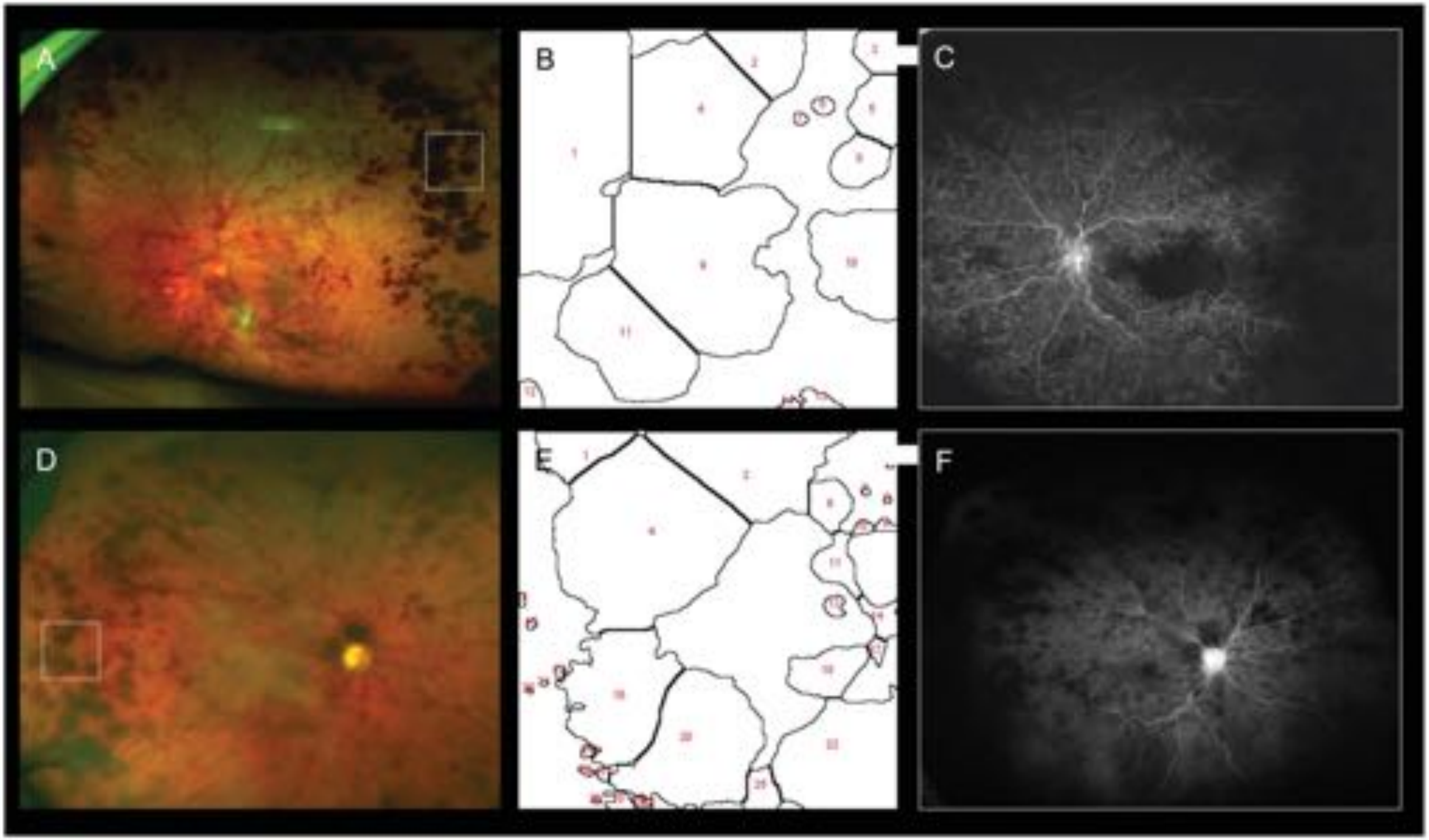


Fig. 3. Large blot hemorrhages visible in the periphery of 2 eyes with ischemic acute CRVO. Ultra-wide field color fundus photographs show large blot hemorrhages predominantly in the retinal periphery (**A** and **D**). **B** and **E.** Results of particle analysis performed to determine the size of peripheral blot hemorrhages at the equatorial retina. The resulting mean sizes of maximum peripheral retinal hemorrhages were 15,269 (**B**) and 22, 262 (**E**) pixels. **C** and **F.** Images from UWF fluorescein angiograms showing large areas of retinal nonperfusion in the periphery (**C** and **F**) and macular ischemia (**C**).

Ischämie = Trigger VEGF

Levels of VEGF but not $VEGF_{165b}$ are Increased in the Vitreous of Patients With Retinal Vein Occlusion

CHRISTOPH EHLKEN, EMMA S. RENNEL, DANIEL MICHELS, BASTIAN GRUNDEL, AMELIE PIELEN, BERND JUNKER, ANDREAS STAHL, LUTZ L. HANSEN, NICOLAS FELTGEN, HANSJÜRGEN T. AGOSTINI, AND GOTTFRIED MARTIN

TABLE 2. Concentration of Total Protein, VEGF, and $VEGF_{165b}$ in Vitreous Fluid of Retinal Vein Occlusion Patients and Controls

		VEGF		$VEGF_{165b}$		$VEGF_{165b}$/VEGF		
Patient Group	Number of Patients	Conc. [pg/mL] ± SEM	Fold Relative to Control (*P* Value)	Conc. [pg/mL] ± SEM	Fold Relative to Control (*P* Value)	Value[b] ± SEM	Fold Relative to Control (*P* Value)	Protein Conc. [mg/mL] ± SEM
CRVO	17	8653 ± 3020	33.8 (.013)[a]	27 ± 7.5	0.54 (.046)[a]	0.0073 ± 0.0026	42.4 (.007)[a]	7.7 ± 0.60[a]
BRVO	19	1994 ± 582	7.8 (.008)[a]	42 ± 10	0.85 (.585)	0.046 ± 0.020	6.4 (.046)[a]	5.2 ± 0.29
Control	32	256 ± 43	—	49 ± 8.1	—	0.31 ± 0.15	—	5.1 ± 0.25

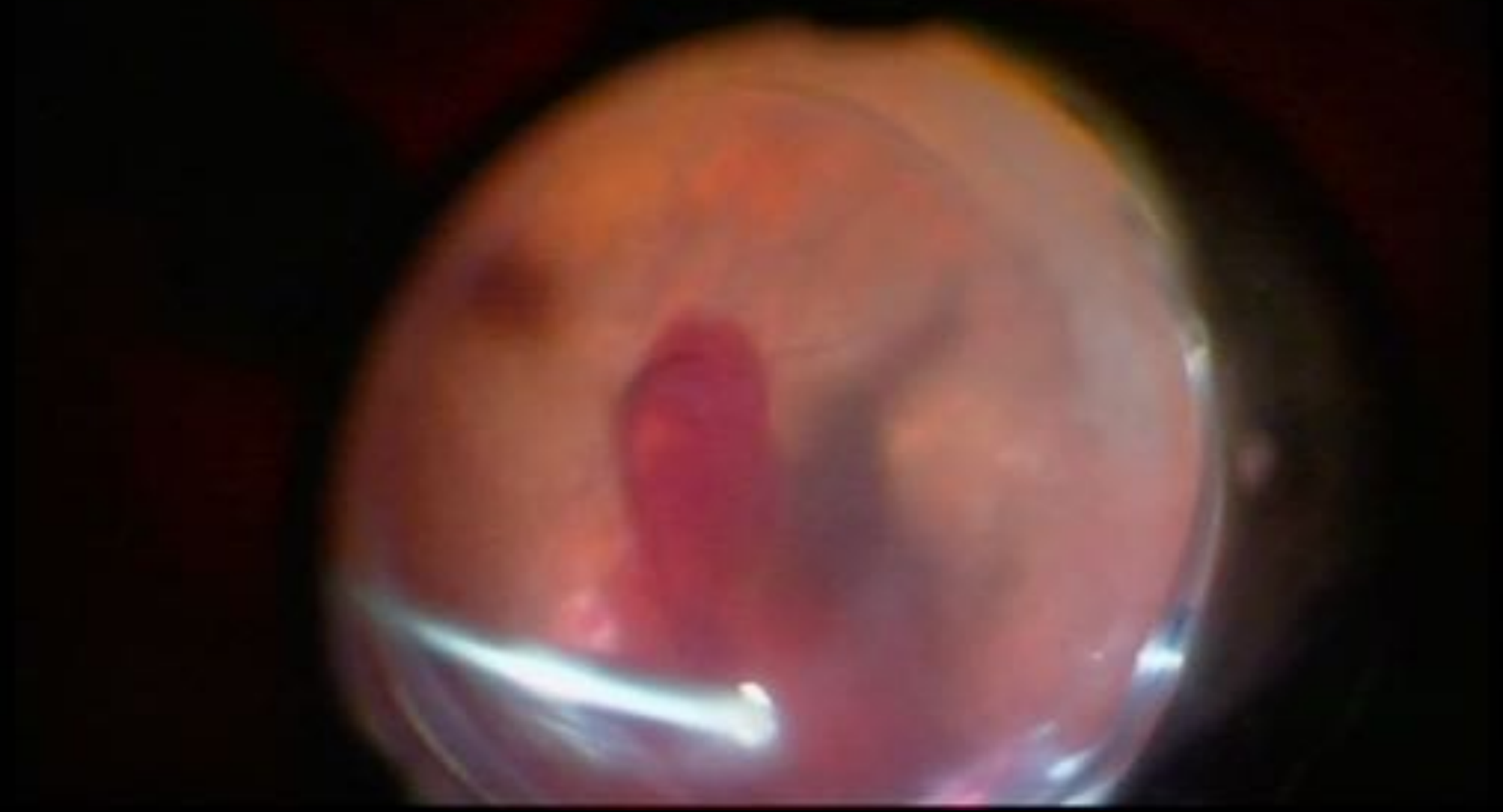
— = not applicable; BRVO = branch retinal vein occlusion; Conc. = concentration; CRVO = central retinal vein occlusion; SEM = standard error of mean; VEGF = vascular endothelial growth factor.

[a]Significant as determined by *t* test ($P < .05$).

[b]Mean value is based on the individual ratios of $VEGF_{165b}$/VEGF.

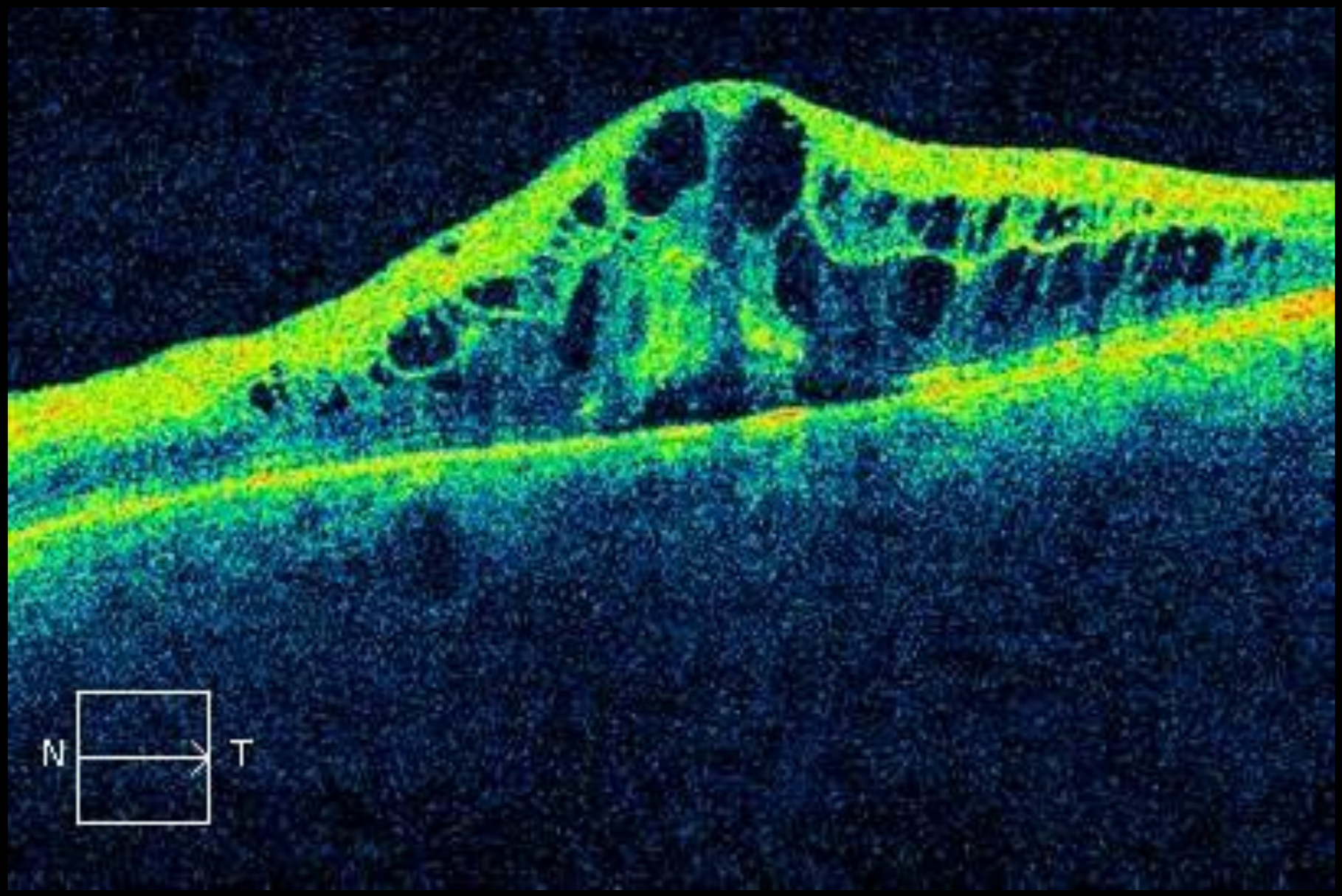
Ehlken et al. Am J Ophthalmol. 2011;152:298-303

VEGF-Effekt: Neovaskularisation



GK-Blutung nach ZVV, Rubeosis iridis

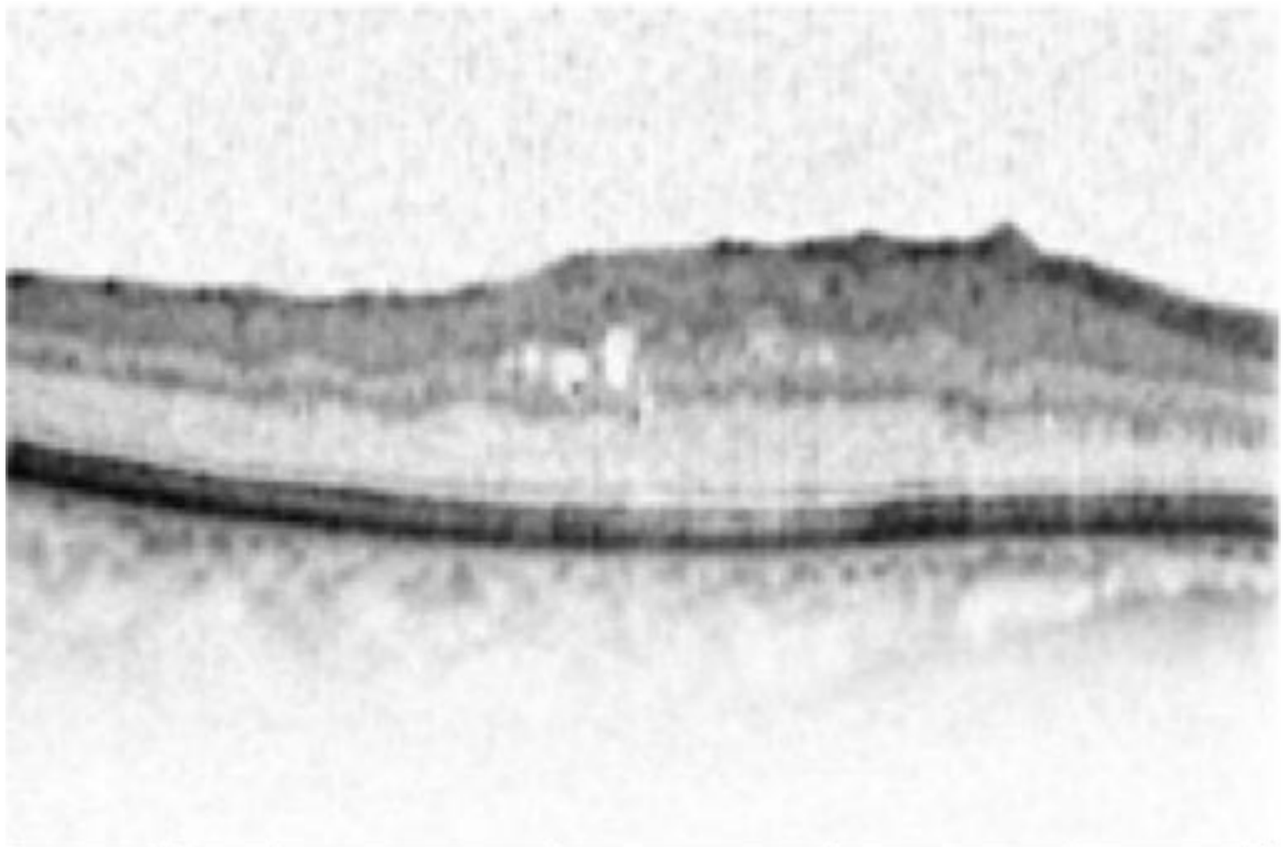
VEGF-Effekt: Schrankenstörung

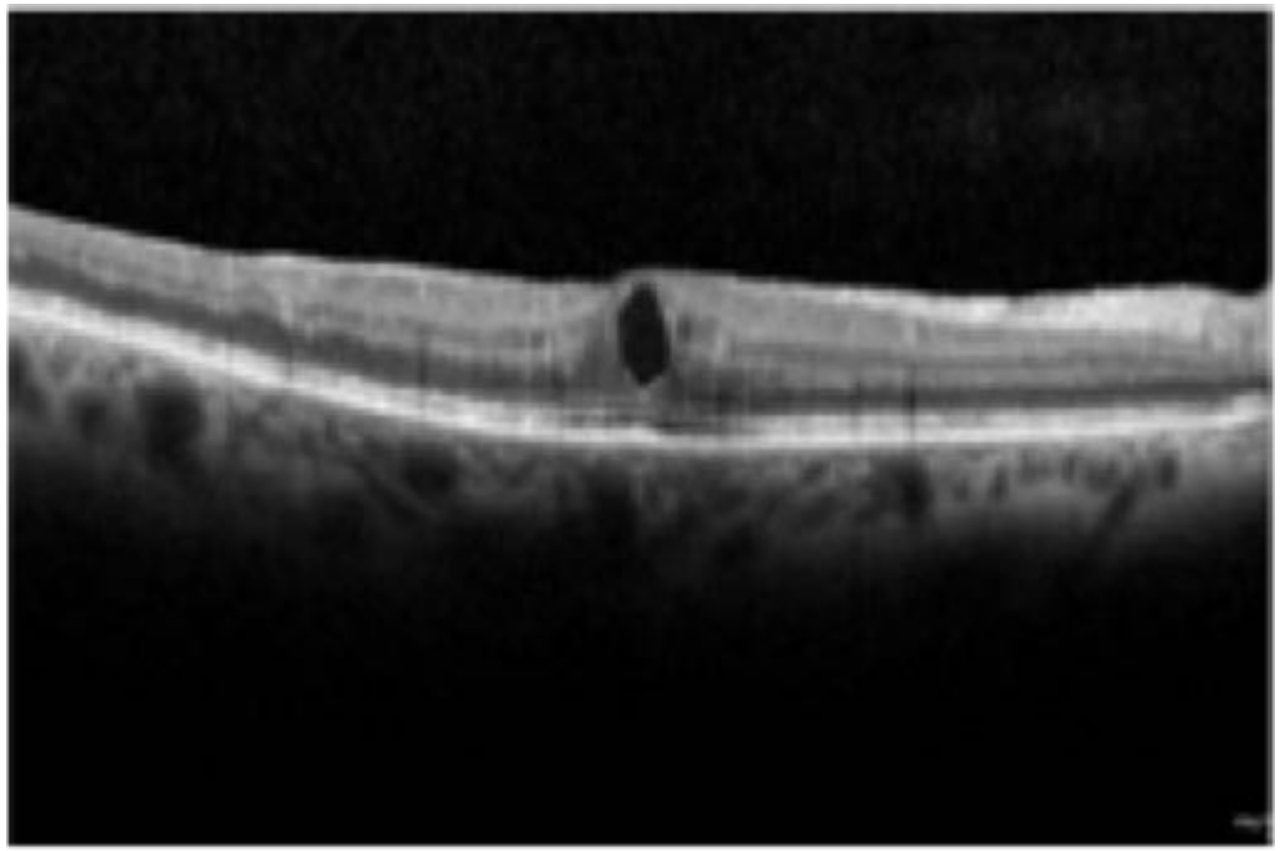


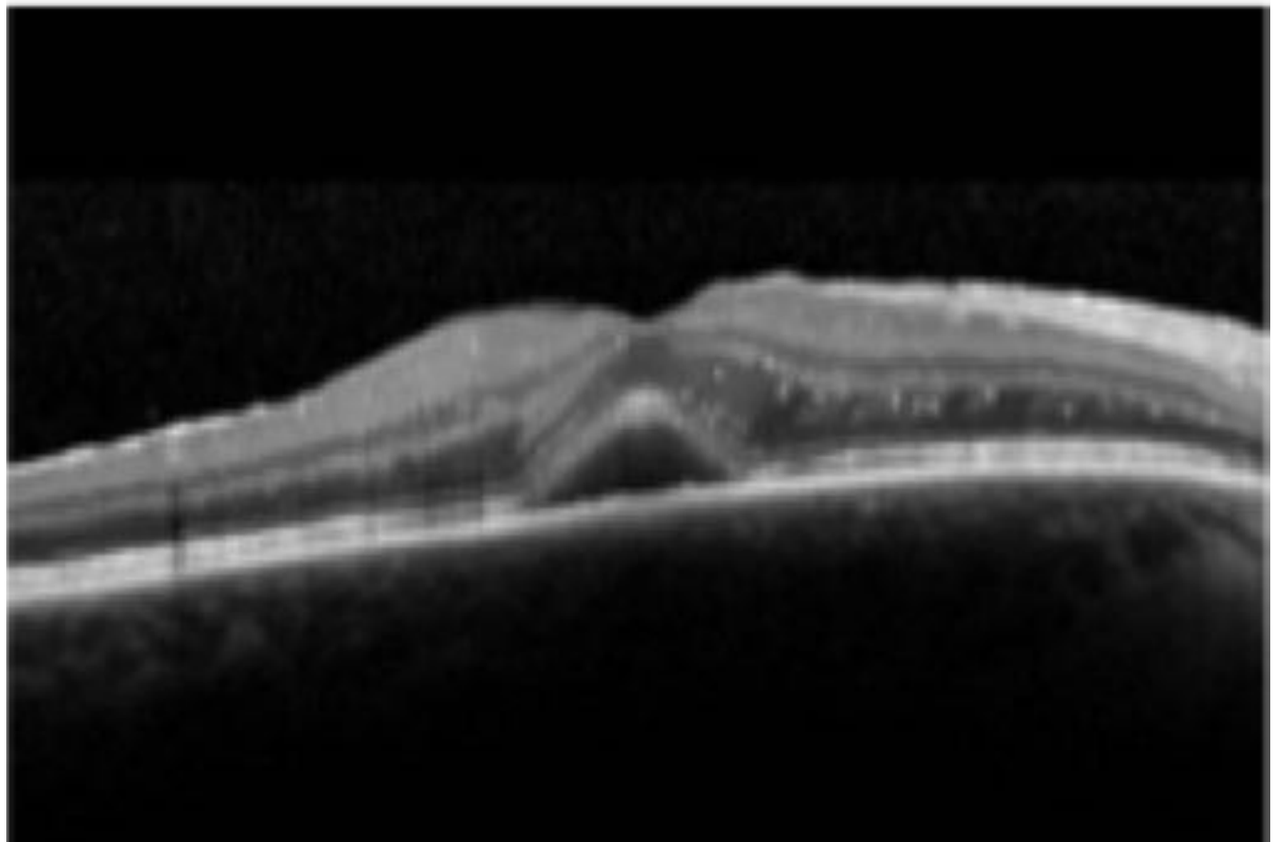
MT 740 µm

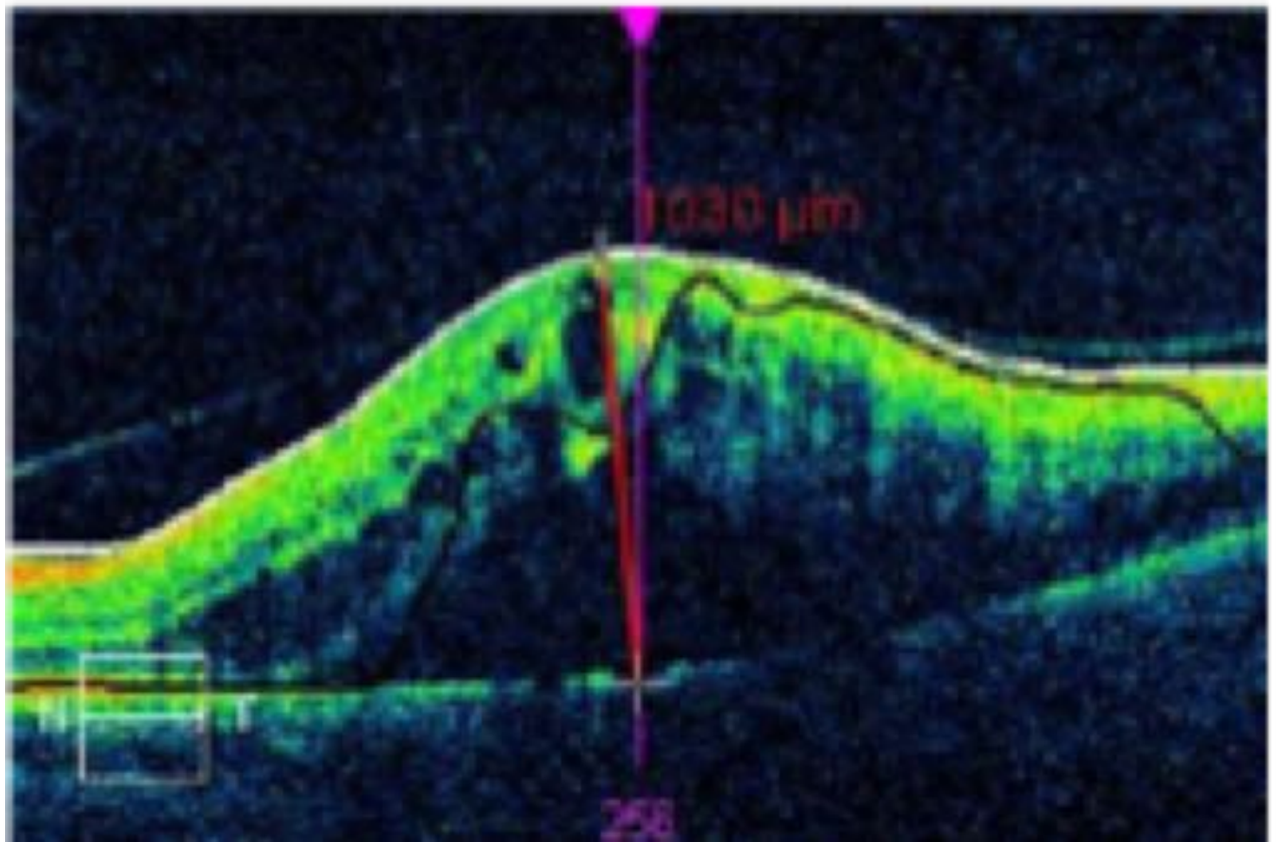
Makulaödem

MÖ : Unterschiedliche Morphologie

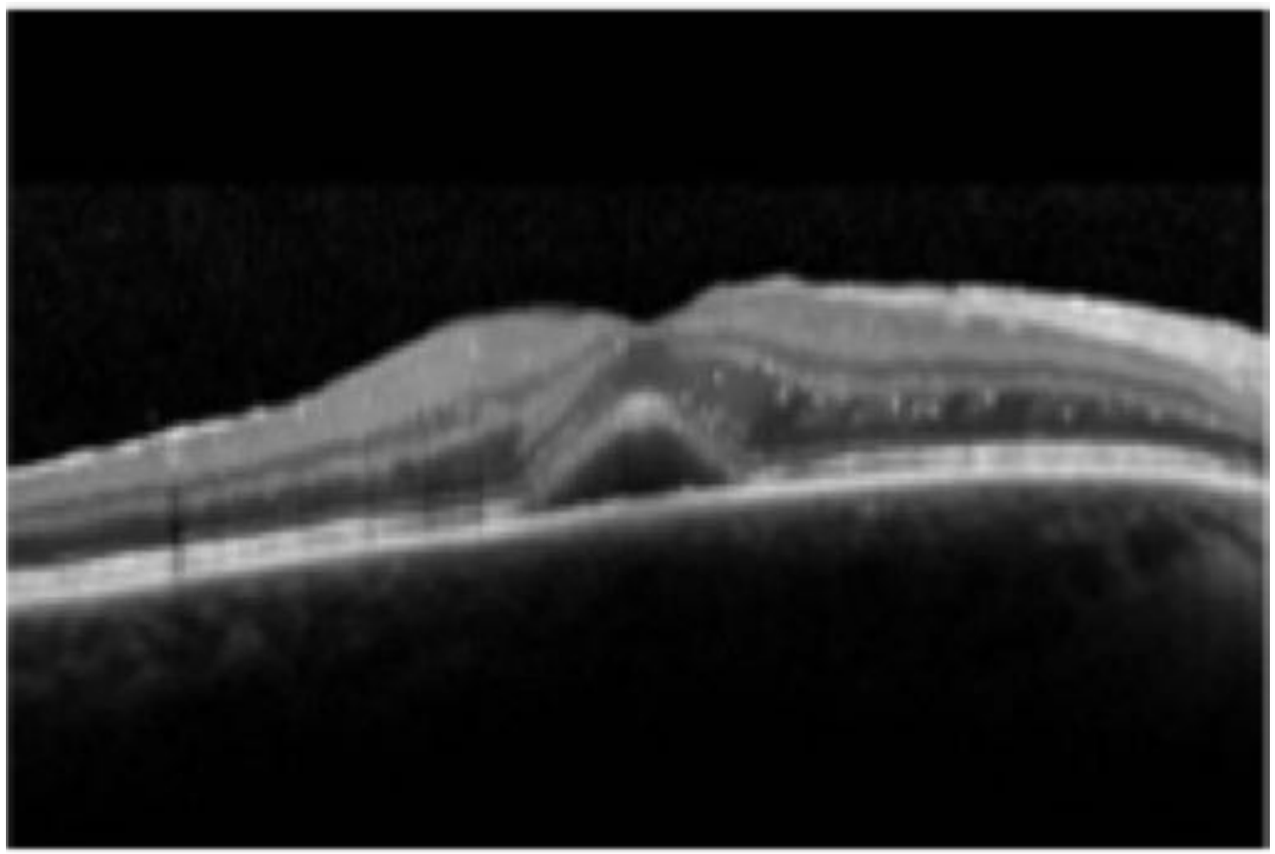


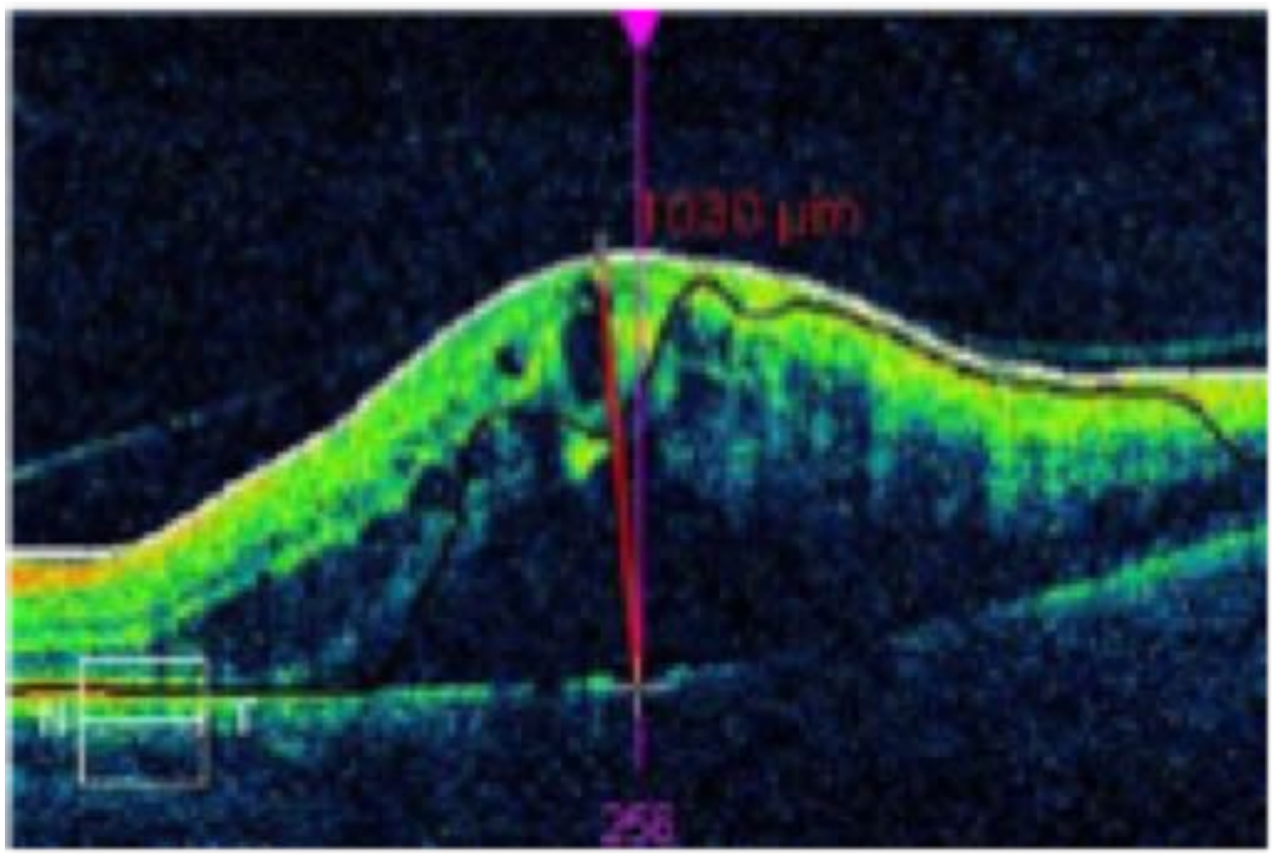






Subretinale Flüssigkeit



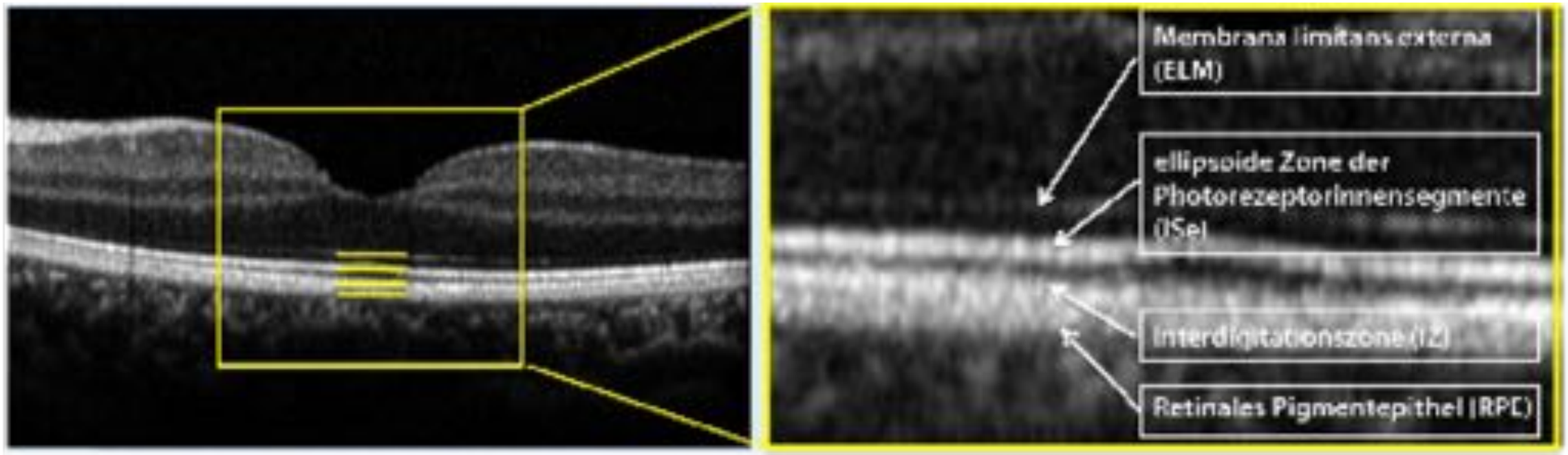


Wang MZ, Feng K, Lu Y, Qian F, Lu XR, Zang SW, Zhao L. Predictors of short-term outcomes related to central subfield foveal thickness after intravitreal bevacizumab for macular edema due to central retinal vein occlusion. Int J Ophthalmol. 2016 Jan 18;9(1):86-92.

Gesamtdicke MÖ entscheidender als subretinale Flüssigkeit ?

K. Schröder · P. Ackermann · M. Brachert · S. Bairov · G. Geerling · R. Guthoff
Augenklinik Universitätsklinikum Düsseldorf, Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Deutschland

Liefert die OCT-Morphologie Hinweise für die Visusprognose nach Venenverschluss?



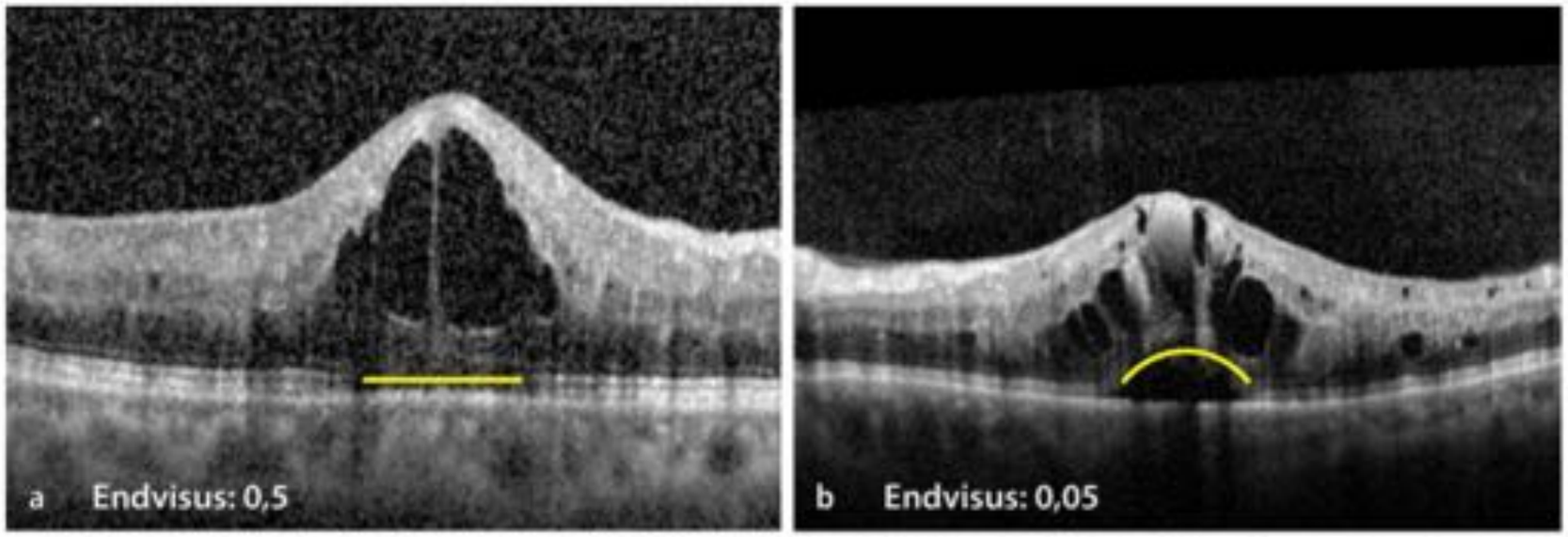
Shin HJ1, Chung H, Kim HC. Association between integrity of foveal photoreceptor layer and visual outcome in retinal vein occlusion. Acta Ophthalmol. 2011;89(1):e35-40.

Zusammenhang zwischen funktionellem Ergebnis und Morphologie

Guter Visus nach Therapie

- = MÖ vor Therapie meist oberhalb ellipsoider Zone der Innensegmente (ISe)

- = Nach Ödemresorption ISe häufiger morphologisch intakt



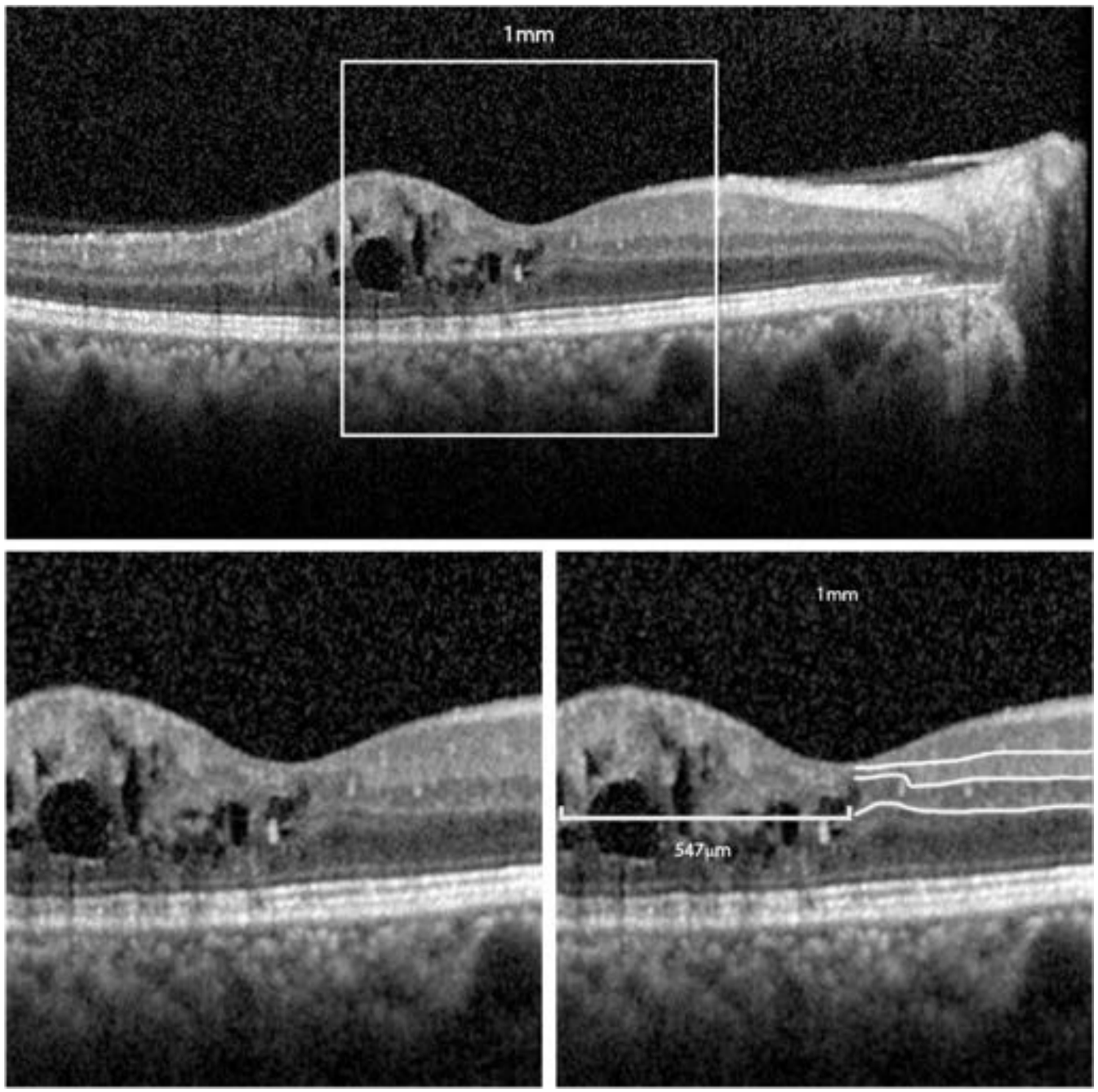
Disorganization of the Retinal Inner Layers as a Predictor of Visual Acuity in Eyes With Macular Edema Secondary to Vein Occlusion

MICHAEL MIMOUNI, OR SEGEV, DALIA DORI, NOA GEFFEN, VICTOR FLORES, AND ORI SEGAL

Am J Ophthalmol 2017;182:160–167

DRIL

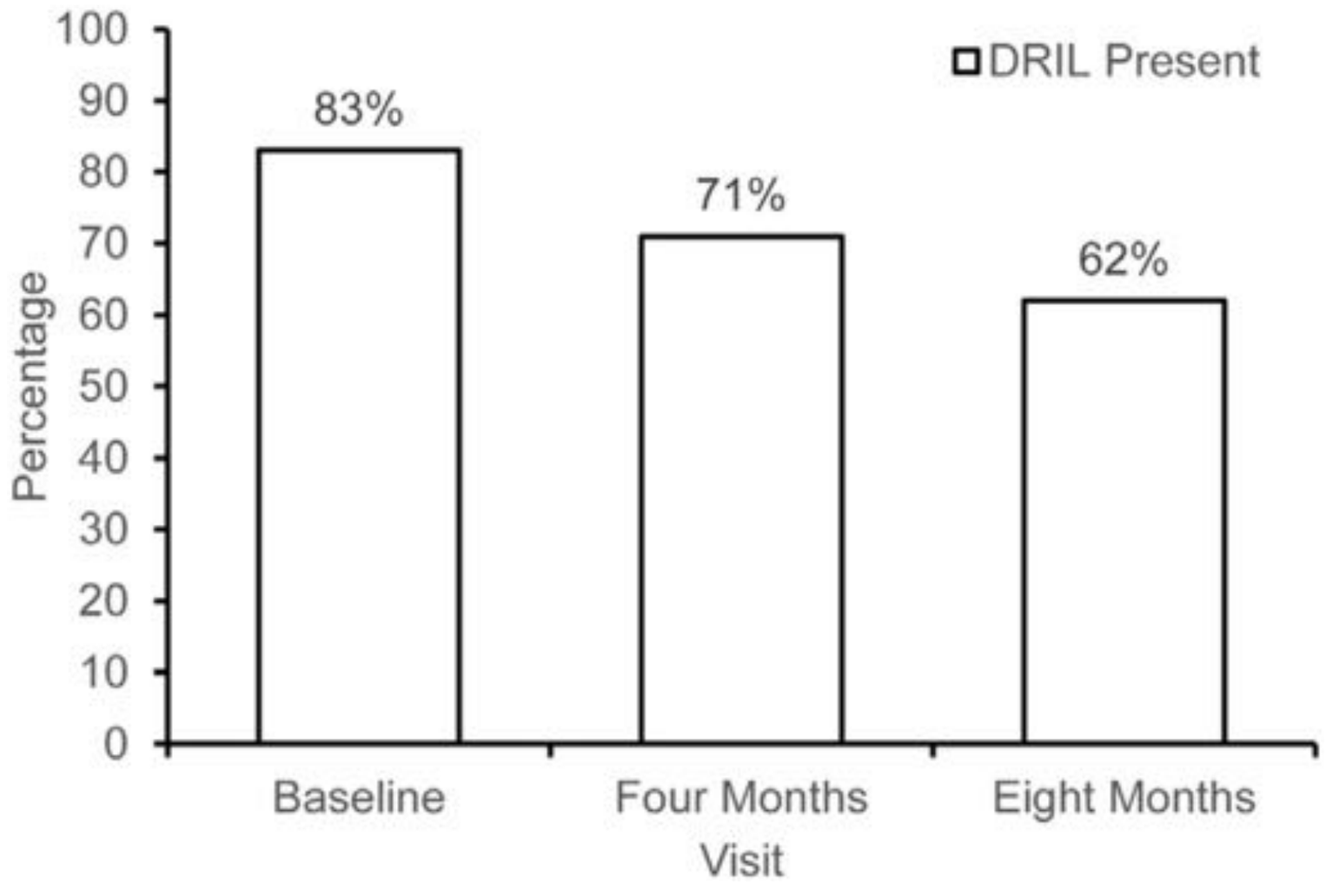
- Meßbereich Fovea (1mm)
- Keine Identifikation der Grenzen zwischen innerer plexiformer Schicht, innerer nukleärer Schicht und äußerer plexiformer Schicht



Disorganization of the Retinal Inner Layers as a Predictor of Visual Acuity in Eyes With Macular Edema Secondary to Vein Occlusion

MICHAEL MIMOUNI, OR SEGEV, DALIA DORI, NOA GEFFEN, VICTOR FLORES, AND ORI SEGAL

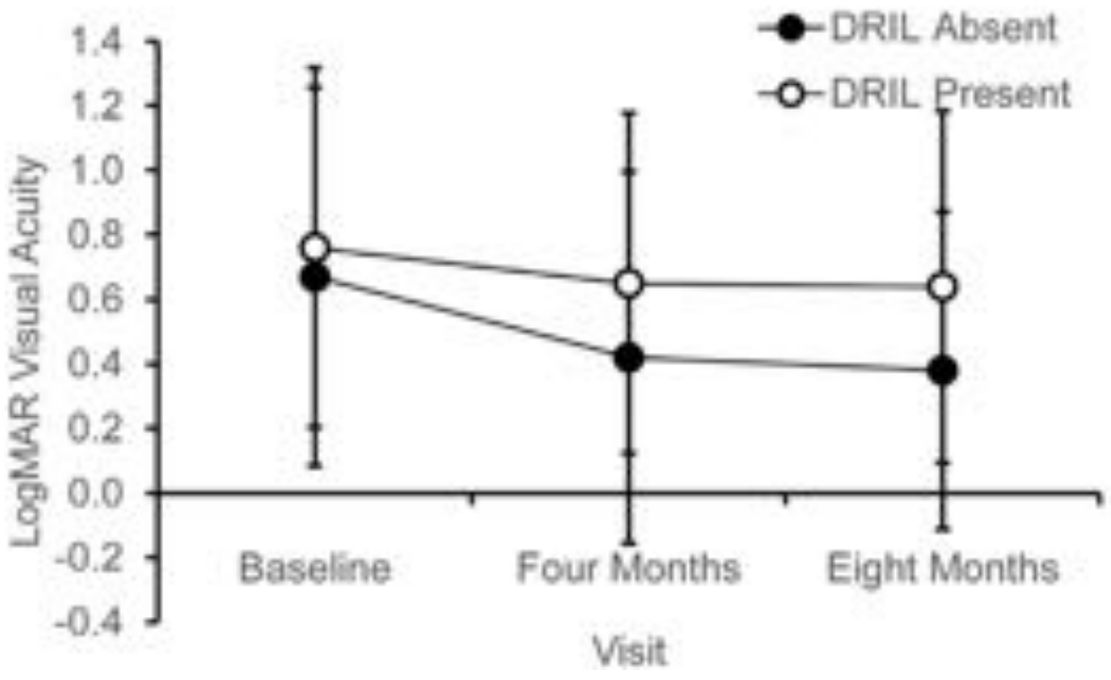
Am J Ophthalmol 2017;182:160–167

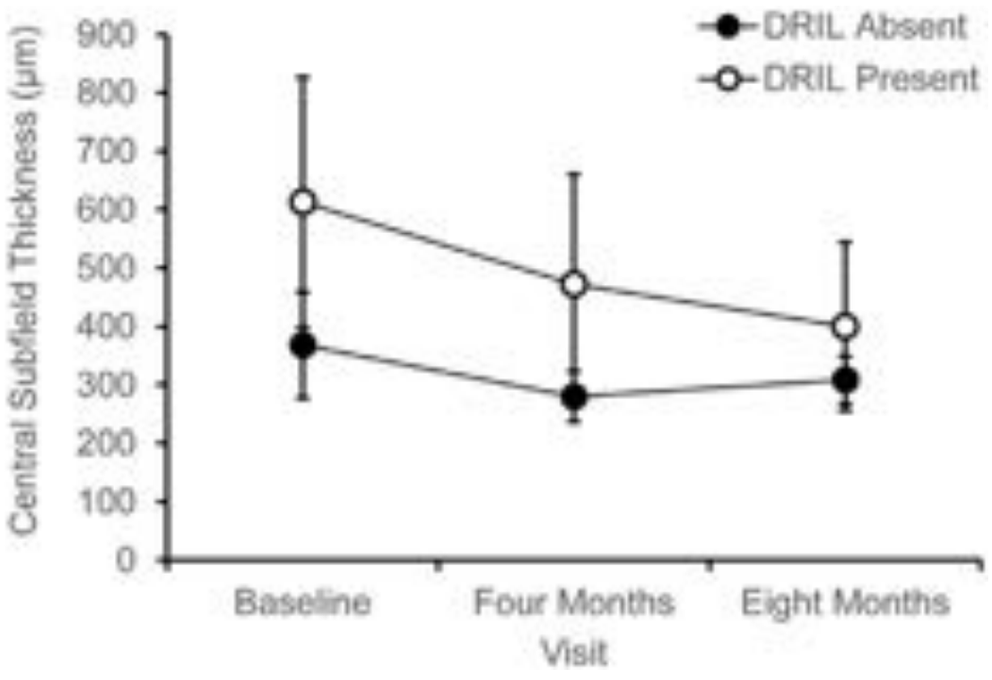


Disorganization of the Retinal Inner Layers as a Predictor of Visual Acuity in Eyes With Macular Edema Secondary to Vein Occlusion

MICHAEL MIMOUNI, OR SEGEV, DALIA DORI, NOA GEFFEN, VICTOR FLORES, AND ORI SEGAL

Am J Ophthalmol 2017;182:160–167





Association Between Hyperreflective Dots on Spectral-Domain Optical Coherence Tomography in Macular Edema and Response to Treatment

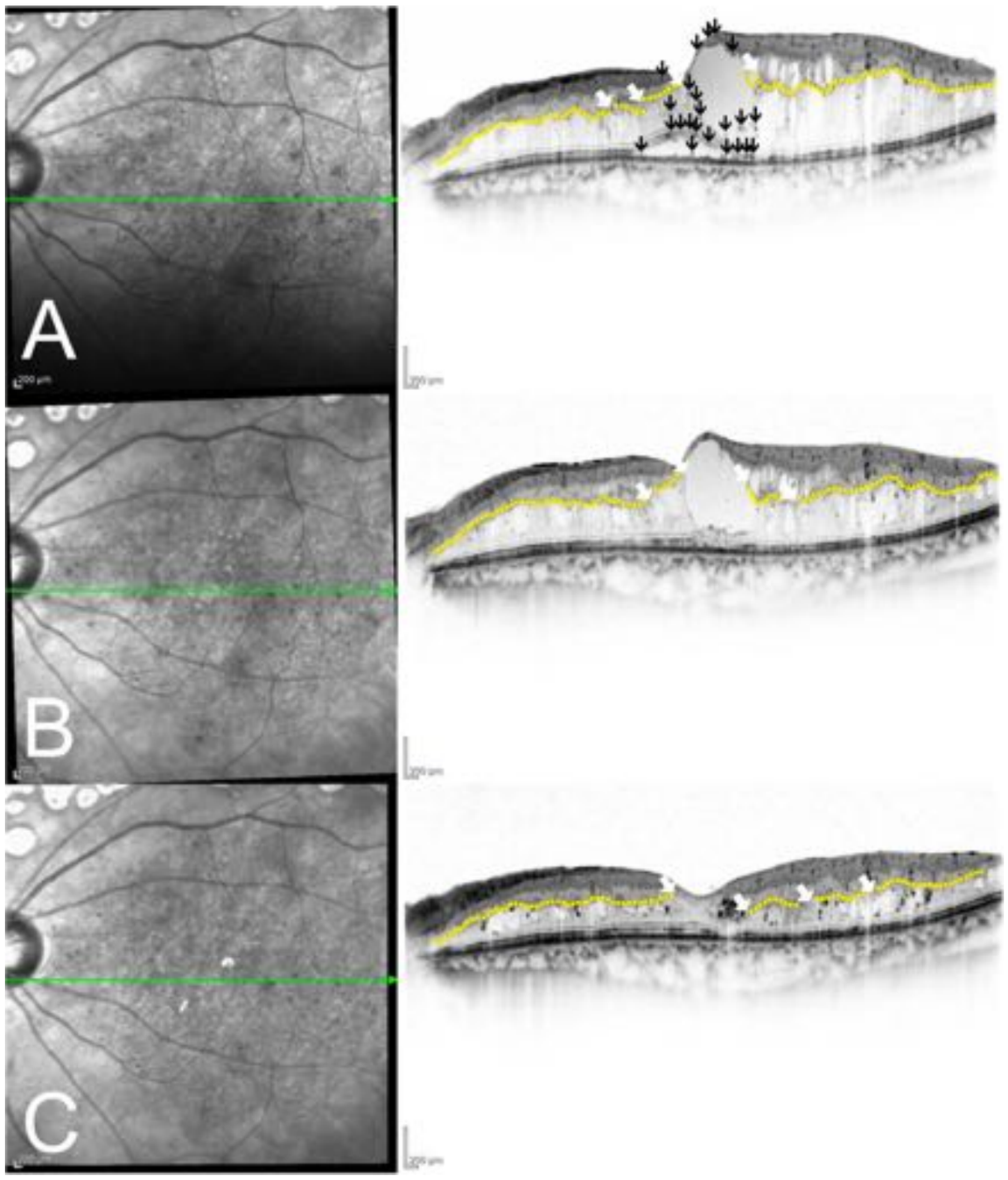
Hye Seong Hwang,[1] Ju Byung Chae,[1] Jin Young Kim,[2] and Dong Yoon Kim[1]

[1]Department of Ophthalmology, Chungbuk National University Hospital, College of Medicine, Chungbuk National University, Cheongju, Korea
[2]Department of Ophthalmology, Jeju National University Hospital, Jeju National University School of Medicine, Jeju, Korea

Invest Ophthalmol Vis Sci 2017;58:5958–5967

Hyperreflective Dots (HRD)

- MÖ bei DR und RVO
- Bevacizumab vs. Bevacizumab x3 + Dexamethason bei Non-Response
- Bevacizumab-Responder = geringe Anzahl HRD
- Dexamethason-Responder = hohe Anzahl HRD
- HRD = Zeichen inflammatorischer Aktivität?



MÖ bei RVO:

Welche Therapie?

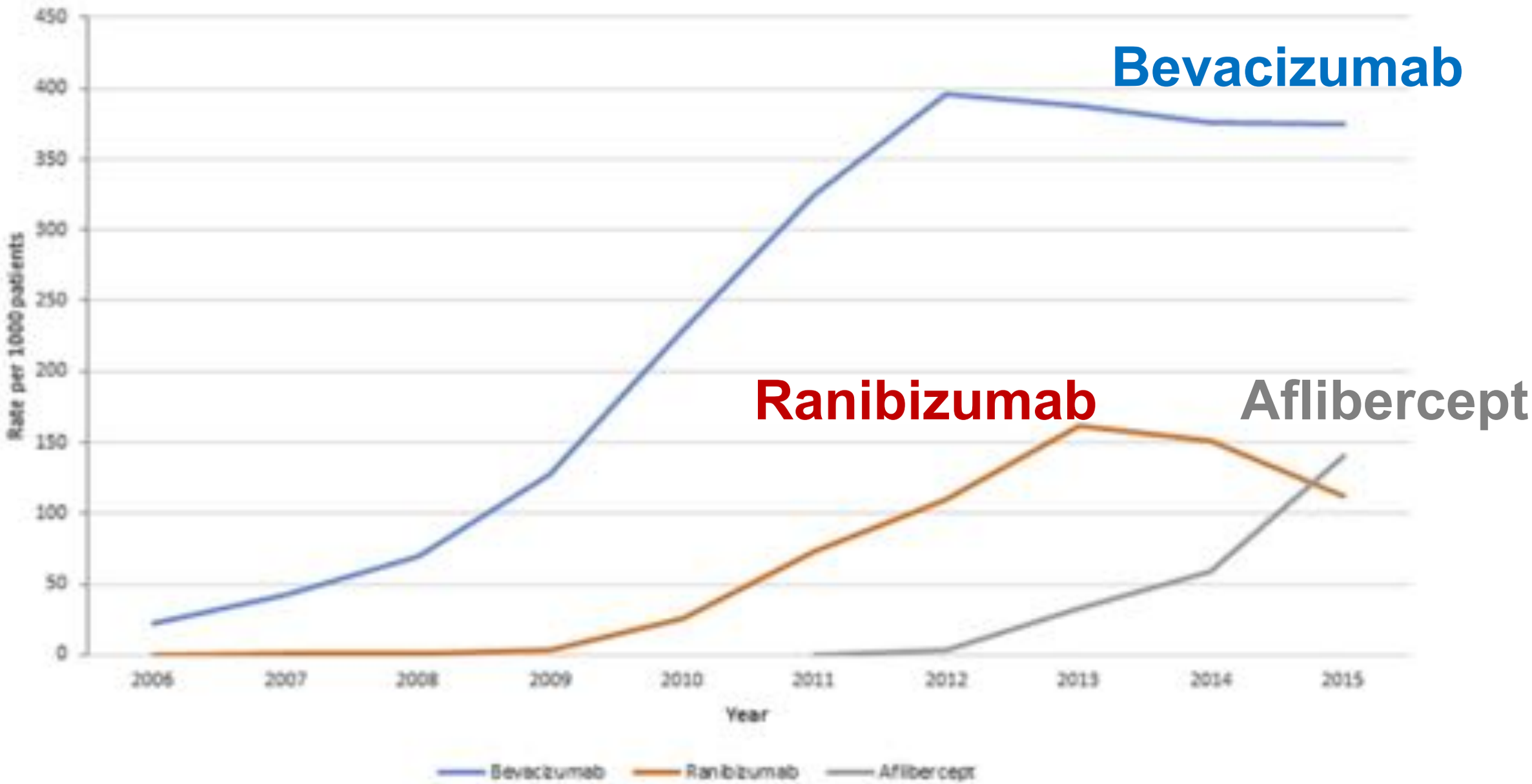
IVOM-Daten USA

Parikh et al. Ophthalmology 2017;124:352-358

- Versichertendaten
- Retrospektive Auswertung (2006-2015)
- 125.000 Patienten in USA
- 960.000 IVOMs
- 8% -> RVV (ca. 75.000 IVOMs)

IVOM USA: On-Label vs. Off-Label

Parikh et al. Ophthalmology 2017;124:352-358



Retina specialists treating cystoid macular oedema secondary to retinal vein occlusion recommend different treatments for patients than they would choose for themselves

Marlene D Wang,[1] Karen W Jeng-Miller,[1] Henry L Feng,[1] Jonathan L Prenner,[1,2] Howard F Fine,[1,2] Sumit P Shah[1,2]

- 2446 Netzhautspezialisten
- 492 (20,1%) Fragebögen beantwortet
- Behandlung Patient vs. Selbst

Group 1 survey

A 70-year-old patient with pseudophakia presents with CMO left eye (OS) secondary to a new onset BRVO. The presenting visual acuity OS is 20/100 and correlates with the diagnosis on clinical examination and optical coherence tomography (OCT). The visual acuity right eye (OD) is 20/20 with mild drusen. There is a medical history of hypertension. How would you initially treat this patient?

1. Bevacizumab (Avastin)
2. Ranibizumab (Lucentis)
3. Aflibercept (Eylea)
4. Intravitreal steroid (dexamethasone implant (Ozurdex) or triamcinolone acetonide (Triesence or Kenalog))
5. Focal laser
6. Observation

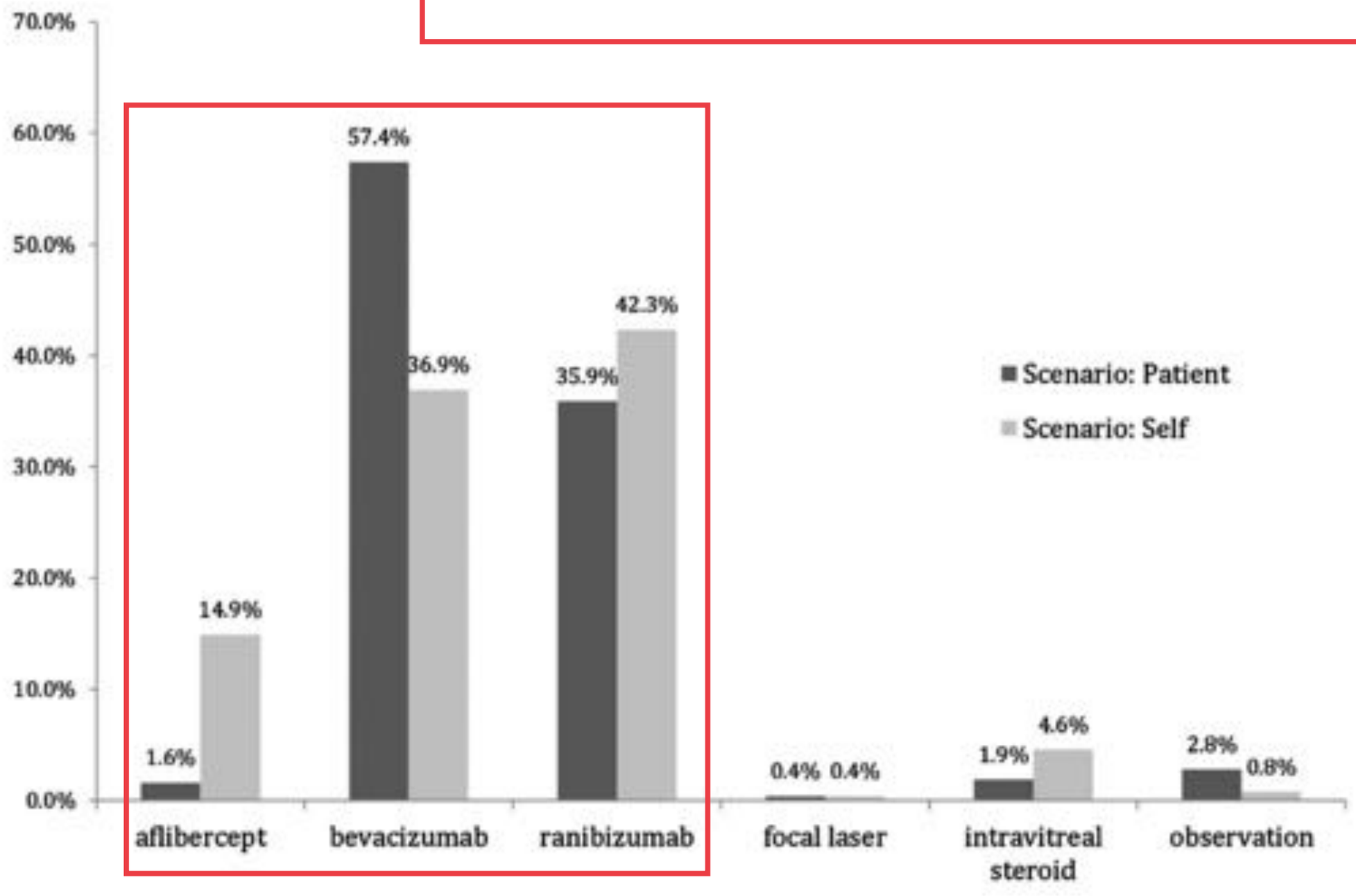
What treatment paradigm would you employ for CMO from a BRVO?

1. Monthly injection of anti-VEGF agent for at least a year
2. Loading followed by a PRN injection of anti-VEGF agent
3. Everything 3-month injection of steroid agent
4. as needed (PRN) injection of steroid agent
5. PRN focal laser
6. Other (please specify)

Wang et al. 2015, BJO, online

Netzhautspezialisten: On-label vs. off-label Anti-VEGF

On-label **Patienten 37,5%** vs. **Selbst 57,2%**



JAMA | Original Investigation

Effect of Bevacizumab vs Aflibercept on Visual Acuity Among Patients With Macular Edema Due to Central Retinal Vein Occlusion
The SCORE2 Randomized Clinical Trial

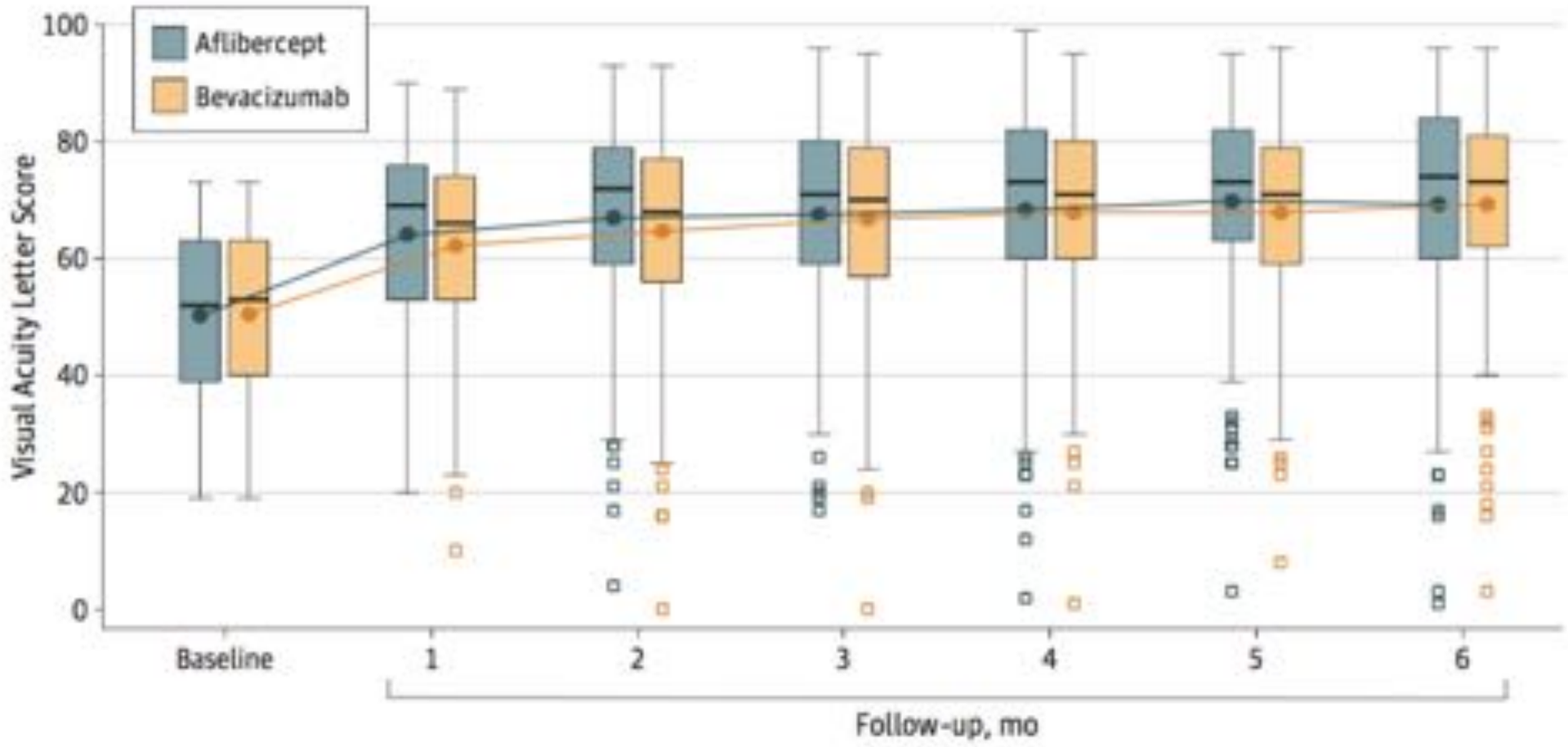
Ingrid U. Scott, MD, MPH; Paul C. VanVeldhuisen, PhD; Michael S. Ip, MD; Barbara A. Blodi, MD; Neal L. Oden, PhD; Carl C. Awh, MD; Derek Y. Kunimoto, MD; Dennis M. Marcus, MD; John J. Wroblewski, MD; Jacqueline King, MS; for the SCORE2 Investigator Group

Scott et al. 2017, JAMA, online

- Prospektiv, randomisiert
- 362 Patienten
- Aflibercept versus Bevacizumab
- ZVV/ Hemi-ZVV
- Monatliche IVOM bis Monat 6

Score2

Figure 2. Electronic Early Treatment Diabetic Retinopathy Study Visual Acuity Letter Score at Baseline and Monthly Through Month 6



Eyes, No.							
Aflibercept	180	179	177	175	173	169	175
Bevacizumab	182	179	179	175	172	171	173

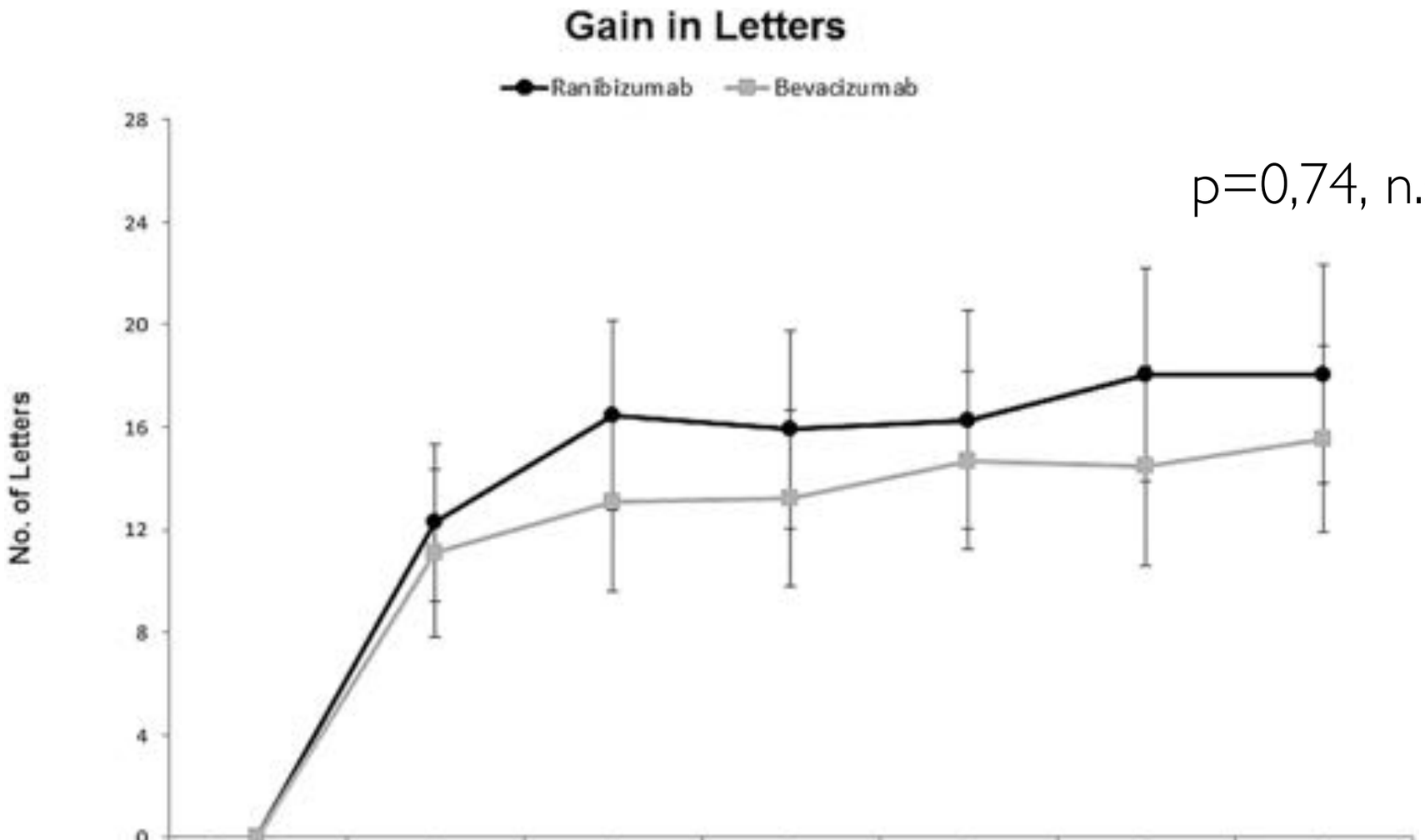
- Aflibercept: +18,3 Bst
- Bevacizumab: +18,9 Bst

A randomised, double-masked, controlled study of the efficacy and safety of intravitreal bevacizumab versus ranibizumab in the treatment of macular oedema due to branch retinal vein occlusion: MARVEL Report No. 1

Raja Narayanan, Bhavik Panchal, Taraprasad Das, Jay Chhablani, Subhadra Jalali, M Hasnat Ali, on behalf of MARVEL study group

- n=75
- 1:1 Randomis.
- 1 Injektion + PRN
- Visus, CRT 6 Monate

p=0,74, n.s.



	Baseline	1	2	3	4	5	6
Ranibizumab	0	12.29	16.45	15.91	16.29	18.05	18.08
Bevacizumab	0	11.1	13.13	13.23	14.71	14.5	15.55
P value	0	0.6	0.2	0.31	0.57	0.22	0.37

Narayanan R, *et al. Br J Ophthalmol* 2015;**99**:954–959. doi:10.1136/bjophthalmol-2014-306543

Anti-VEGF oder Steroide?

Die COMRADE-Studien

AMERICAN JOURNAL OF OPHTHALMOLOGY®

Clinical Efficacy and Safety of Ranibizumab Versus Dexamethasone for Central Retinal Vein Occlusion (COMRADE C): A European Label Study

HANS HOERAUF, NICOLAS FELTGEN, CLAUDIA WEISS, EVA-MARIA PAULUS, STEFFEN SCHMITZ-VALCKENBERG, AMELIE PIELEN, PANKAJ PURI, HÜSNÜ BERK, NICOLE ETER, PETER WIEDEMANN, GABRIELE E. LANG, MATUS REHAK, ARMIN WOLF, THOMAS BERTELMANN, AND LARS-OLOF HATTENBACH, ON BEHALF OF THE COMRADE-C STUDY GROUP

Acta Ophthalmologica

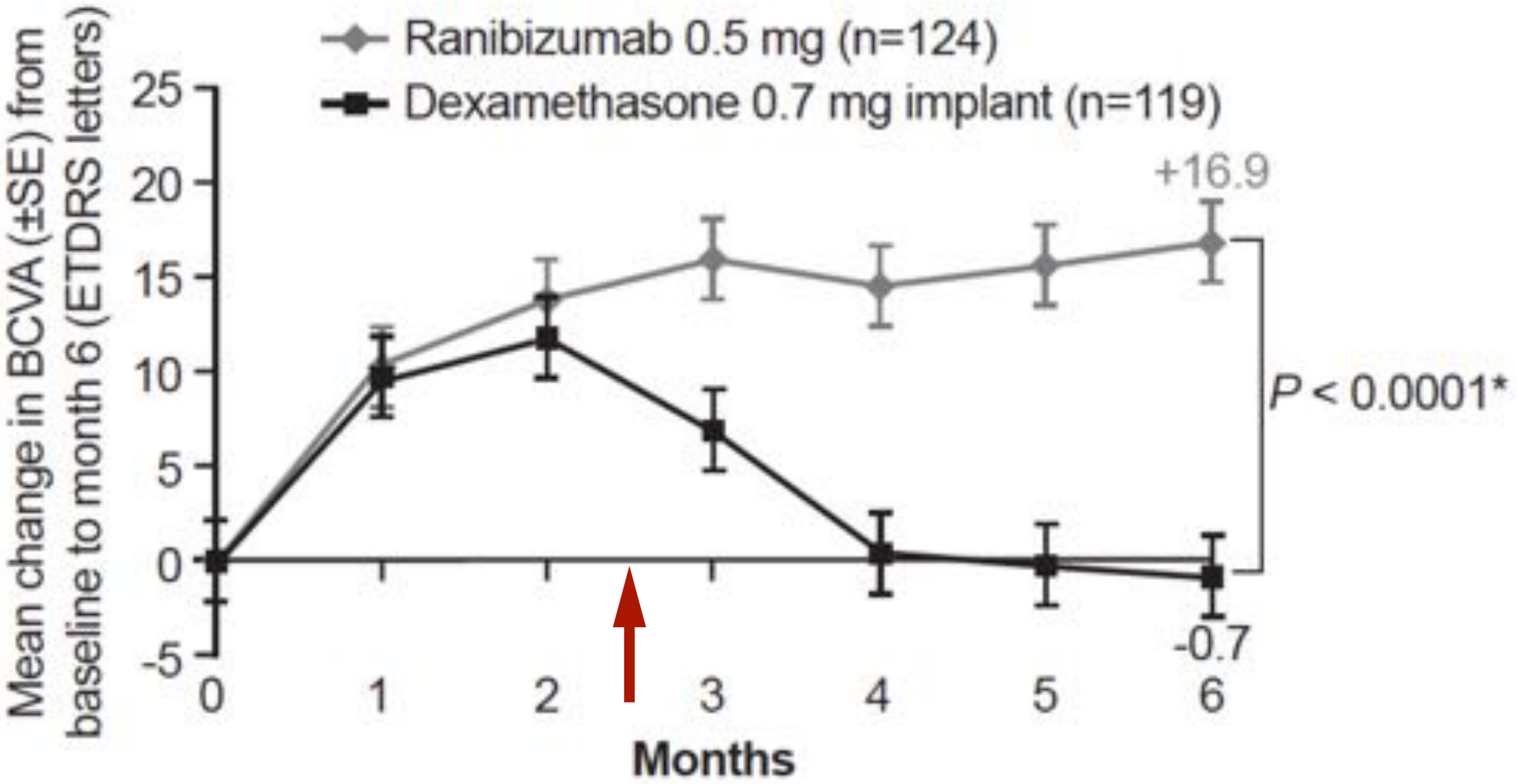
Acta Ophthalmologica 2017

Head-to-head comparison of ranibizumab PRN versus single-dose dexamethasone for branch retinal vein occlusion (COMRADE-B)

Lars-Olof Hattenbach,[1] Nicolas Feltgen,[2] Thomas Bertelmann,[2,3] Steffen Schmitz-Valckenberg,[4] Hüsnü Berk,[5] Nicole Eter,[6] Gabriele E. Lang,[7] Matus Rehak,[8,9] Simon R. Taylor,[10] Armin Wolf,[11] Claudia Weiss,[3] Eva-Maria Paulus[3] Amelie Pielen[12] and Hans Hoerauf[2] on behalf of the COMRADE-B Study Group

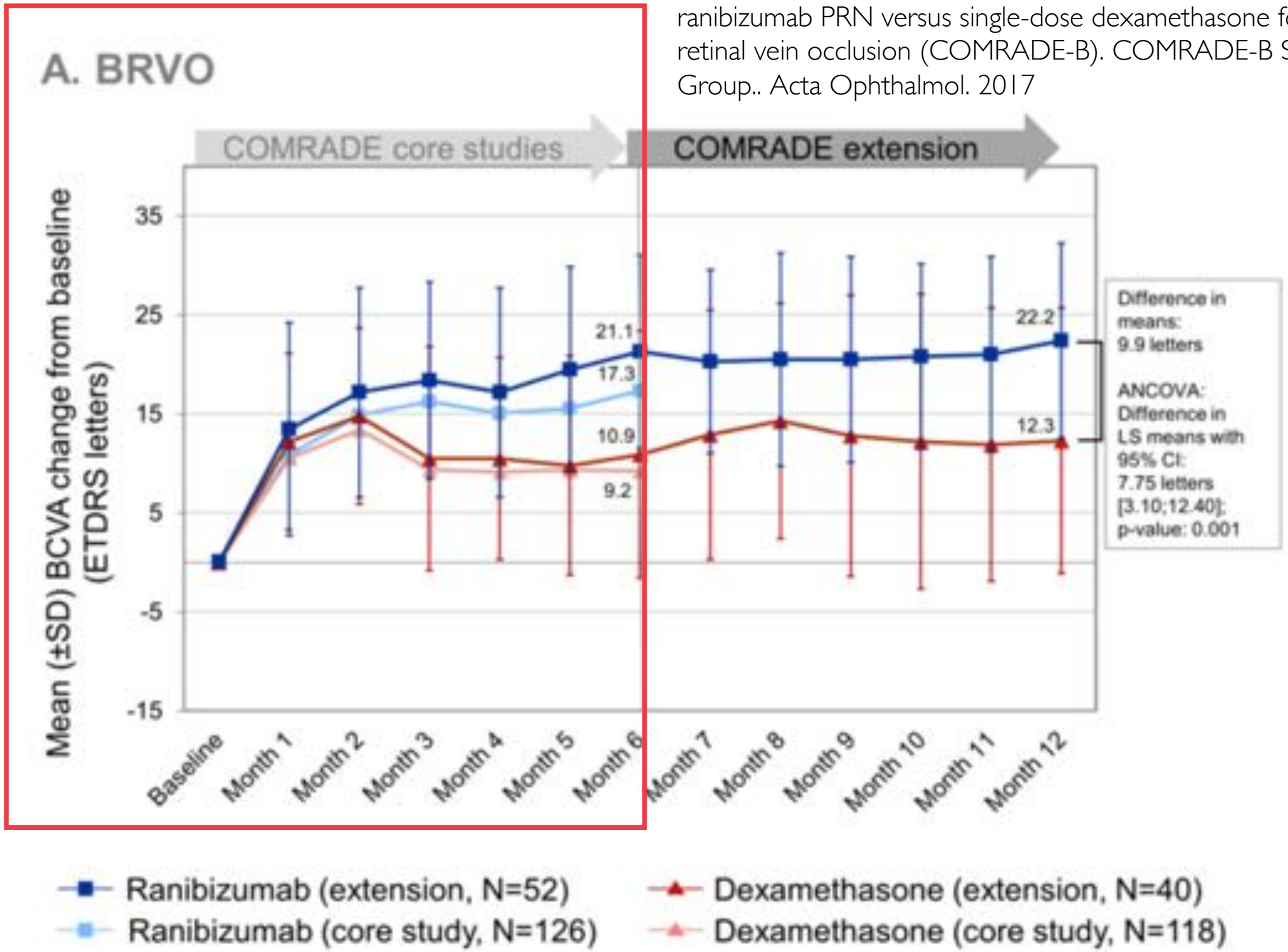
[1]Department of Ophthalmology, Ludwigshafen Hospital, Ludwigshafen, Germany; [2]Department of Ophthalmology, Georg-August-University Göttingen, Göttingen, Germany; [3]Novartis Pharma GmbH, Nuremberg, Germany; [4]Department of Ophthalmology, GRADE Reading Center, University of Bonn, Bonn, Germany; [5]Department of Ophthalmology, St. Elisabeth-Hospital, Koeln-Hohenlind, Germany; [6]Department of Ophthalmology, University of Münster Medical Center, Münster, Germany; [7]Department of Ophthalmology, University of Ulm, Ulm, Germany; [8]Department of Ophthalmology, University of Leipzig, Leipzig, Germany; [9]Department of Ophthalmology, Charité – Universitätsmedizin, Berlin, Germany; [10]Department of Ophthalmology, University of Surrey, Guildford, UK; [11]Department of Ophthalmology, Ludwig-Maximilians University, Munich, Germany; [12]Department of Ophthalmology, Medizinische Hochschule Hannover, Hannover, Germany

COMRADE-C: Visusverlauf (BCVA von Baseline)

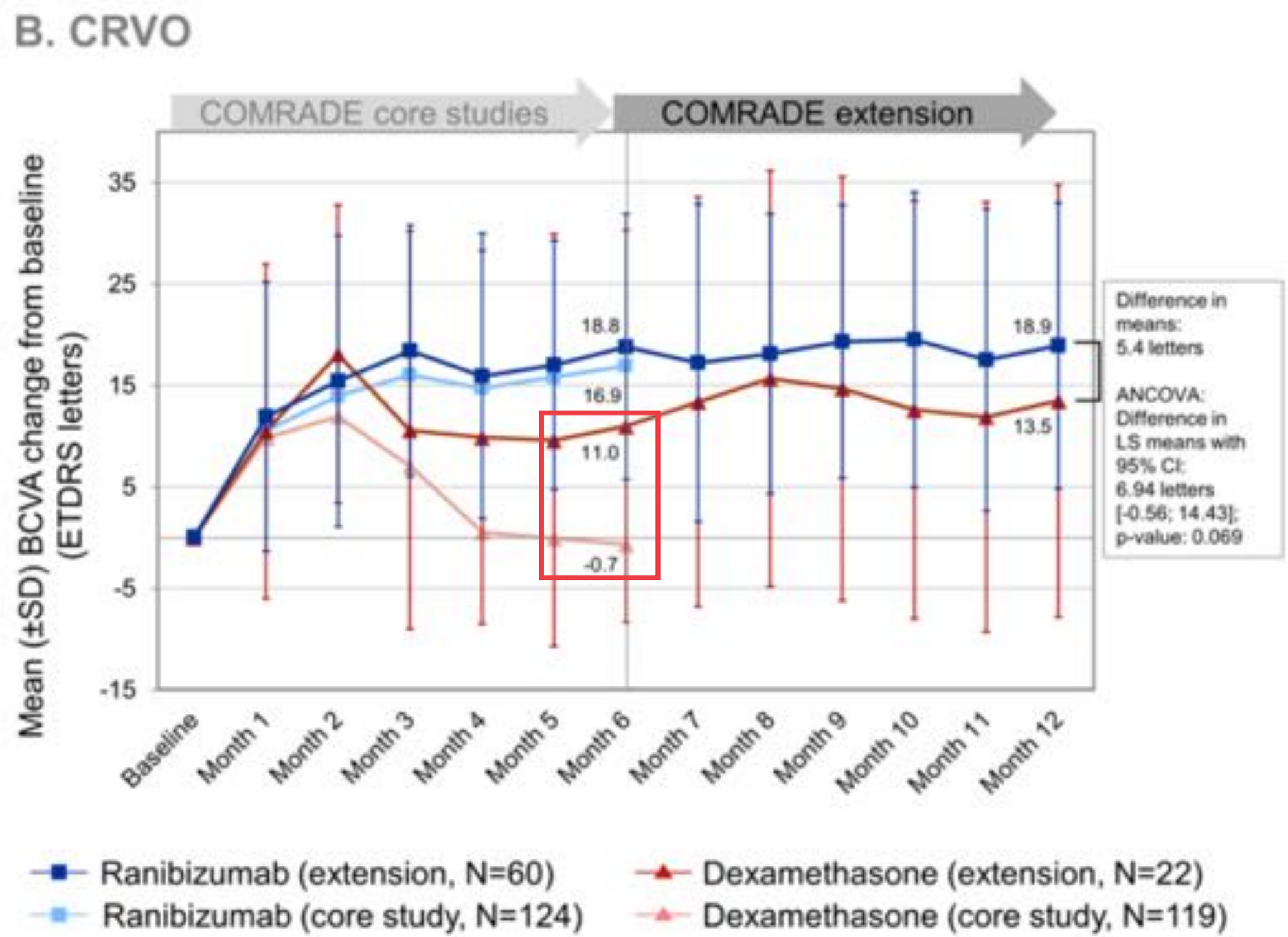


COMRADE-B und -Extension

Hattenbach LO, Feltgen N, Bertelmann T, Schmitz-Valckenberg S, Berk H, Eter N, Lang GE, Rehak M, Taylor SR, Wolf A, Weiss C, Paulus EM, Pielen A, Hoerauf H. Head-to-head comparison of ranibizumab PRN versus single-dose dexamethasone for branch retinal vein occlusion (COMRADE-B). COMRADE-B Study Group.. Acta Ophthalmol. 2017



COMRADE-Extension



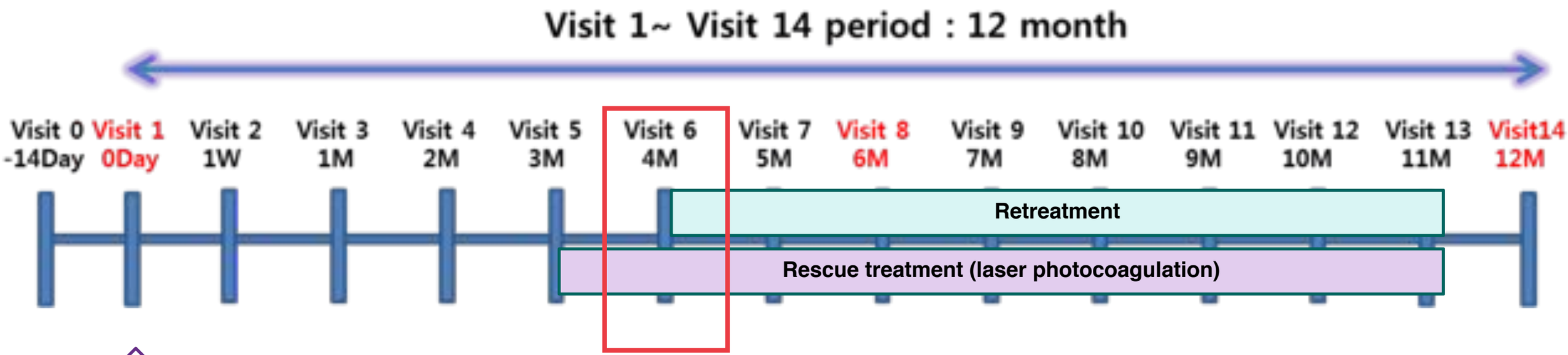
Feltgen, Hattenbach et al. for the COMRADE Study Group 2016

COBALT STUDY

A 12-Month, Open Label, Multicenter study to Assess the Safety and Efficacy of DEX implant Implant 700μg (Dexamethasone) in the Treatment of Patients with Macular Edema associated with Branch Retinal Vein Occlusion at Korean clinical settings

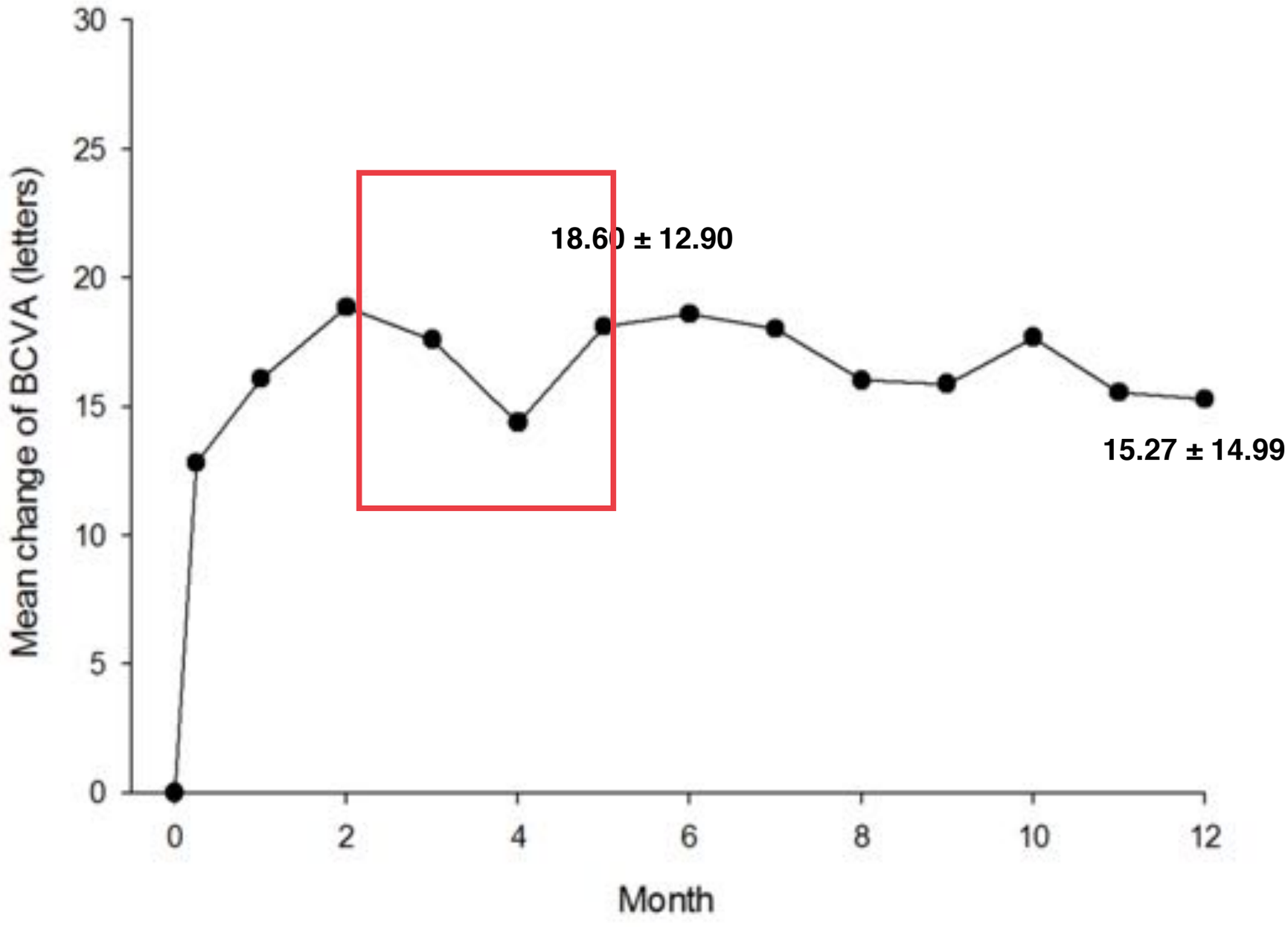
INT/0398/2016
Date of Preparation: July 2016

Study design



Yoon YH, et al. Poster Presented at the Association for Research in Vision and Ophthalmology (ARVO) 2016 Annual Meeting, May 1–5, 2016; Seattle, WA, USA. D0066

Mean change of BCVA from baseline at each visit

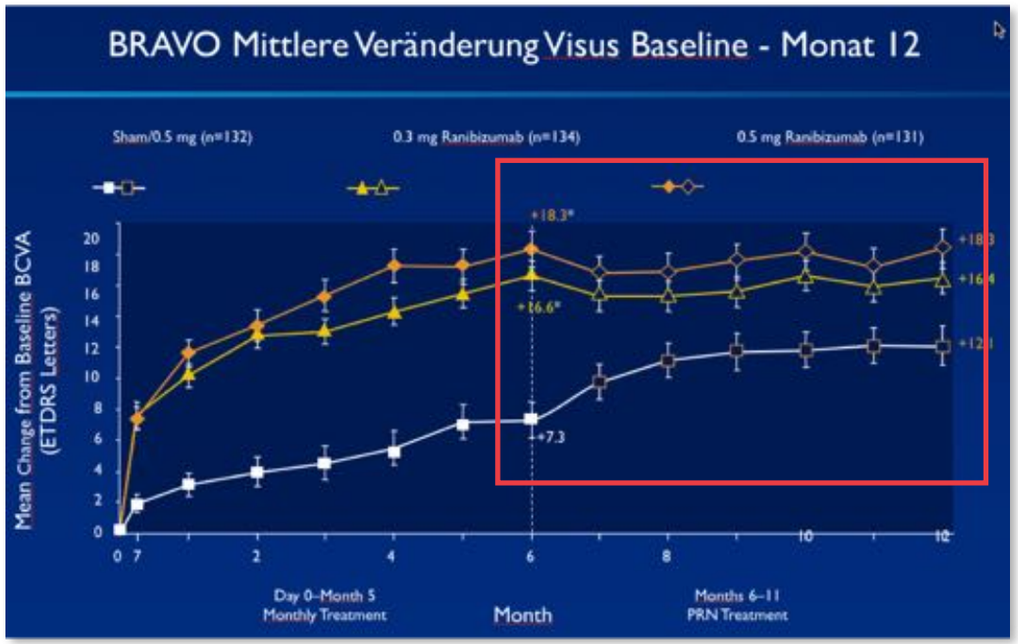


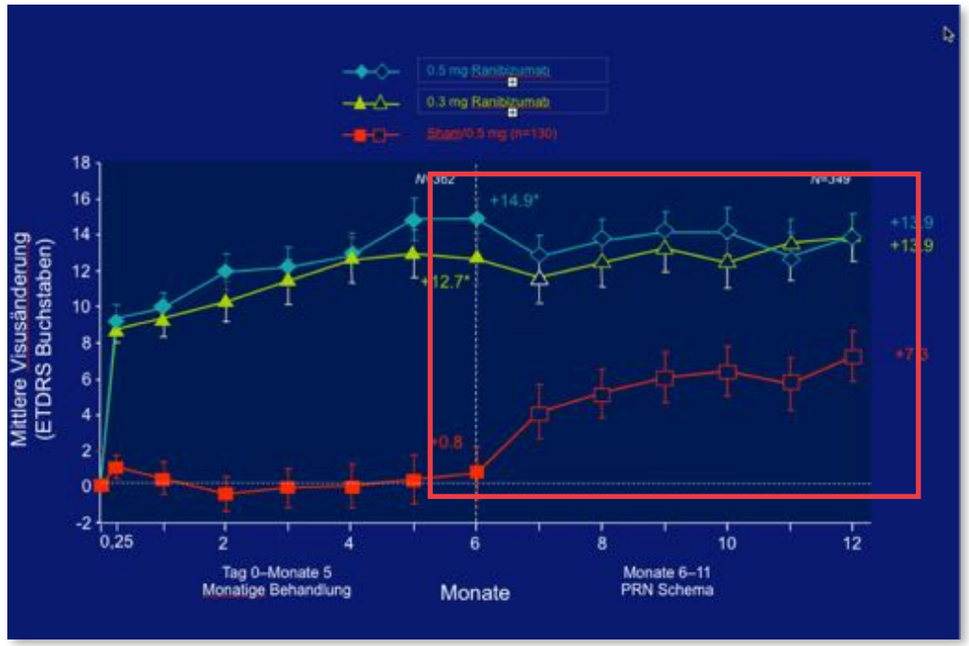
Yoon YH, et al. Poster Presented at the Association for Research in Vision and Ophthalmology (ARVO) 2016 Annual Meeting, May 1–5, 2016; Seattle, WA, USA. D0066

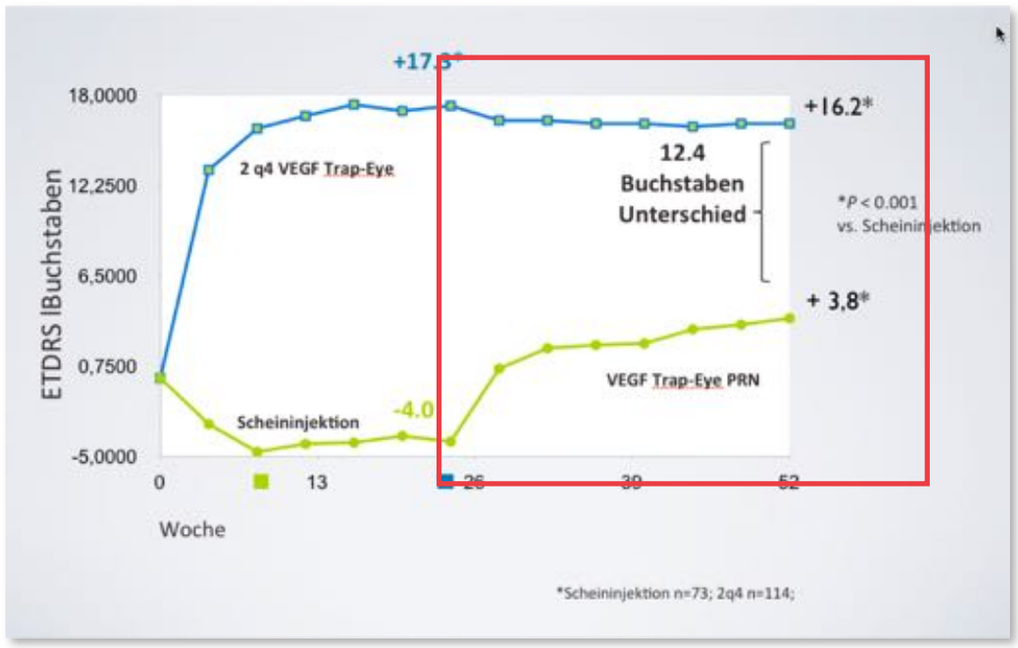
MÖ-Therapie bei RVO:

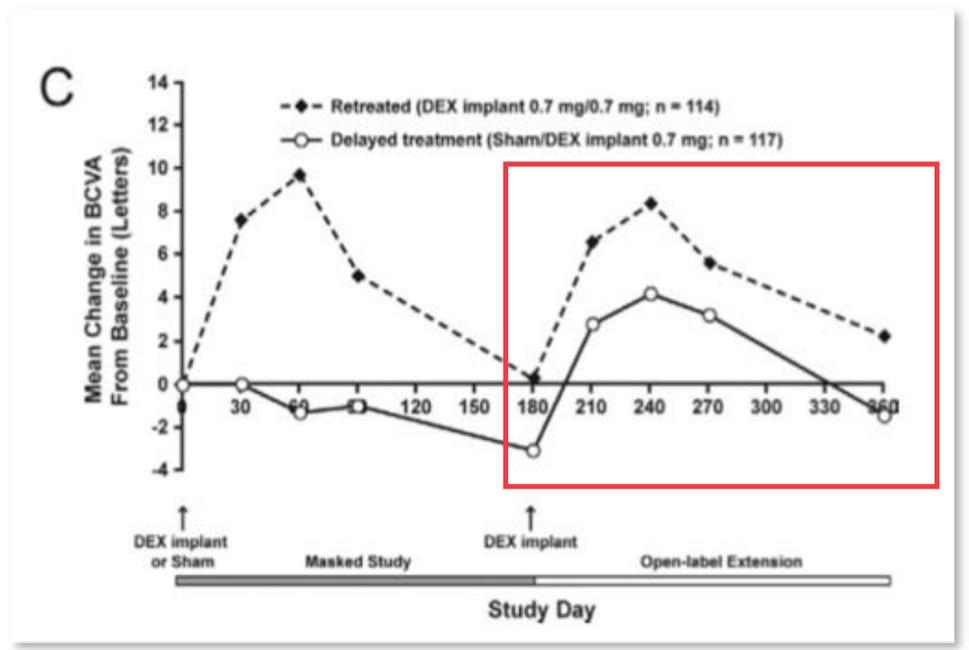
Frühzeitig, lückenlos und nachhaltig!

Je früher, desto besser !









AMERICAN ACADEMY™
OF OPHTHALMOLOGY

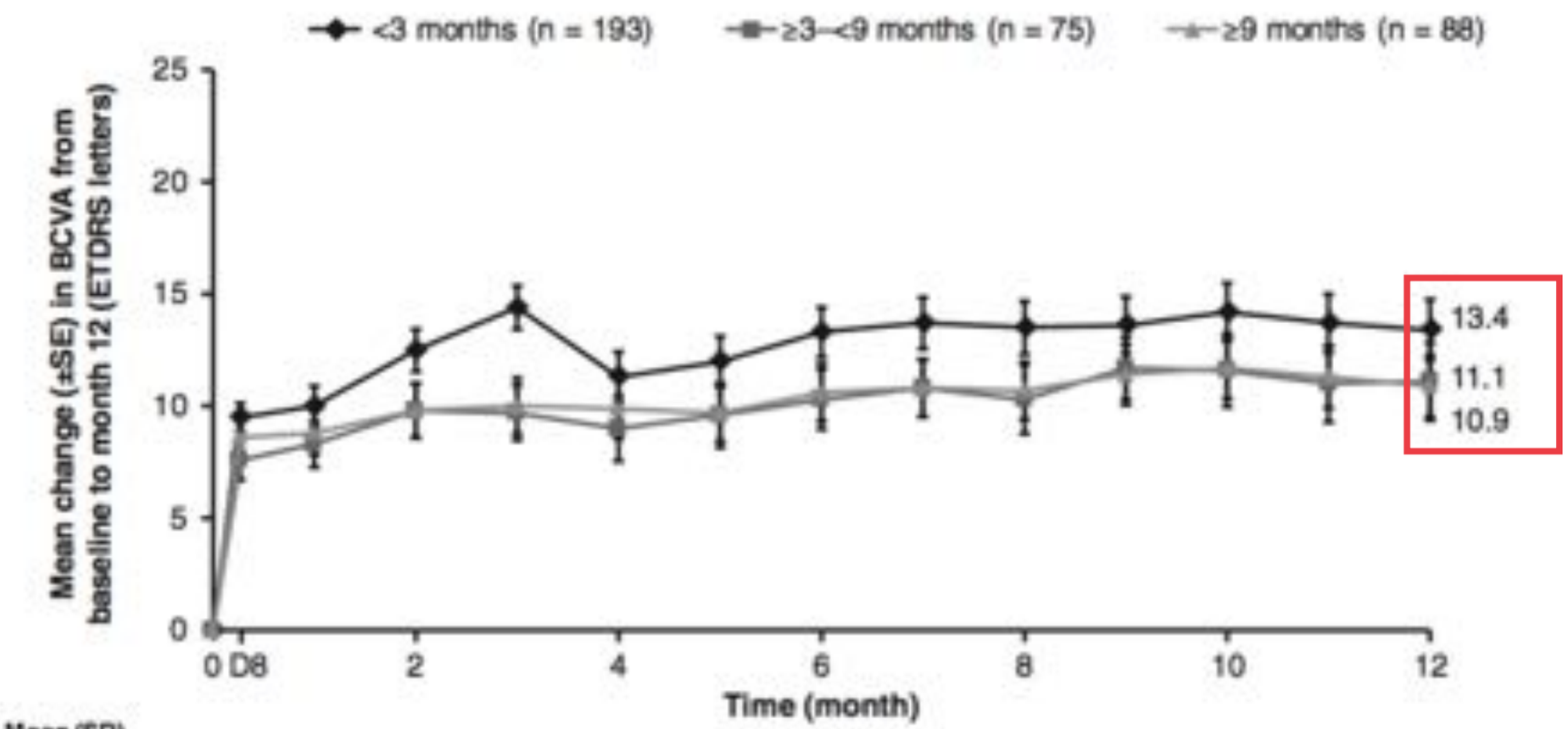
Individualized Ranibizumab Regimen Driven by Stabilization Criteria for Central Retinal Vein Occlusion

Twelve-Month Results of the CRYSTAL Study

*Michael Larsen, MD,[1] Sebastian M. Waldstein, MD,[2] Francesco Boscia, MD,[3] Heinrich Gerding, MD,[4] Jordi Monés, MD, PhD,[5] Ramin Tadayoni, MD, PhD,[6] Siegfried Priglinger, MD,[7] Andreas Wenzel, PhD,[8] Elizabeth Barnes, PhD,[8] Stefan Pilz, PhD,[8] William Stubbings, PhD,[8] Ian Pearce, MD,[9] on behalf of the CRYSTAL Study Group**

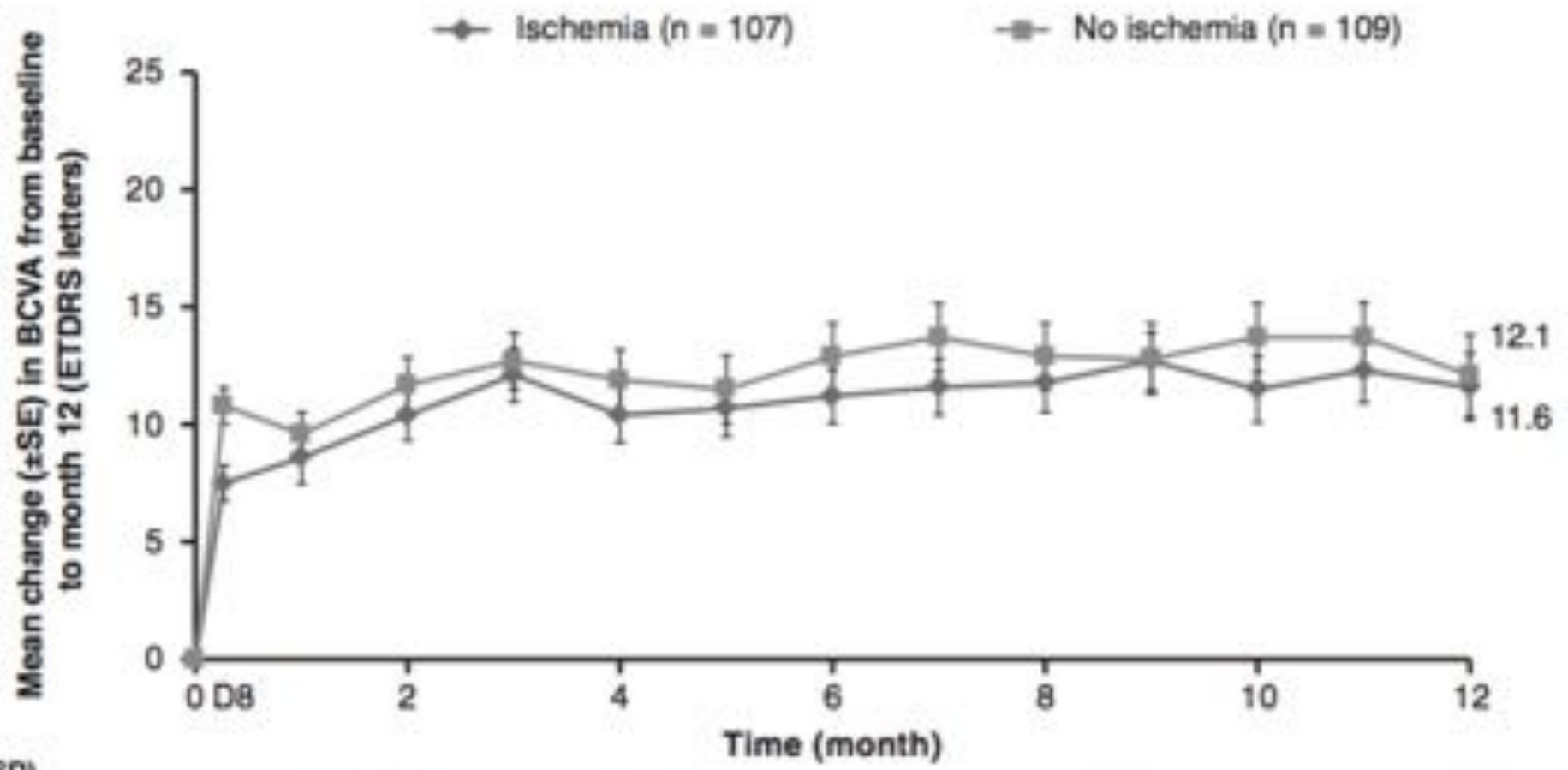
12-month efficacy and safety profile of an individualized regimen of ranibizumab 0.5 mg driven by stabilization criteria in patients with macular edema secondary to central retinal vein occlusion (CRVO).

CRYSTAL: Frühe vs. späte Therapie



Mean (SD) BCVA letters (absolute value)	Baseline	Day 8	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
< 3 months	54.0 (14.90)	63.5 (15.13)	64.0 (16.99)	66.6 (16.86)	66.4 (16.78)	65.3 (18.46)	66.0 (18.55)	67.4 (18.29)	67.7 (18.93)	67.6 (18.80)	67.7 (19.59)	68.2 (19.36)	67.7 (19.67)	67.4 (20.56)
≥ 3–<9 months	50.9 (16.52)	58.4 (18.16)	59.1 (18.06)	60.7 (18.63)	60.5 (19.61)	59.8 (19.40)	60.5 (20.42)	61.2 (20.02)	61.7 (18.42)	61.1 (20.95)	62.5 (19.62)	62.5 (19.97)	61.8 (20.54)	62.0 (20.66)
≥ 9 months	52.4 (13.88)	60.9 (14.92)	61.1 (16.43)	62.2 (17.71)	62.3 (18.06)	62.3 (18.00)	62.1 (17.38)	63.0 (18.15)	63.2 (18.37)	63.1 (18.09)	63.8 (18.54)	64.0 (17.63)	63.6 (18.46)	63.2 (18.14)

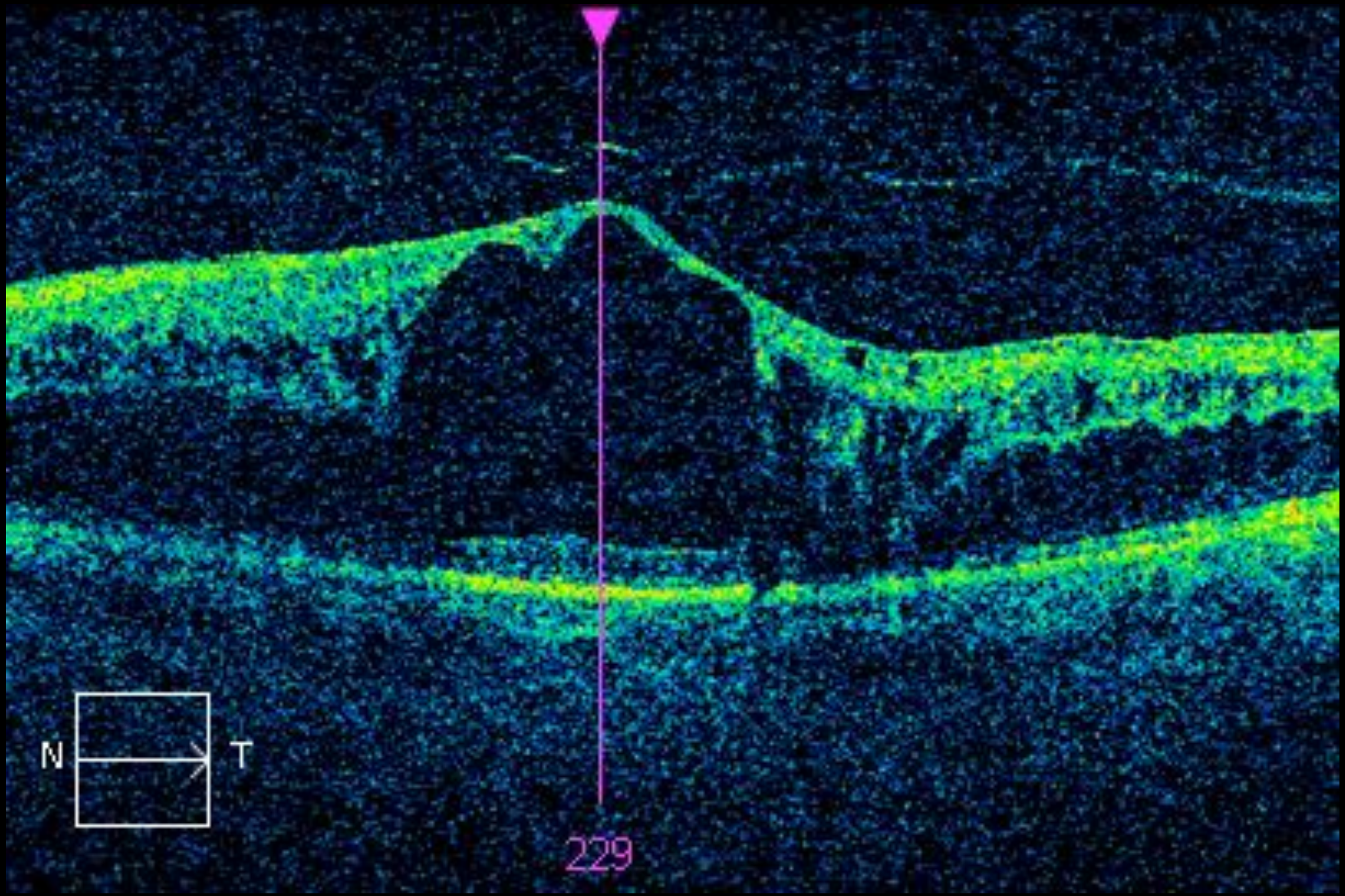
CRYSTAL: Ischämisch vs. nicht-ischämisch



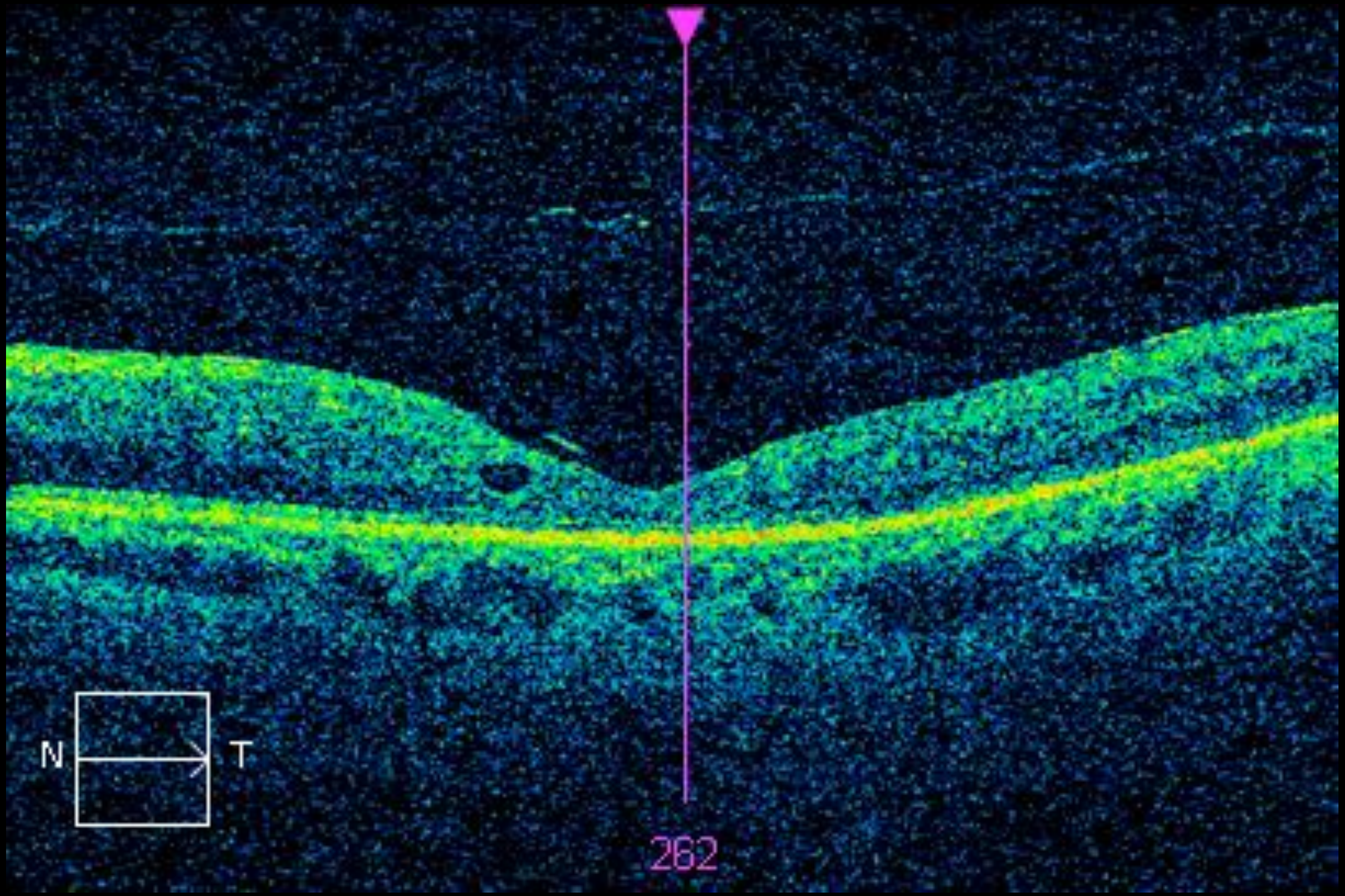
Mean (SD) BCVA letters (absolute value)	Baseline	Day 8	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
Ischemia	54.5 (14.06)	61.9 (15.99)	63.1 (17.77)	64.8 (17.32)	66.6 (17.93)	64.9 (17.81)	65.1 (18.01)	65.7 (18.27)	66.1 (18.16)	66.3 (17.38)	67.2 (18.06)	66.0 (18.53)	66.7 (18.71)	66.1 (18.96)
No ischemia	55.5 (14.87)	66.3 (15.77)	65.2 (16.94)	67.3 (18.02)	68.3 (18.41)	67.4 (18.95)	67.1 (19.92)	68.5 (19.29)	69.3 (19.71)	68.5 (19.80)	68.4 (19.90)	69.3 (19.34)	69.3 (20.29)	67.7 (21.23)

CRYSTAL:
Ranibizumab bei ZVV mit unterschiedlichen Ausgangsbedingungen

	CRUISE[1] (N = 392)*	**GALILEO[2] (N = 171)**	**COPERNICUS[3] (N = 114)**	**COMRADE-C[4] (N = 243)**	**CRYSTAL[5] (N = 357)†**
Inclusion criteria *Disease duration prior to study entry*	<12 months	<9 months	<9 months	<6 months	Any
Mean disease duration at baseline *Months (SD)*	3.3 (3.7)	2.72** (2.84)	2.40 (2.80)	1.50** (1.60)	8.9 (20.7)
Mean baseline BCVA *ETDRS letters (SD)*	48.1 (14.6)	52.2 (15.7)	50.0 (14.1)	51.6 (16.1)	53.0 (15.0)



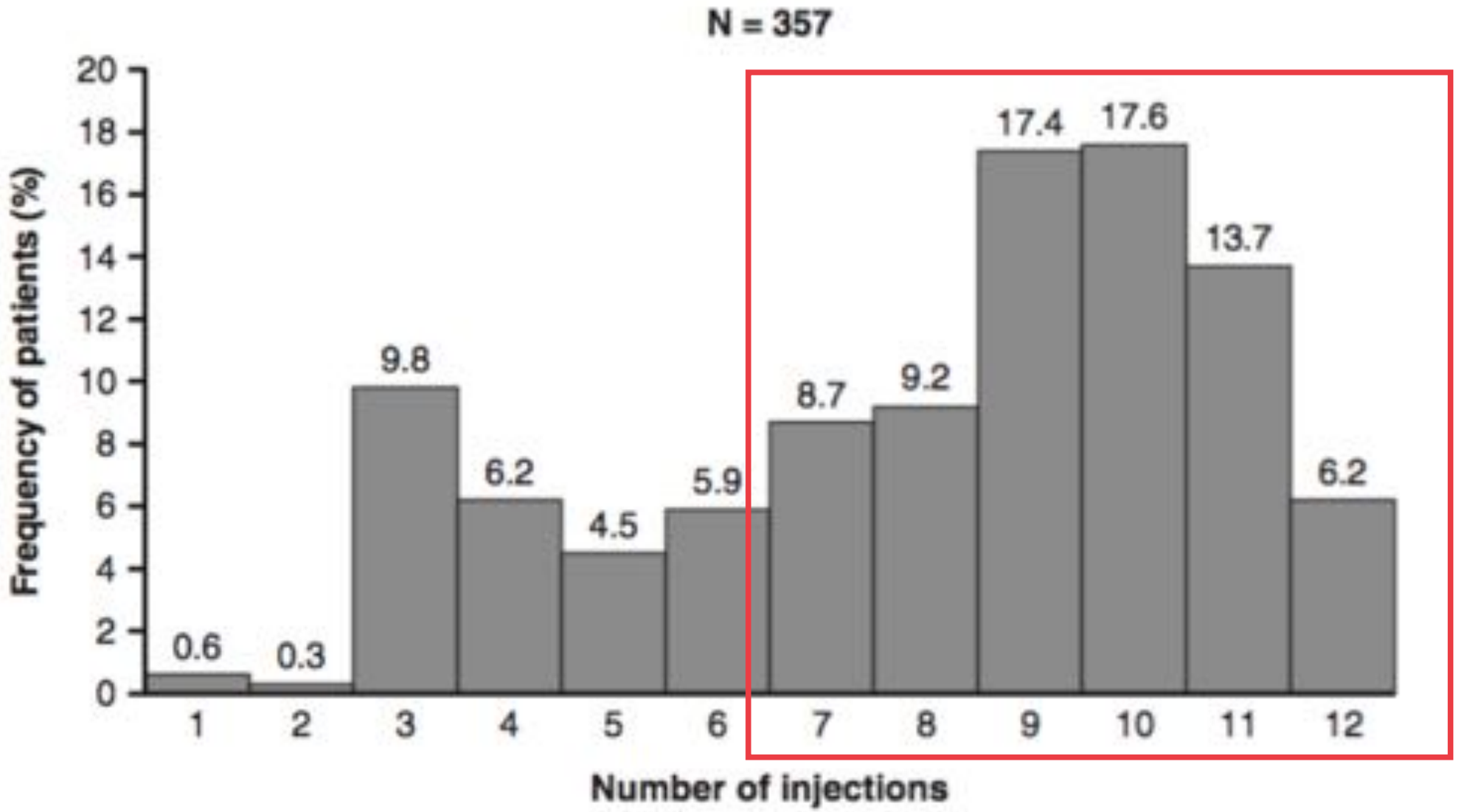
ZVV vor 13 J. (!), Rezidiv prominentes „dome shaped“ MÖ, Visus 0,05



Befund 3 Monate später, Z.n. 3x Ranibizumab, Visus 0,1

CRYSTAL: Injektionshäufigkeit

62,8% >6 Injektionen, Mittel 8,1



RANIBIZUMAB FOR MACULAR EDEMA AFTER BRANCH RETINAL VEIN OCCLUSION

One Initial Injection Versus Three Monthly Injections

YUKO MIWA, MD,* YUKI MURAOKA, MD, PHD,* RIE OSAKA, MD,† SOTARO OOTO, MD, PHD,* TOMOAKI MURAKAMI, MD, PHD,* KIYOSHI SUZUMA, MD, PHD,* AYAKO TAKAHASHI, MD,* YUTO IIDA, MD,* NAGAHISA YOSHIMURA, MD, PHD,* AKITAKA TSUJIKAWA, MD, PHD†

Purpose: To compare the 12-month-efficacy of 1 initial intravitreal ranibizumab injection (IVR) followed by pro re nata (PRN) dosing with that of three initial monthly IVR followed by PRN dosing in patients with macular edema (ME) after branch retinal vein occlusion.

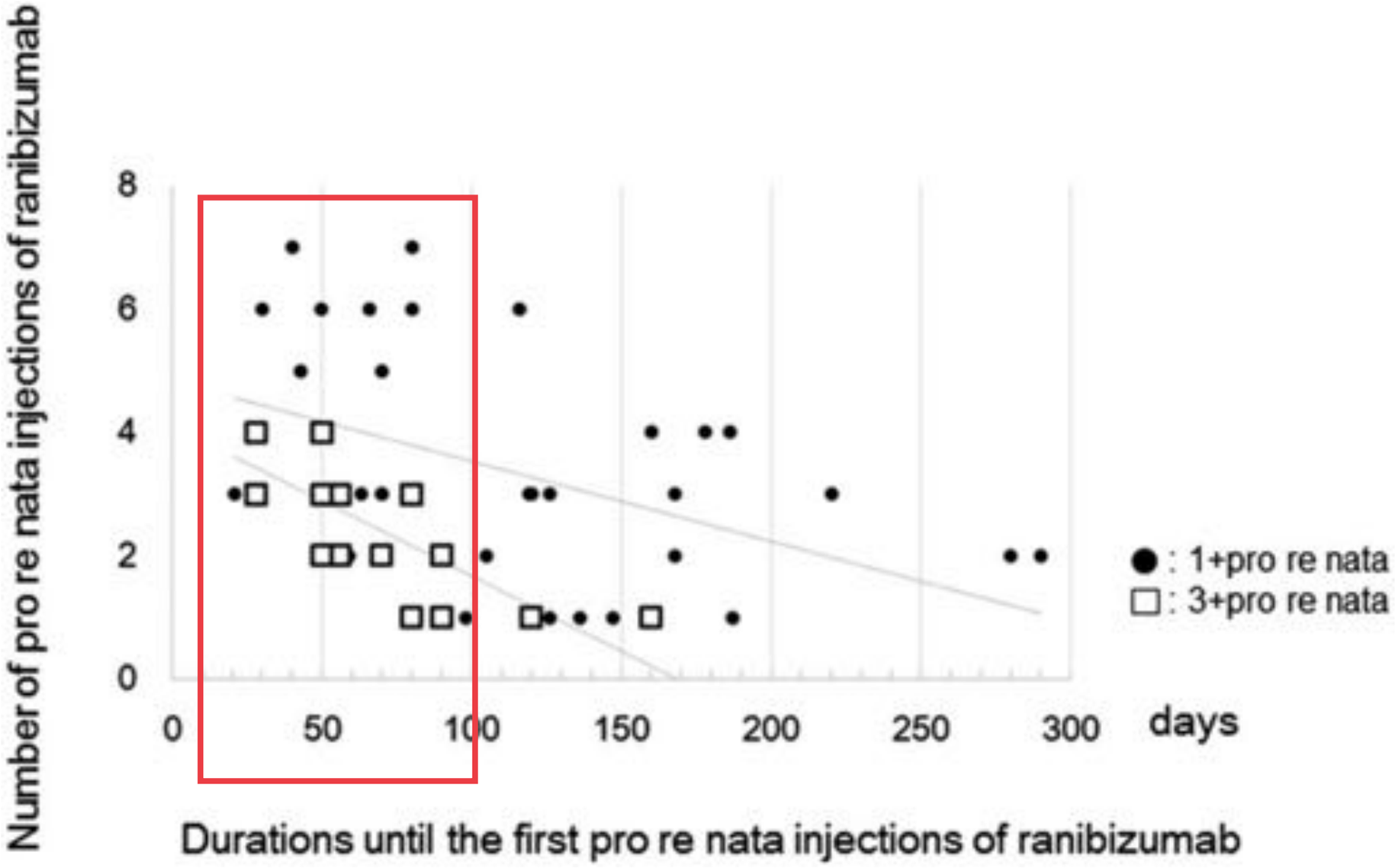
Design: Prospective, interventional study.

Methods: Of 81 eyes, 42 received 1 initial IVR injection (1+PRN group) and 39 eyes received 3 monthly IVRs (3+PRN). Pro re nata injections were performed when fovea exudative changes were evident.

Results: At Month 12, the visual acuity (VA) changes from baseline were -0.245 ± 0.227 and -0.287 ± 0.222, in the 1+PRN and 3+PRN groups, respectively; there were no significant difference between groups ($P = 0.728$). The stratified analysis showed that patients with better VA (baseline VA >20/40) had similar significant improvement in VA at Month 12 ($P < 0.001$) to that of those with poorer VA (≤20/40). Better VA at Month 12 was significantly associated with younger age, better baseline VA, and thinner baseline central foveal thickness ($P = 0.003$, < 0.001, and < 0.001, respectively). Mean total number of IVR injections in the 1+PRN and 3+PRN groups were 3.8 ± 1.8 and 4.6 ± 1.4, respectively ($P = 0.060$). In both groups, shorter durations to the first PRN injection were associated with greater total PRN injection number (1+PRN, $P = 0.006$; 3+PRN; group, $P < 0.001$).

Conclusion: In IVR treatment for ME after branch retinal vein occlusion, 1+PRN and 3+PRN regimens achieved similar 12-month functional outcomes. Patients with shorter durations to initial PRN injection may require more PRN treatments.

RETINA 0:1–8, 2016



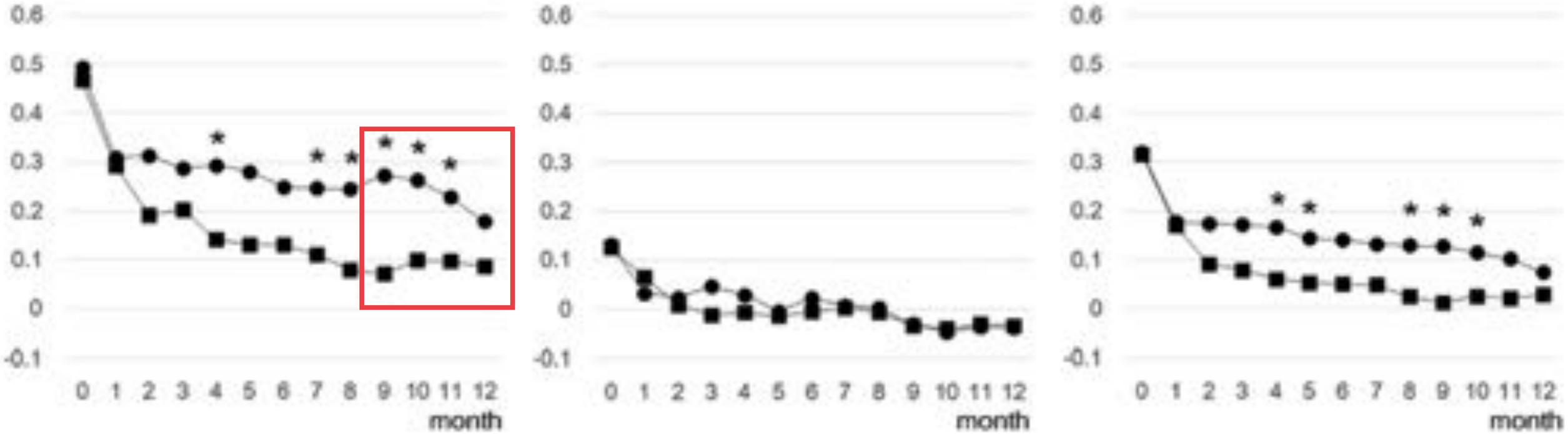
Anti-VEGF (Ranibizumab) PRN:

Frühe Wiederbehandlung = Indikator für häufige Injektionen

Visus ≤0,5

Visus >0,5

Visus gesamt



A B C

Fig. 4. Longitudinal changes in LogMAR visual acuity (VA) in the poorer VA subgroup (patients with a baseline Snellen equivalent of ≤20/40, [**A**]), in the better VA subgroup (patients with a baseline Snellen equivalent of >20/40, [**B**]), and in the total patient group (**C**). Mean baseline VA was 0.481 ± 0.210 (Snellen 20/61) in the poorer VA subgroup and 0.129 ± 0.091 (Snellen 20/27) in the better VA subgroup, both of these values improved to 0.135 ± 0.221 (Snellen 20/27) and −0.036 ± 0.115 at Month 12 in the poorer and better VA subgroup, respectively ($P < 0.001$ for both, compared with baseline). Comparisons of the 12-month outcomes between the 1+pro re nata (PRN) and 3+PRN groups show there were no significant difference in final VA (0.179 ± 0.257 [20/30] vs. 0.086 ± 0.166 [Snellen 20/24], $P = 0.178$) at Month 12 in the poorer VA subgroup. However, during the course of the 12-month observation period, the VA tended to be worse in the 1+PRN group than in the 3+PRN group. In contrast, in the better VA subgroup, VA longitudinally changed in relatively similar manner in both the 1+PRN and 3+PRN groups; there were no significant differences between groups over the entire observation.

Anti-VEGF (Ranibizumab) PRN: Je fortgeschritterer RVO, desto intensiver !

Acta Ophthalmologica

Acta Ophthalmologica 2015

Anti-VEGF treatment in branch retinal vein occlusion: a real-world experience over 4 years

Sandra Rezar, Katharina Eibenberger, Wolf Bühl, Michael Georgopoulos, Ursula Schmidt-Erfurth and Stefan Sacu on behalf of Macula Study Group Vienna

Department of Ophthalmology, Medical University of Vienna, Vienna, Austria

- MÖ bei **VAV**
- retrospektive Auswertung, Follow-Up 4 Jahre (!)
- n=28
- RAN **PRN** ab Baseline vs. BEV 3+**PRN**
- Nach 4 Jahren nur in 2/28 Fällen Weiterbehandlung erforderlich
- 3monatliche Kontrollen bei stabilem Befund
- Langzeit-Visus bei Pat. Symptomatik <3Monate 76 Buchstaben ETDRS vs. 55 bei Pat. Sympt. >3Monate

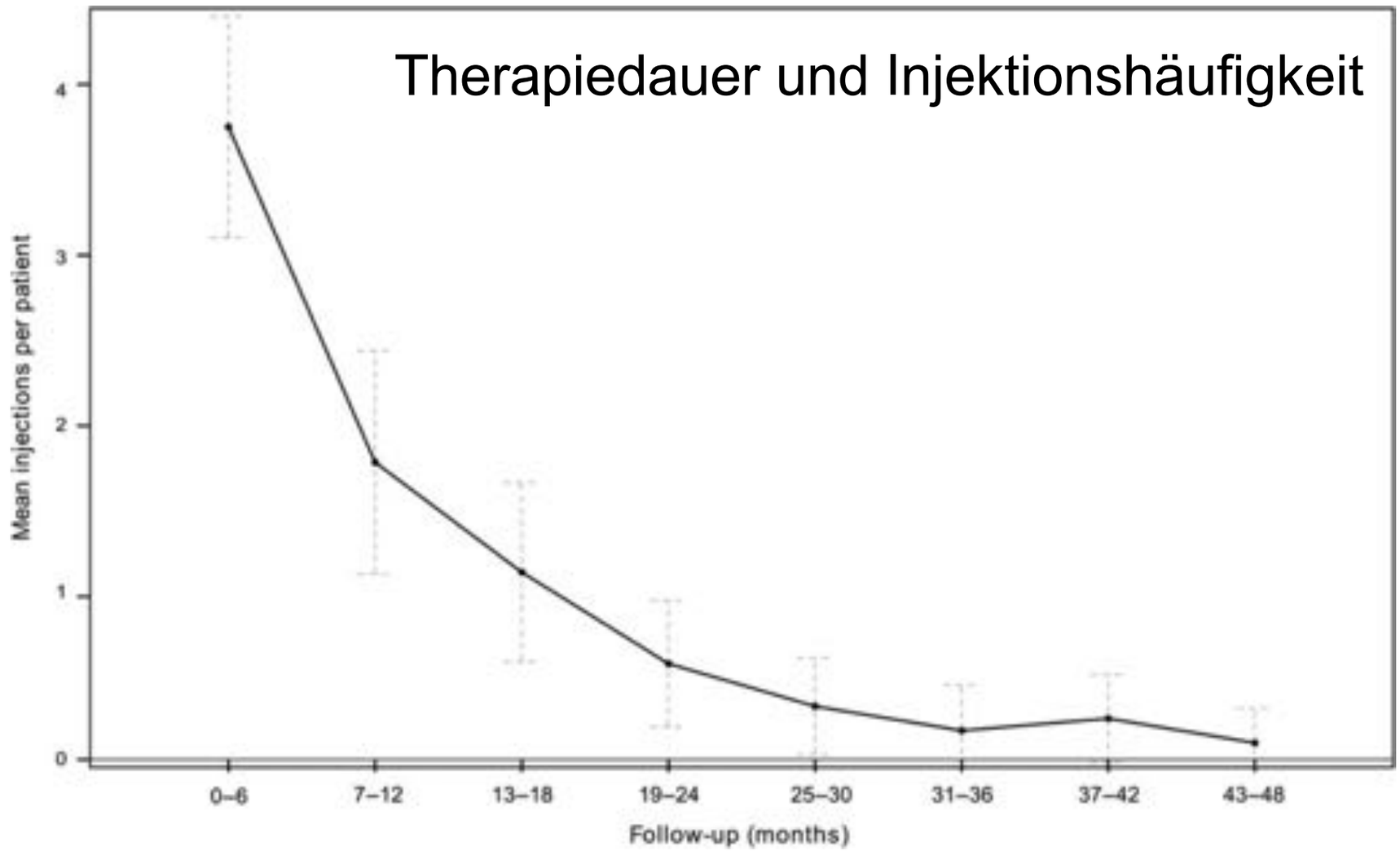
Acta Ophthalmologica

Acta Ophthalmologica 2015

Anti-VEGF treatment in branch retinal vein occlusion: a real-world experience over 4 years

Sandra Rezar, Katharina Eibenberger, Wolf Bühl, Michael Georgopoulos, Ursula Schmidt-Erfurth and Stefan Sacu on behalf of Macula Study Group Vienna

Department of Ophthalmology, Medical University of Vienna, Vienna, Austria



Acta Ophthalmologica

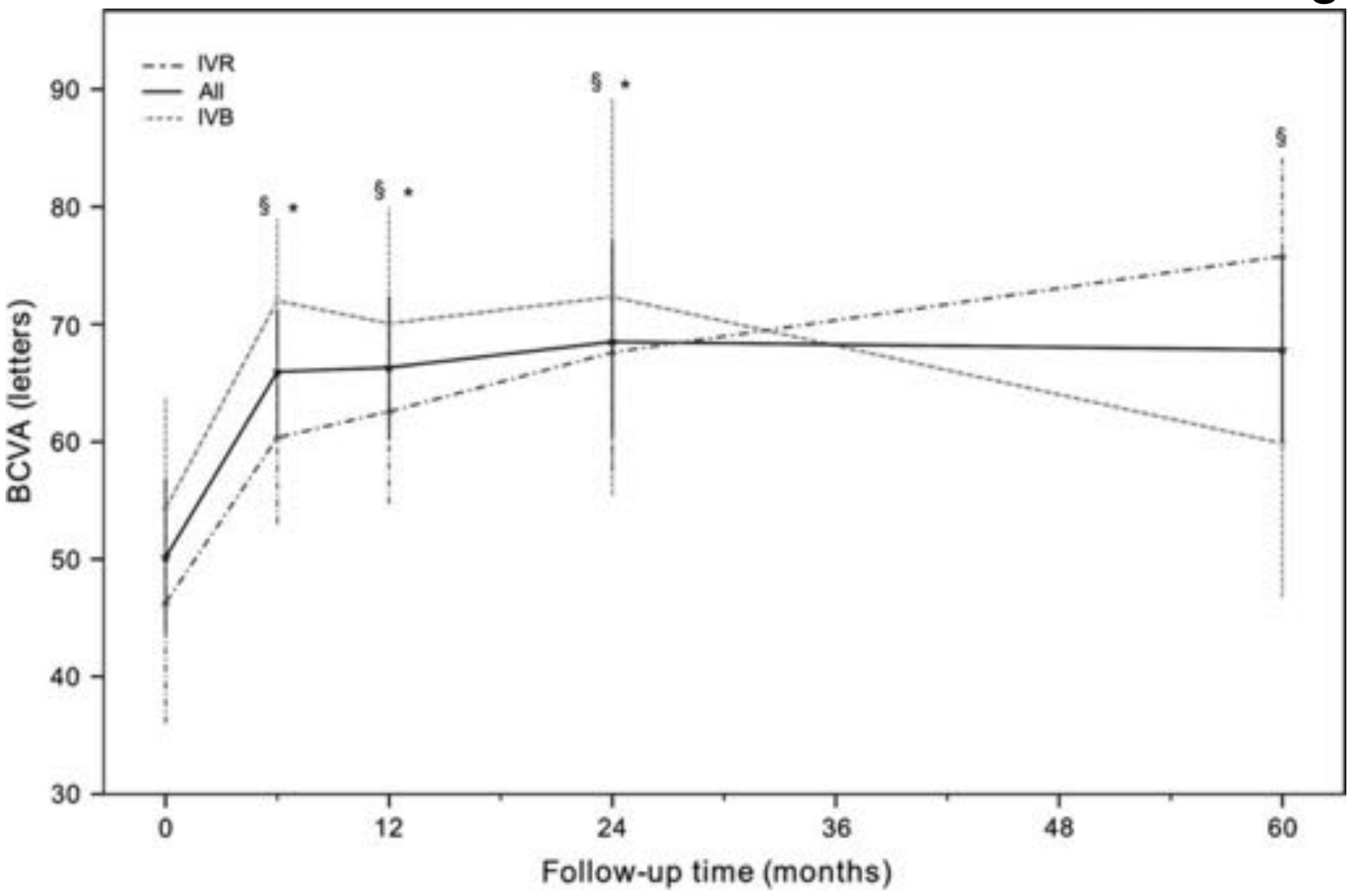
Acta Ophthalmologica 2015

Anti-VEGF treatment in branch retinal vein occlusion: a real-world experience over 4 years

Sandra Rezar, Katharina Eibenberger, Wolf Bühl, Michael Georgopoulos, Ursula Schmidt-Erfurth and Stefan Sacu on behalf of Macula Study Group Vienna

Department of Ophthalmology, Medical University of Vienna, Vienna, Austria

Visusentwicklung



„Switching“

Ophthalmologica

Original Paper

Ophthalmologica 2017;238:110–118
DOI: 10.1159/000473864

Received: January 25, 2017
Accepted after revision: March 28, 2017
Published online: May 24, 2017

Comparison of Intravitreal Ranibizumab, Aflibercept, and Dexamethasone Implant after Bevacizumab Failure in Macular Edema Secondary to Retinal Vascular Occlusions

Joel Hanhart Yaacov Rozenman

Department of Ophthalmology, Shaare Zedek Medical Center, Jerusalem, Israel

3 -12 bevacizumab injections delivered over 3 -15 months average interval between injections 1 to 1.4 months

Table 2. Visual and anatomic outcomes (mean ± SD)

	Before switch	12 months after switch	*p* value
Ranibizumab			
CMT	431.67±96.84	300.07±52.04	<0.001
VA	0.35±0.19	0.49±0.26	<0.001
Aflibercept			
CMT	425.33±85.26	280.67±41.62	<0.001
VA	0.39±0.22	0.51±0.30	<0.05
Dexamethasone implant			
CMT	433.50±98.77	293.00±33.00	<0.001
VA	0.34±0.19	0.51±0.26	<0.01

Ophthalmologica

Original Paper

Ophthalmologica 2017;238:110–118
DOI: 10.1159/000473864

Received: January 25, 2017
Accepted after revision: March 28, 2017
Published online: May 24, 2017

Comparison of Intravitreal Ranibizumab, Aflibercept, and Dexamethasone Implant after Bevacizumab Failure in Macular Edema Secondary to Retinal Vascular Occlusions

Joel Hanhart Yaacov Rozenman

Department of Ophthalmology, Shaare Zedek Medical Center, Jerusalem, Israel

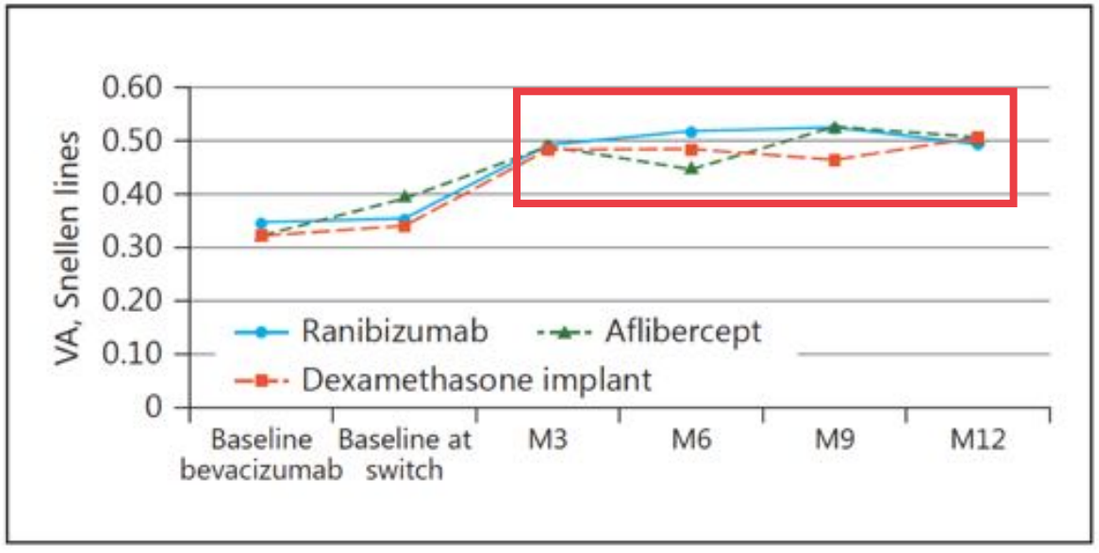


Fig. 2. Functional response to bevacizumab and second-line agents.

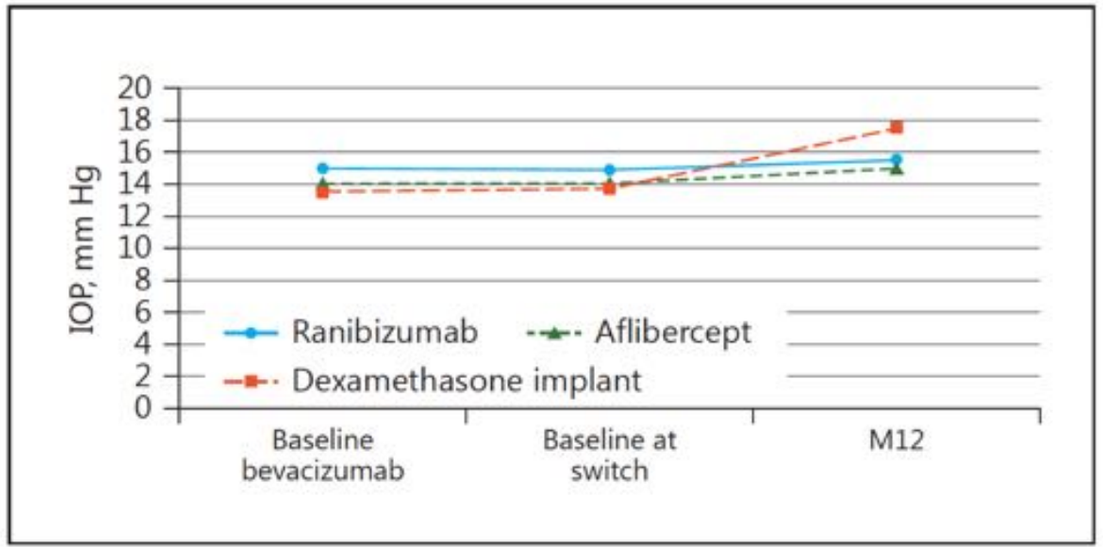
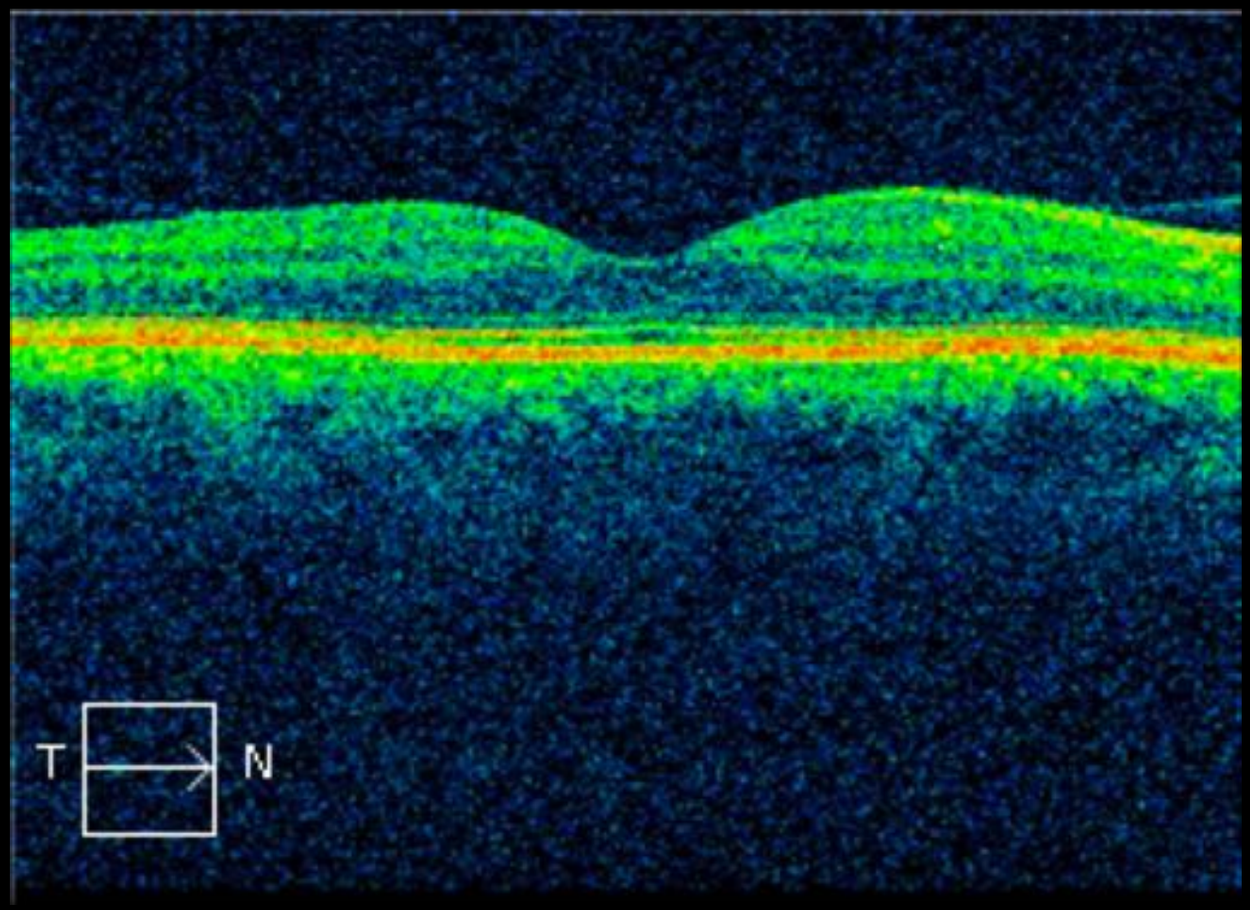
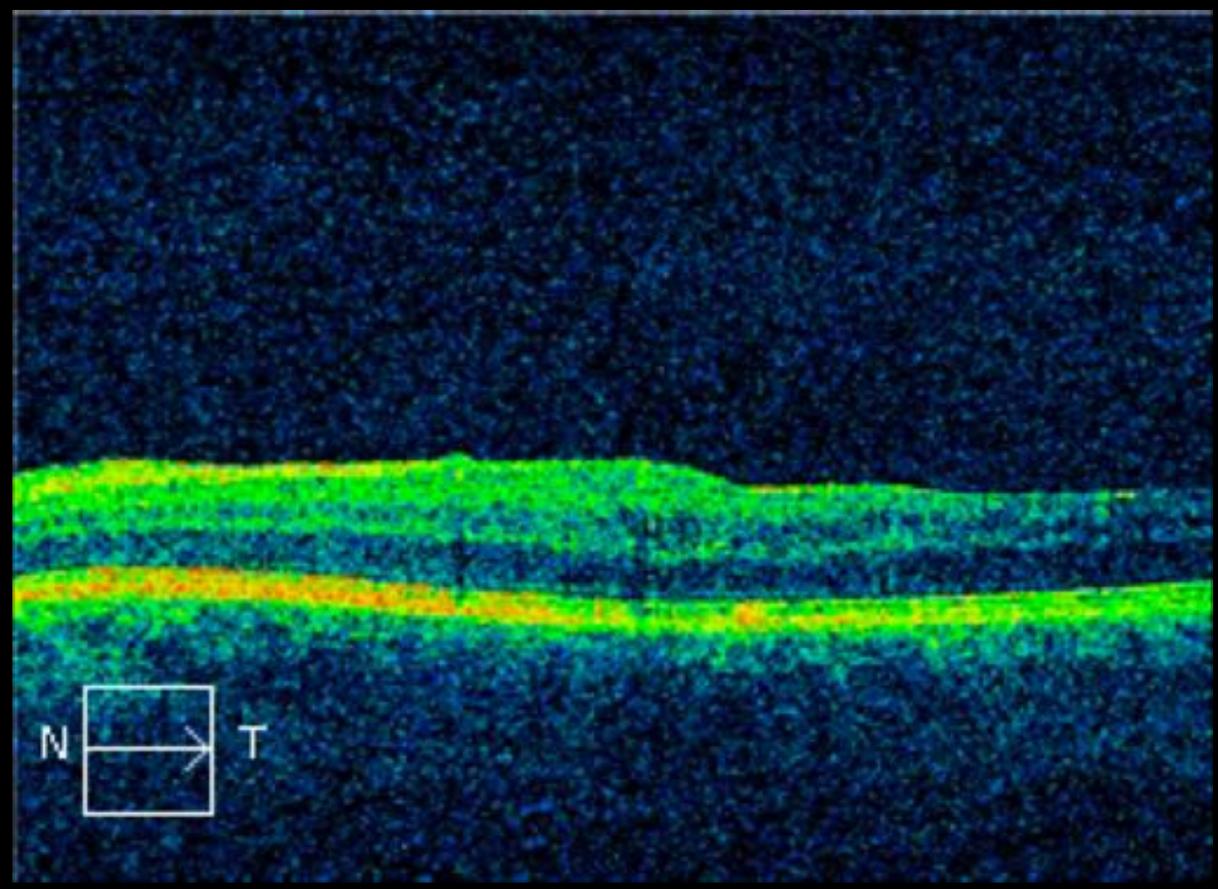


Fig. 3. IOP changes during treatment.

Und Switching von “On label“ auf “Off label“?

Pat., m., 60 Jahre



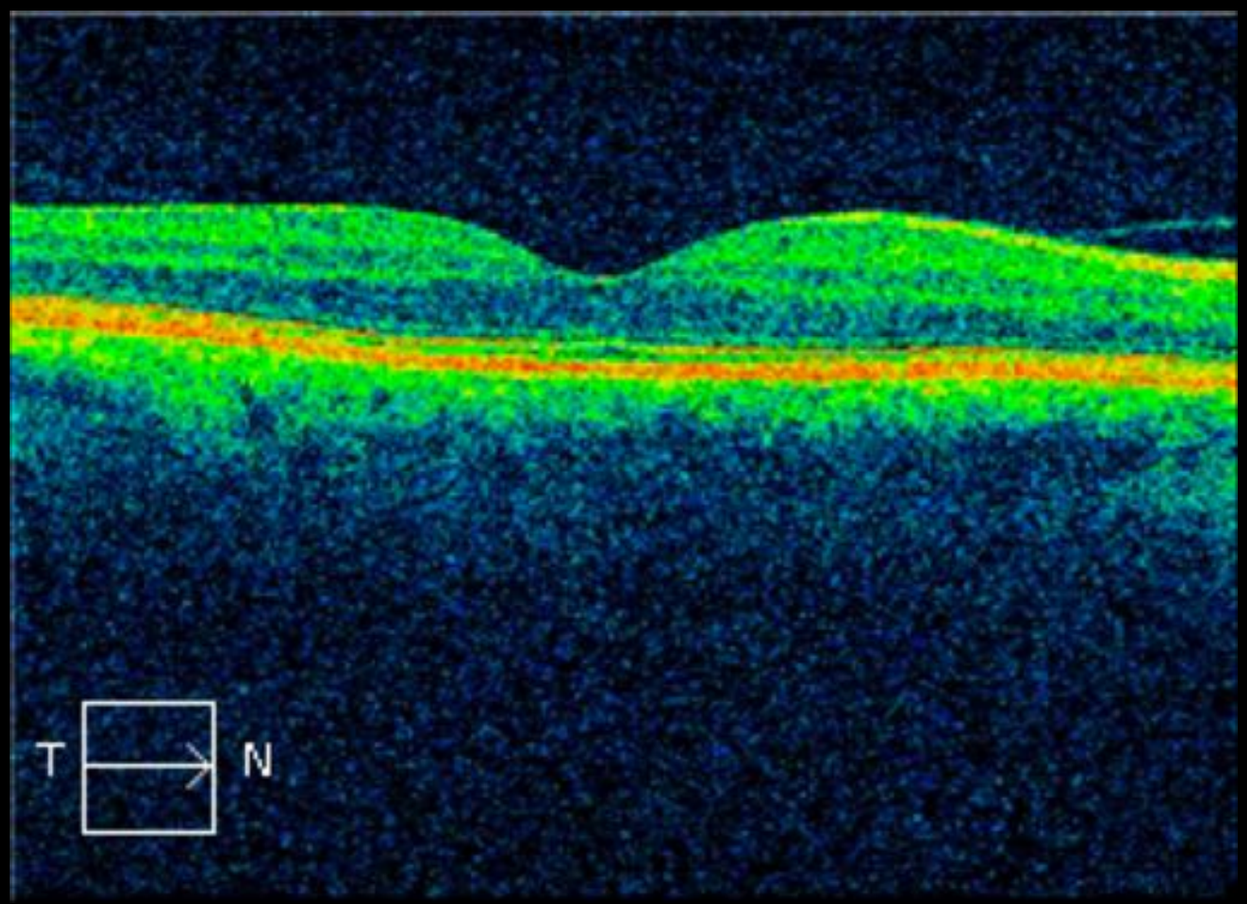


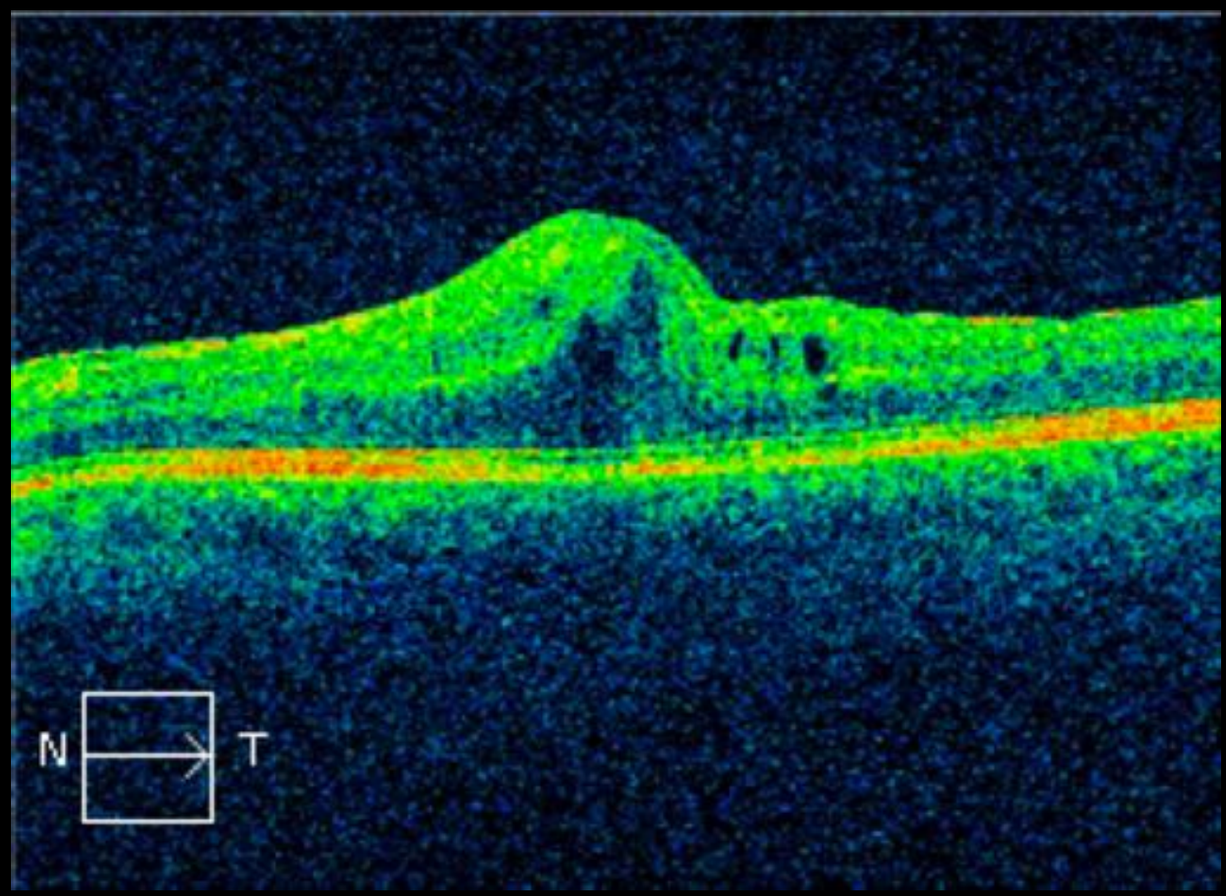
05/2017

LA Z.n. rezidivierendem MÖ nach VAV
Z.n. Dexamethason x1, Steroidresponder, lokale antiglaukomatöse Therapie
Z.n. Ranibizumab x21 (!)
Z.n. PPV+Peeling wg. Epiretinaler Gliose
Z.n. Aflibercept x15 + Versuch T&E Aflibercept x5 monatlich, keine Verlängerung Injektionsintervall

Visus RA 1,0 / LA Visus 0,5

Pat., m., 69 Jahre

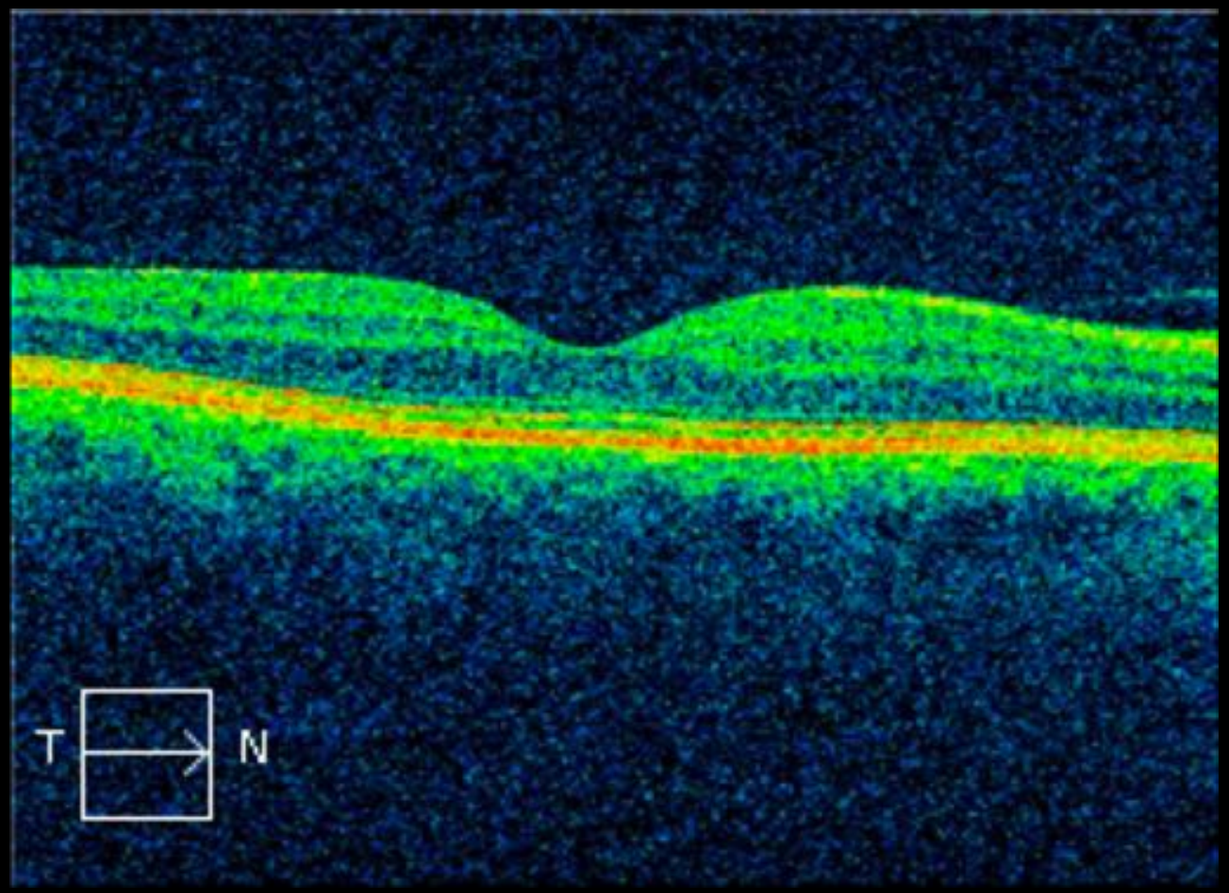


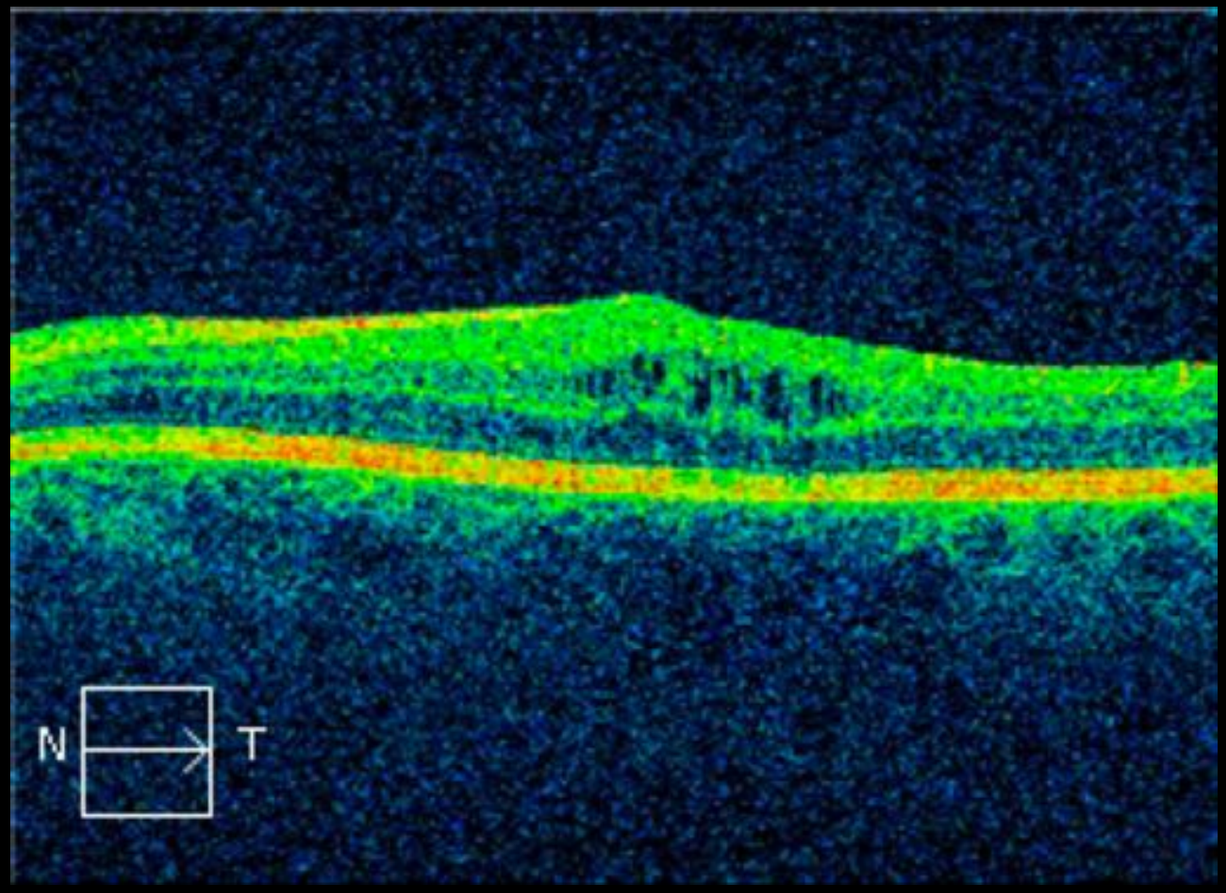


06/2017

LA Kontrolle nach 1 Monat post weiteren x5 Aflibercept monatlich

Pat., m., 69 Jahre





09/2017

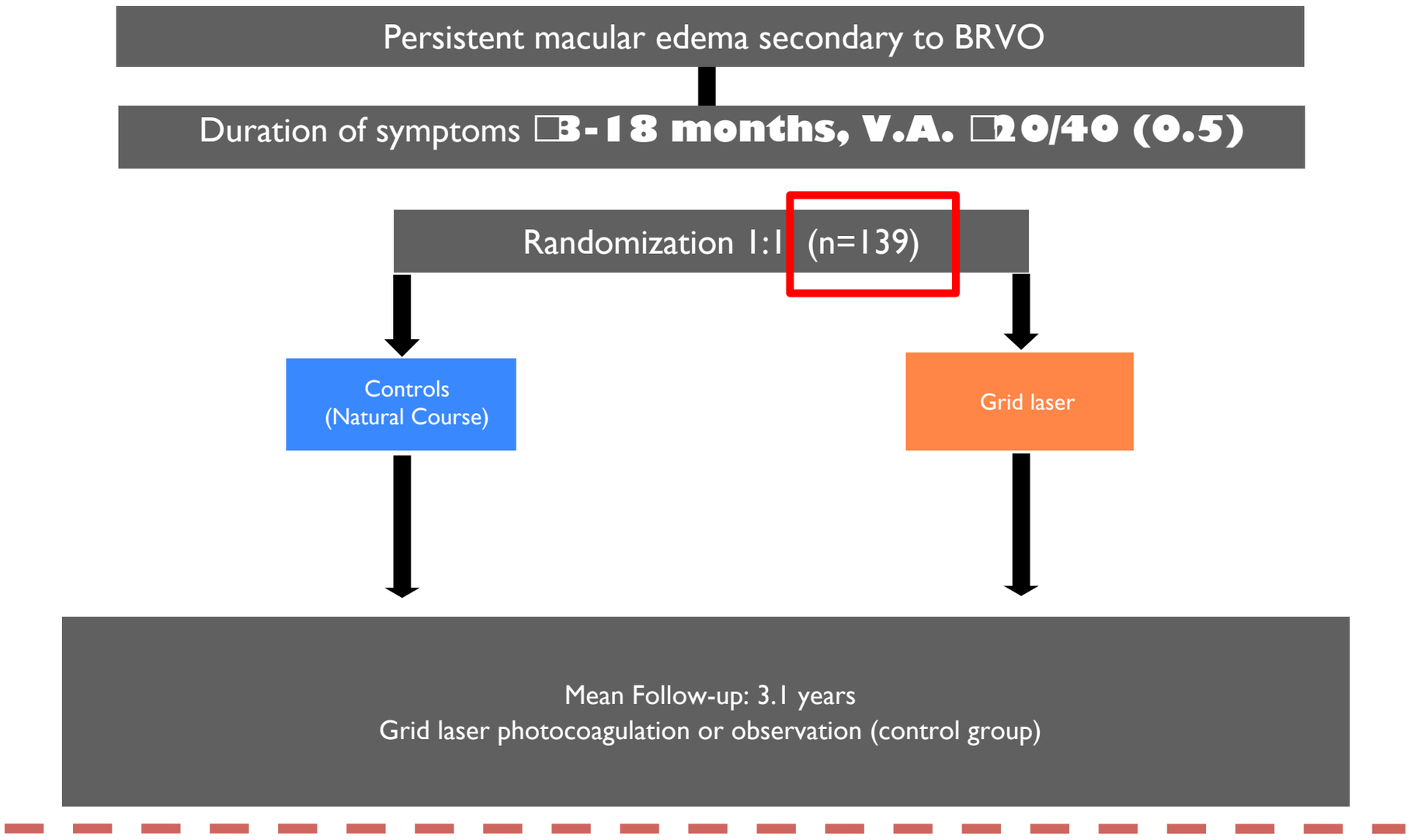
LA Z .n. Switching auf Bevacizumab x3

Visus RA 1,0 / LA Visus 0,5

Ist bei Venenastverschlüssen eine Grid-Laserkoagulation noch sinnvoll?

1984: Branch Vein Occlusion Study

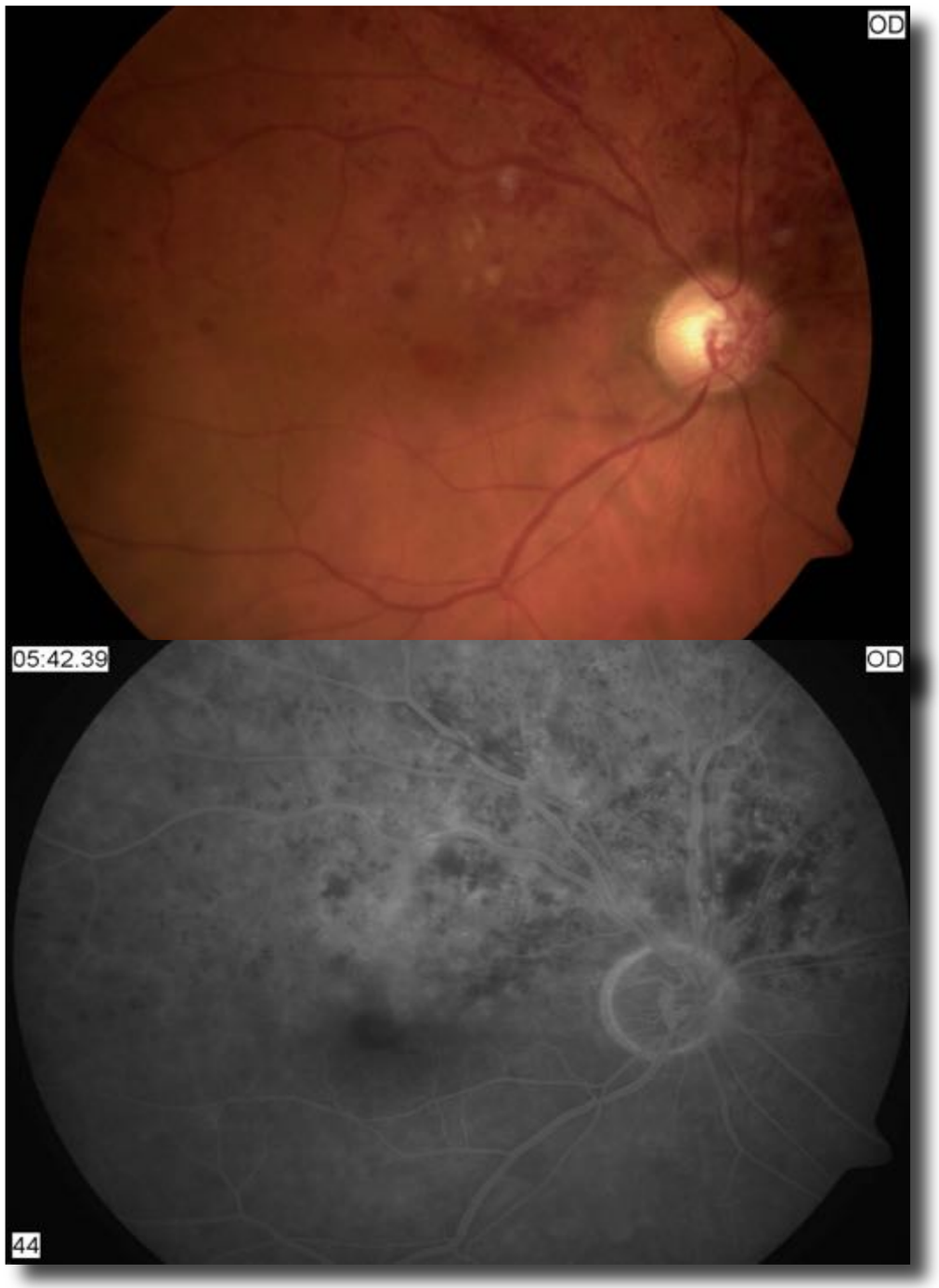
BVOS: Prospective randomized multicenter trial (BRVO Study Group)



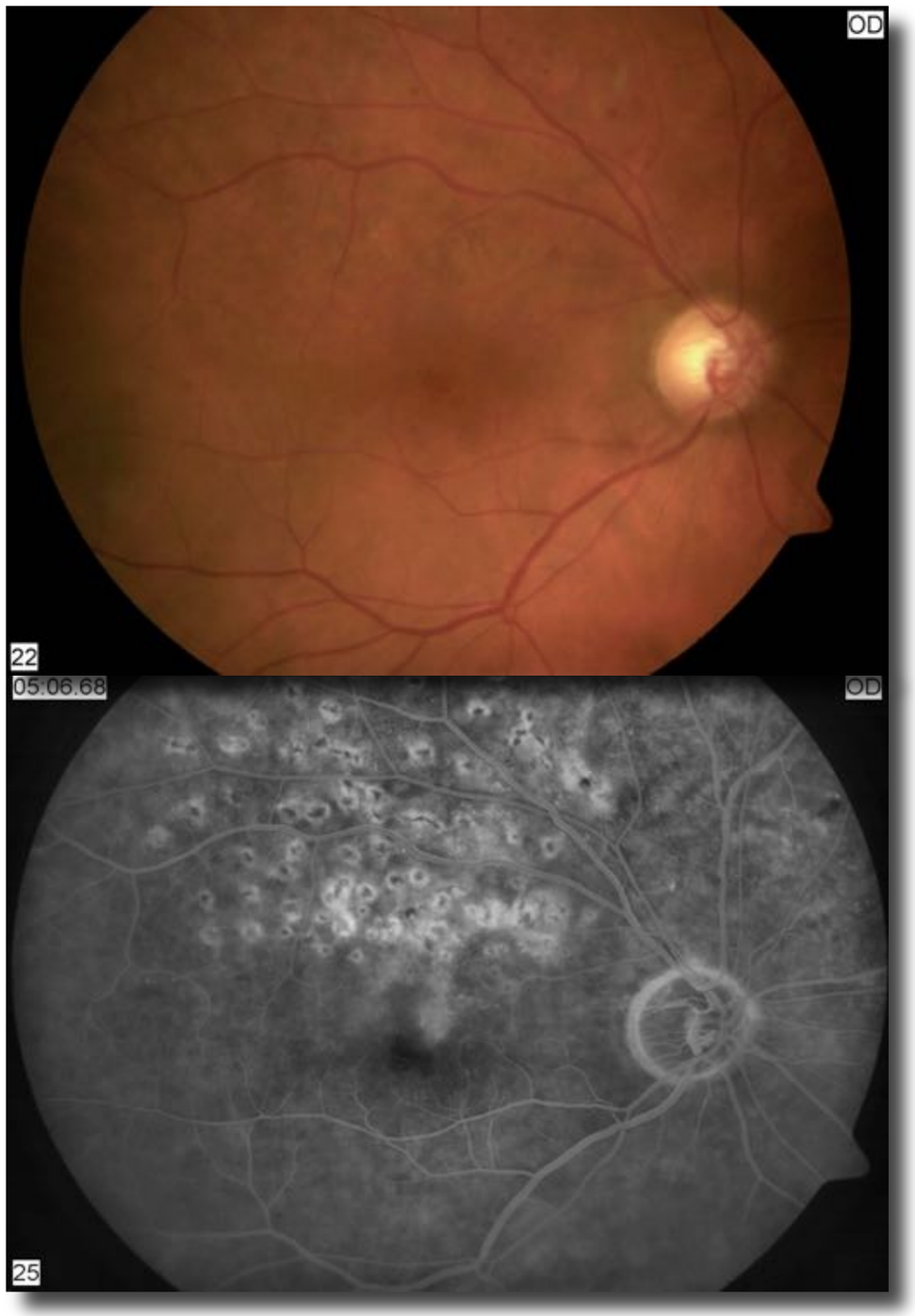
BRVO=branch retinal vein occlusion

Argon laser photocoagulation for macular edema in branch vein occlusion. The Branch Vein Occlusion Study Group. Am J Ophthalmol 1984;98:271-82.

Grid-Laserkoagulation bei VAV

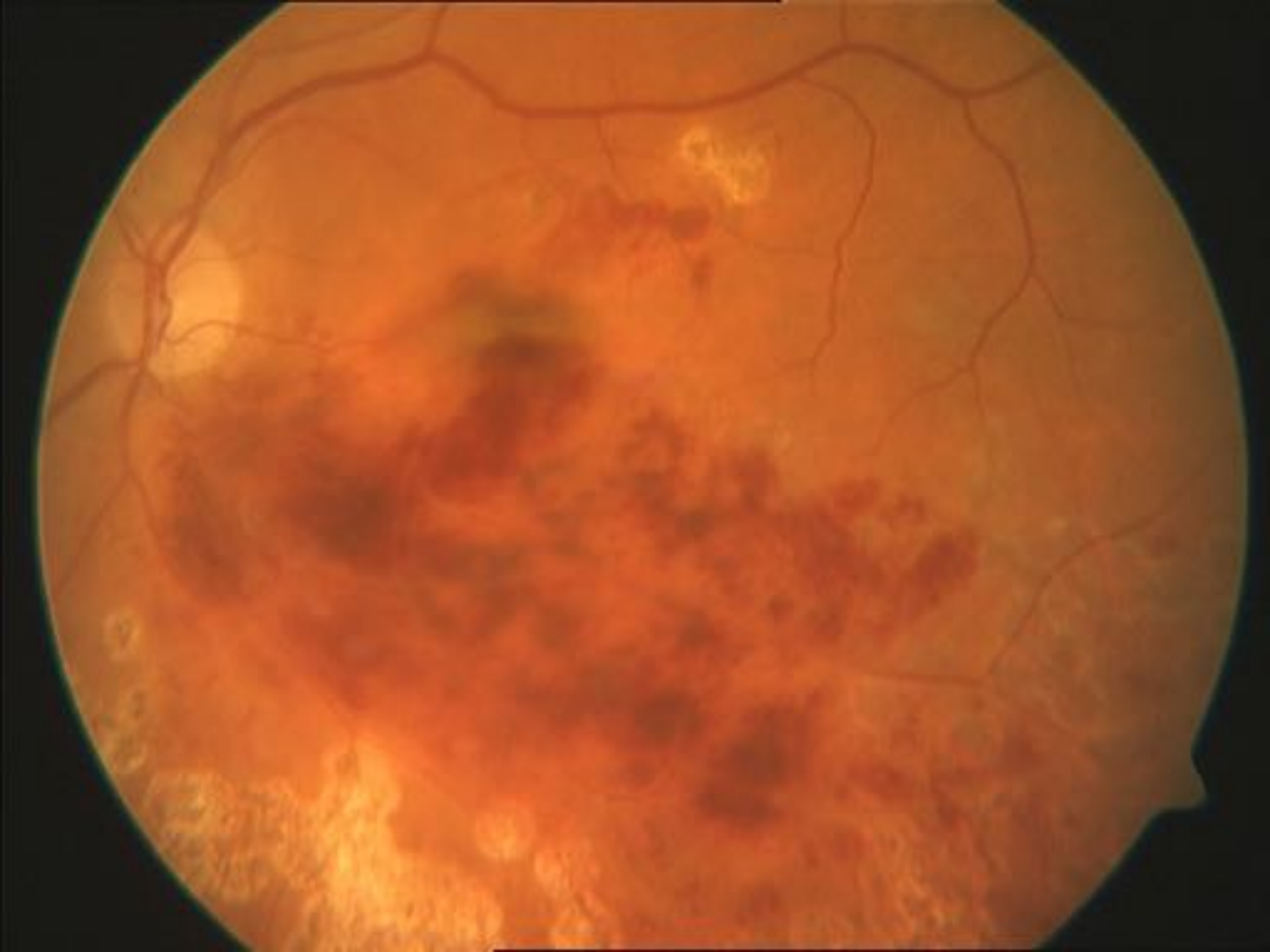


Visus 0,3



Visus 0,6 (6 Mon.)

Grid Laser bei VAV: Keine Akuttherapie !



VIBRANT:
Aflibercept vs. Laser bei VAV

LOCF (Primäre Analyse)

*p<0,0001 vs. Laser

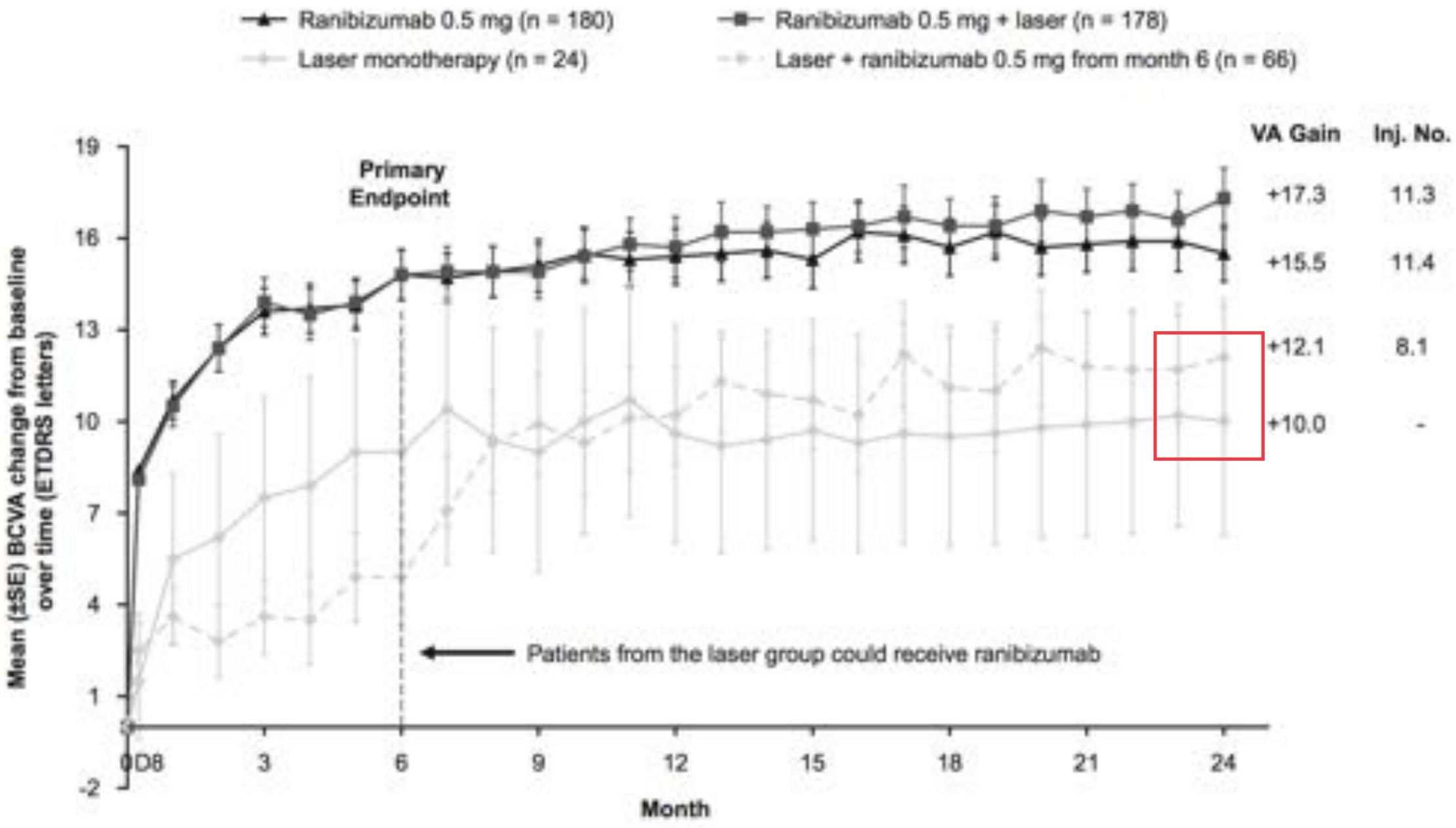
**p<0,004 vs. Laser

Laserarm konnte Laser-Zusatzbehandlungen in den Wochen 12, 16 und 20 erhalten

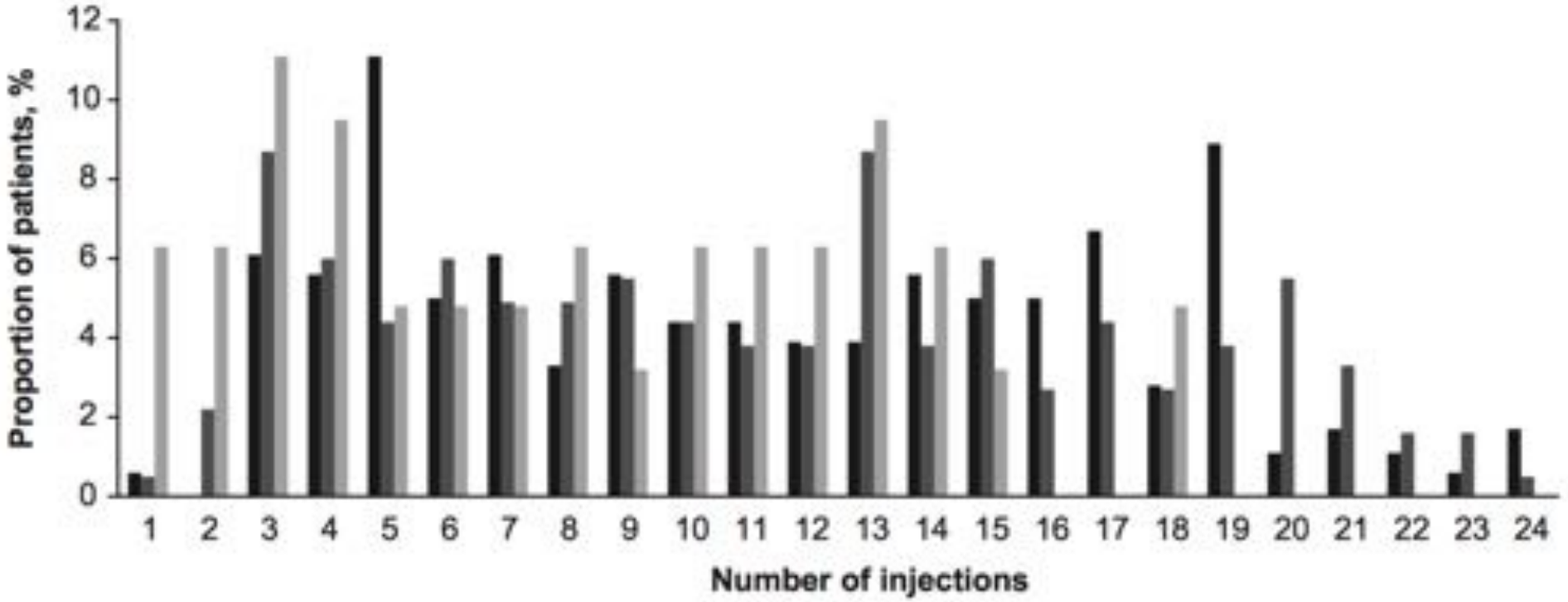
#Bei Erfüllung der Kriterien für eine Zusatzbehandlung erhielten Pat. initial 3 x monatl. AFL-Injektionen gefolgt von 2-monatl. Injektionen
AFL, Aflibercept; BCVA, bestkorrigierte Sehschärfe; ETDRS, Early Treatment Diabetic Retinopathy Study; LOCF, last observation carried forward;

1. Campochiaro PA et al. Intravitreal aflibercept for macular edema following branch retinal vein occlusion: 24-week results of the VIBRANT study; Ophthalmology 2014, epub ehead of print, doi:10.1016/j.ophtha.2014.08.031, 2. Regeneron/Bayer data on file

BRIGHTER: Ranibizumab vs. Laser

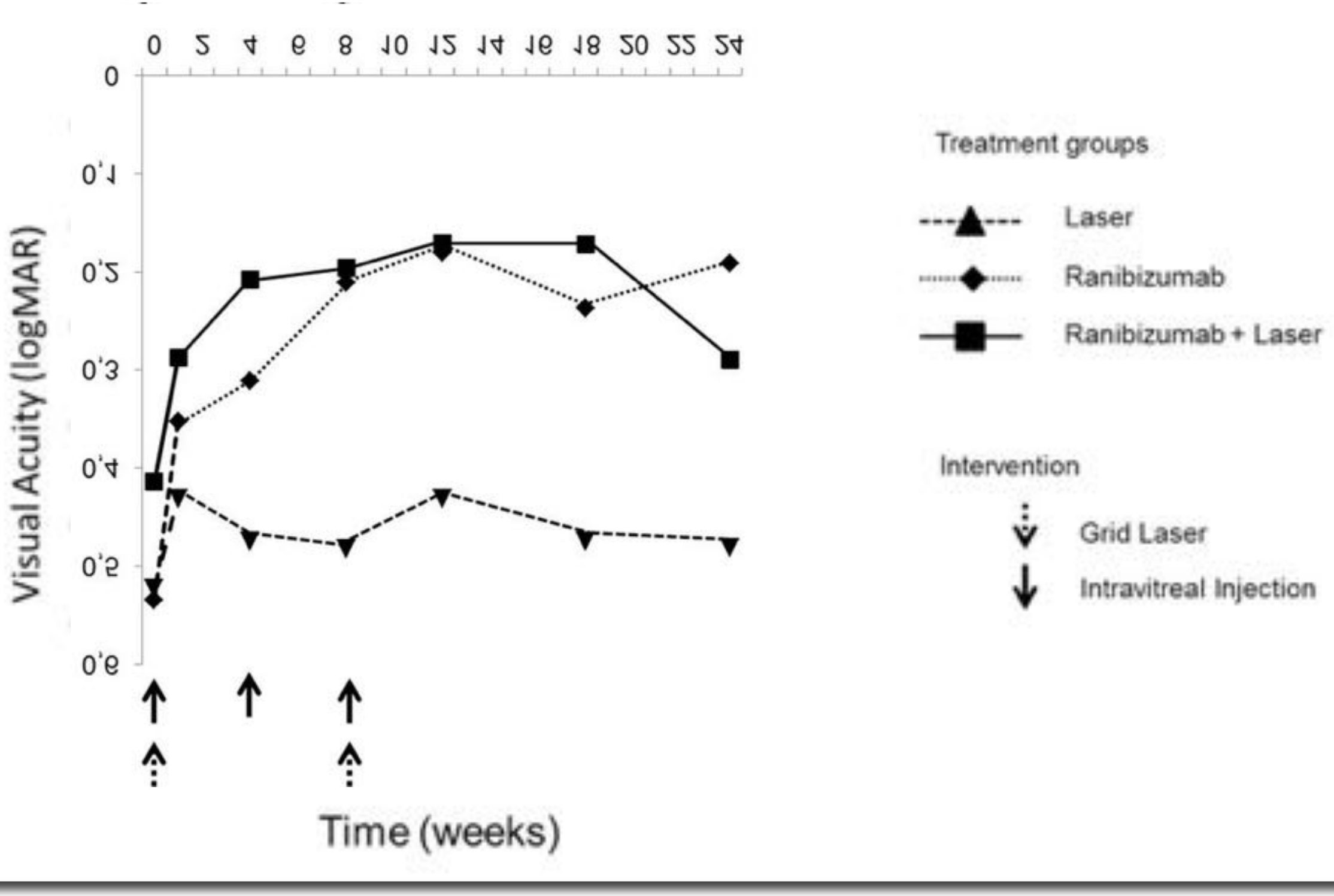


BRIGHTER: Ranibizumab vs. Laser: Injektionshäufigkeit



	Ranibizumab 0.5 mg (n = 180)	Ranibizumab 0.5 mg + laser (n = 183)	Laser + ranibizumab 0.5 mg from month 6 (n = 63)
Number of injections			
Mean (SD)	11.4 (5.81)	11.3 (6.02)	8.1 (4.86)
Median	11.0	11.0	8.0

RABAMES: Ranibizumab vs. Grid vs. Kombination



Ranibizumab for Branch Retinal Vein Occlusion Associated Macular Edema Study (RABAMES): six-month results of a prospective randomized clinical trial. Acta Ophthalmol. 2014

Empfehlung Leitlinie aktuell

• Zur Behandlung des Makulaödems beim ZVV soll keine fokale Lasertherapie erfolgen.	⇓⇓
• Zur Behandlung des Makulaödems beim VAV kann eine fokale Laserkoagulation zur Minderung des Makulaödems sinnvoll sein. Diese sollte aber erst im Verlauf der Behandlung bei unzureichendem Erfolg der IVOM angewendet werden.	⇔ ⇑

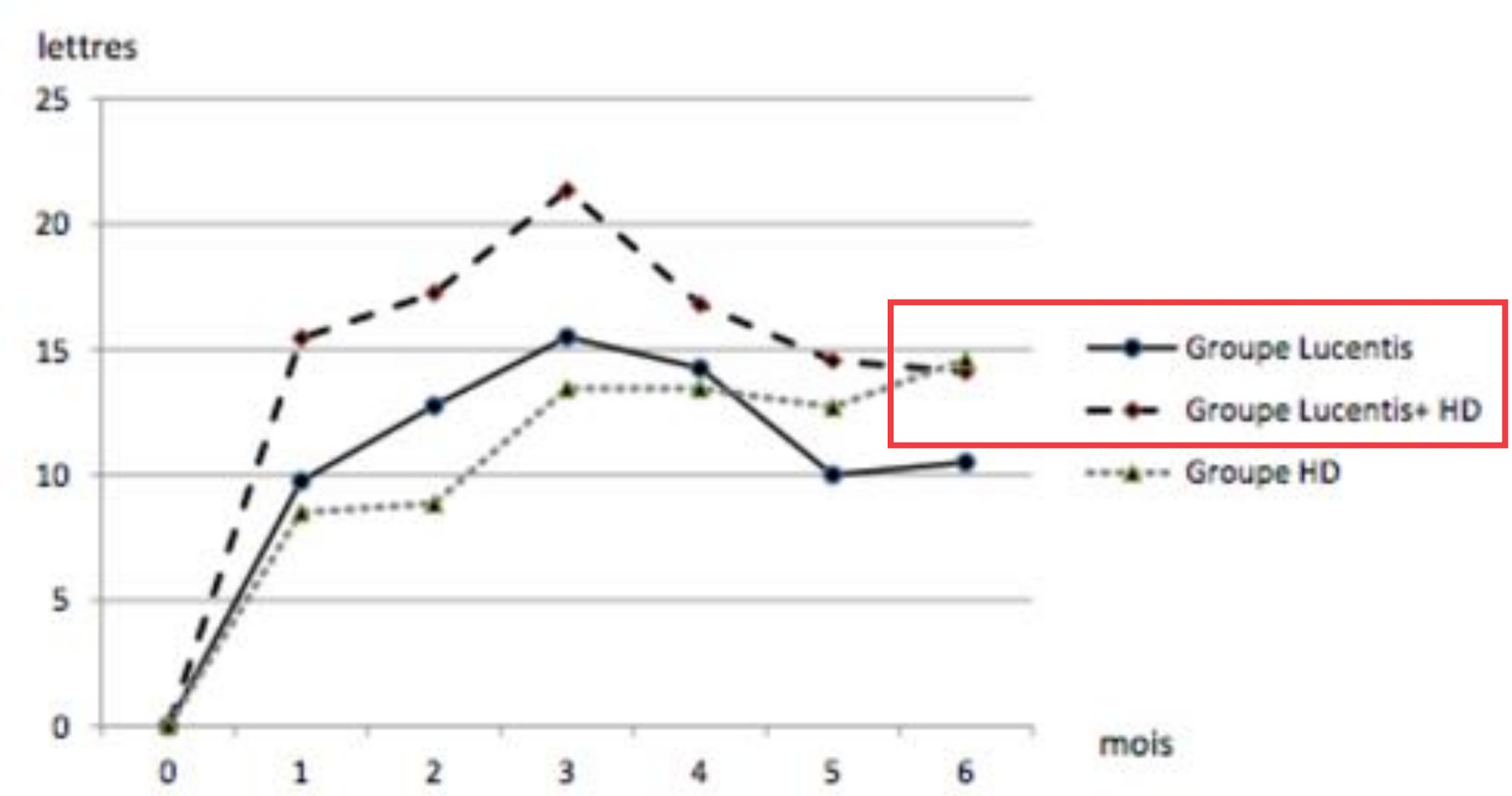
Ist die Hämodilution noch eine Therapieoption bei venösen Netzhautgefäßverschlüssen?

Comparaison de la prise en charge précoce des occlusions de la veine centrale de la rétine par ranibizumab et/ou hémodilution Ajout d'une étoile "en dur" pour les articles de JRDIA - 09/11/15

Comparison of early management of central retinal vein occlusion with ranibizumab versus hemodilution

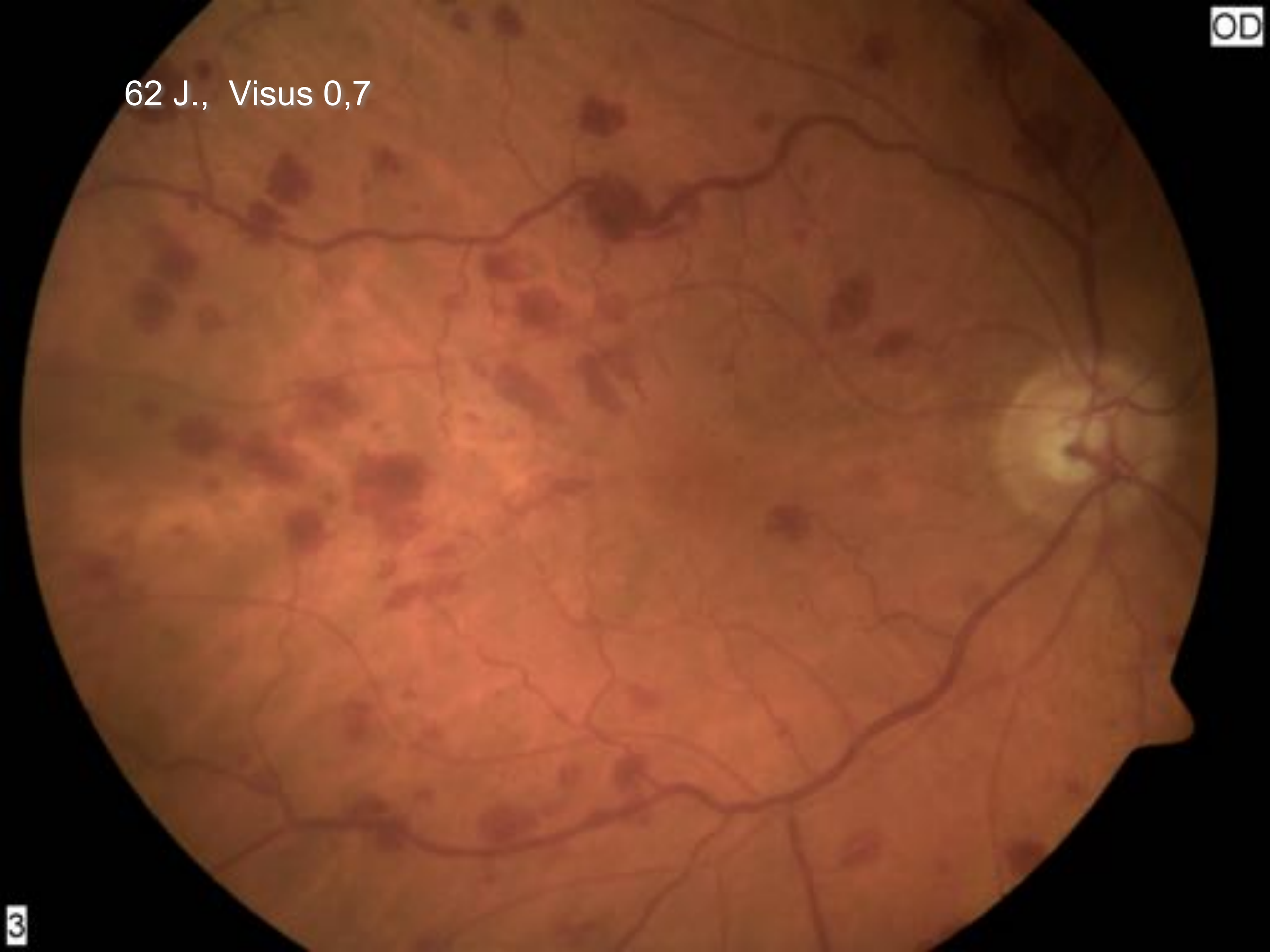
Doi : 10.1016/j.jfo.2015.03.016

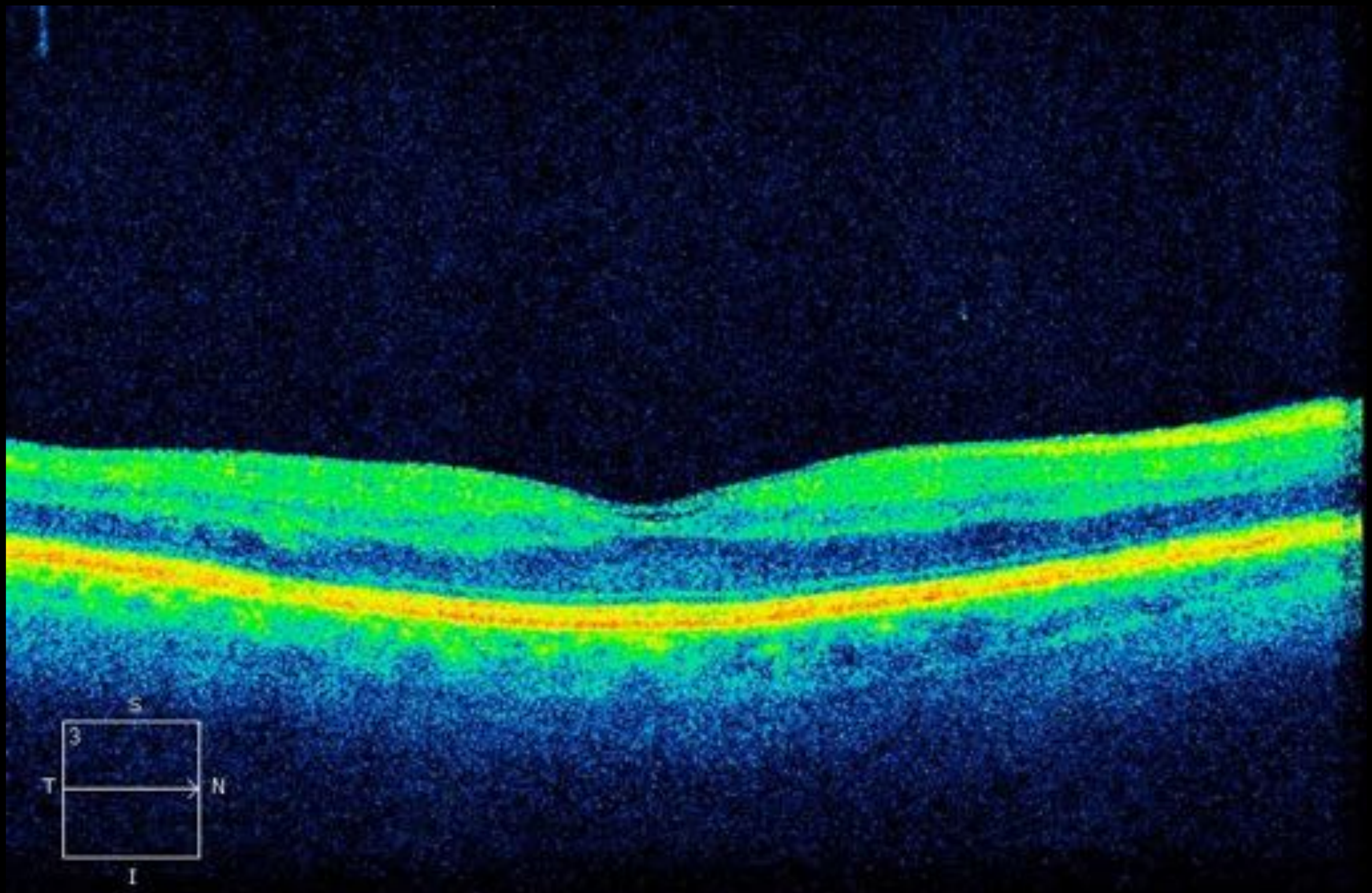
M. Graber [a] [*] , A. Glacet-Bernard [a], C. Fardeau [b], N. Massamba [a], M. Atassi [b], O. Rostaqui [a], F. Coscas [a], P. Le Hoang [b], E.H. Souied [a]



- CRVO (n=44), HD vs. Ranibizumab vs. Ranibizumab+HD
- Kein Unterschied BCVA oder CRT nach 6 Mon.
- HD Therapieoption bei jungen Patienten (?)

62 J., Visus 0,7





Kein Makulaödem: Hämodilution

Hämodilution als therapeutische Option

hypervolämisch	▪Plasmaersatzmittel (HES) ▪Hämatokritabsenkung 2-4% ▪Rheologika (Pentoxifyllin)
isovolämisch	▪ Plasmaersatz (HES) ▪ Aderlaß ▪ Hämatokritabsenkung >10% ▪ Rheologika (Pentoxifyllin)

“Black Box“ Warnung HAES-steril 6/2013

FDA Safety Communication: Boxed Warning on increased mortality and severe renal injury, and additional warning on risk of bleeding, for use of hydroxyethyl starch solutions in some settings

Date: June 24 2013

Purpose: FDA has analyzed recent data that indicate an increased risk of (i) mortality and renal injury requiring renal replacement therapy in critically ill adult patients, including patients with sepsis and those admitted to the ICU; and (ii) excess bleeding particularly in patients undergoing open heart surgery in association with cardiopulmonary bypass. Additional caution regarding the use of these products is warranted.

Hämodilution: Augenheilkunde vs. Intensivmedizin

- Anderes Patientenkollektiv (Schwerstkranke bzw. Intensivpatienten!)
- Patienten erhielten Volumina weit über isovolämischer Hämodilution (50ml/kg KG = 4000ml/d 80 kg KG)
- Andere Indikation: Hydroxyethylstärke Plasmaersatz statt Rheologikum (=„Ophthalmologische Indikation“)

Hämodilution: Ersatzpräparate HAES (cave Evidenzlevel! Off label)

- Voluven® 10% Infusionslösung, Fresenius Kabi
- Poly[O-2-hydroxyethyl]stärke 100g in 1000 ml
- Molare Substitution 0,38-0,45
- Mittleres Molekulargew. 130.000 Da

- Volulyte® 6% Infusionslösung, Fresenius Kabi
- Poly[O-2-hydroxyethyl]stärke 60g in 1000 ml
- Molare Substitution 0,4
- Mittleres Molekulargew. 130.000 Da

Patientennummer:
Fallnummer:

Diomed

Info MT 1

Behandlung von Erkrankungen/ Verletzungen mit Medikamenten

Klinik/Praxis:

KliLu
Wir leben Medizin.

Liebe Patientin, lieber Patient, liebe Eltern,

dieser Aufklärungsbogen dient Ihrer Information. Bitte lesen Sie ihn aufmerksam vor dem Aufklärungsgespräch und füllen Sie den Fragebogen gewissenhaft aus.

Warum und wie wird behandelt?

Nach den Ergebnissen der Untersuchungen leiden Sie/Ihr Kind an folgender Erkrankung/Verletzung:
z.B. Zentralvenenverschluss LA

Wir raten zur **Behandlung mit dem/den Medikament(en):**
Isovolämische Hämodilution:
Voluven = HAES (als Infusion), Trental = Pentoxifyllin (als Infusion und Tablette)
ggf. Aderlässe je nach Labor

Wirkung des Medikaments

Mit der Anwendung des Medikaments wollen wir erreichen:

- ☐ Heilung
- ☐ kürzeren Krankheitsverlauf
- ☐ Unterstützung der Vitalfunktionen
- ☐ Unterstützung der Immunabwehr
- ☐ Schmerzlinderung
- ☐ Verhinderung/Verzögerung des Fortschreitens der Erkrankung (z.B. rheumatoide Arthritis)
- ☐ Verhinderung von Folgeerkrankungen/Spätschäden (z.B. art. Hypertonie)
- ☐ Behandlung von Krankheitsfolgen
- ☐ Ersetzung körpereigener Hormone oder Botenstoffe (Substitutionstherapie)
- ☒ *Verbesserung der Durchblutung*

Die Behandlung

Vorgesehen ist die Gabe des Medikaments mittels

☐ **Einspritzung**

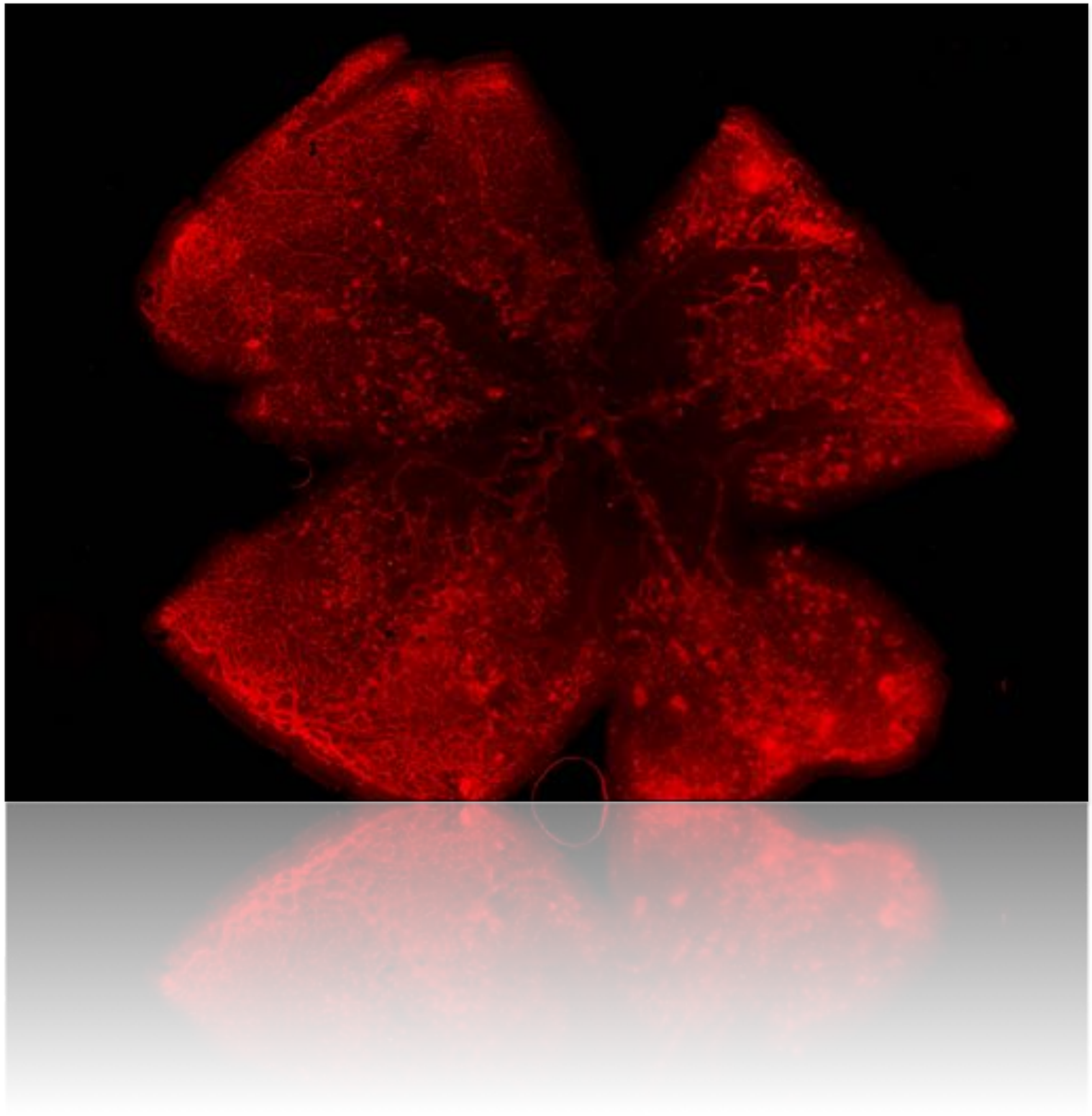
☐ unter die Haut	☐ in Muskeln/Weichteile	☐ in die Rippenfellhöhle
☐ in eine Vene	☐ in Gelenke/Wirbelgelenke	☐ in die Bauchhöhle
☐ in eine Arterie	☐ in den Rückenmarkskanal	☐ ______ (ggf. bezeichnen)

☒ **Infusion in eine Vene**

______
(Bitte z.B. Blutgefäße, Gelenke und/oder Lokalisation der Injektion/Infusion näher bezeichnen)

Red. 10/2014v4
BestellNr. 6051

Vielen Dank !



Venöse retinale Gefäßverschlüsse:

Diagnostik, Risikofaktoren, Therapie

Lars-Olof Hattenbach

Augenklinik des
Klinikums Ludwigshafen

AAD 2018