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Comparing the efficacy of bevacizumab to ranibizumab in patients with retinal vein occlusion. The BRVO study

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- Bayer
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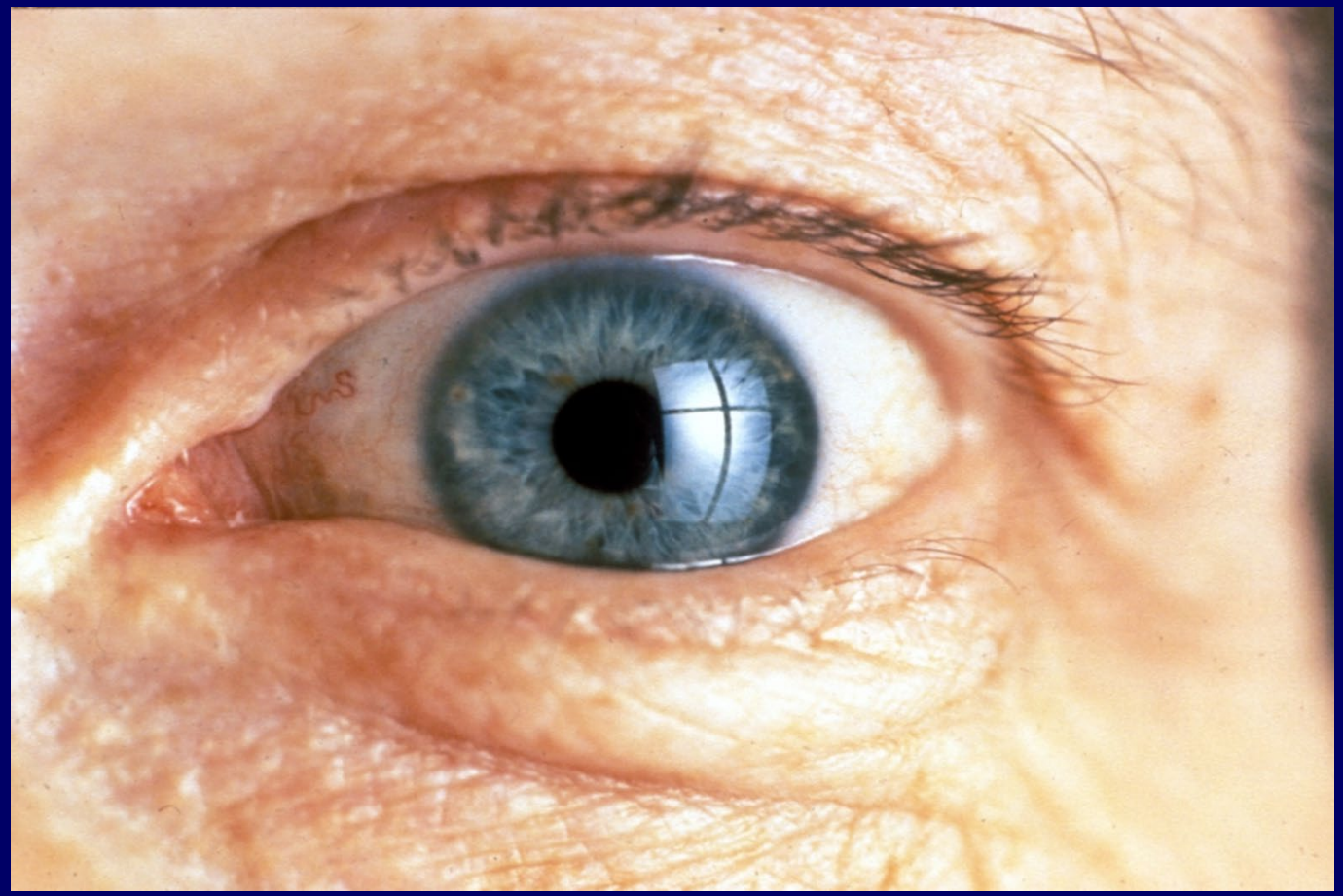
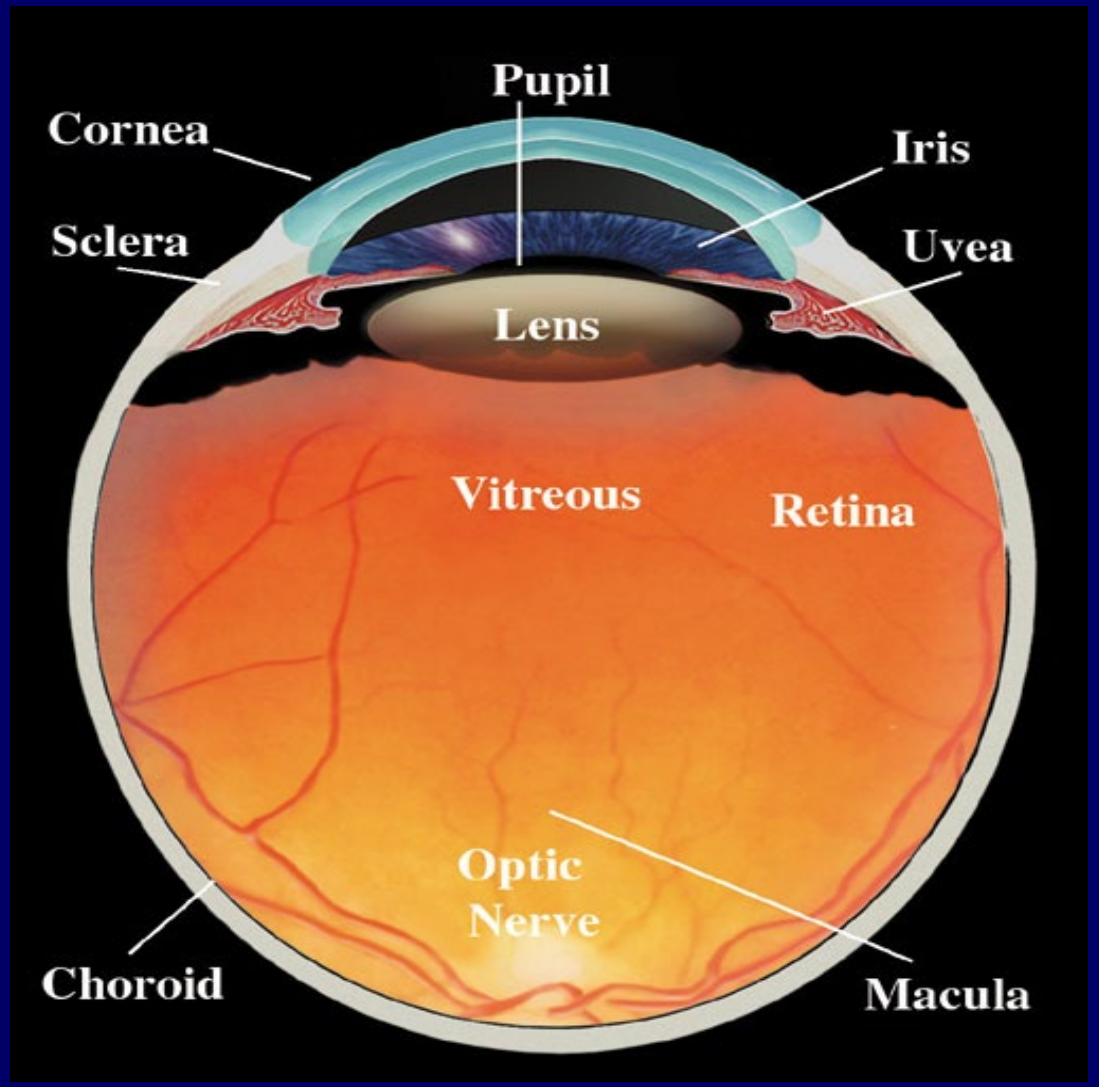
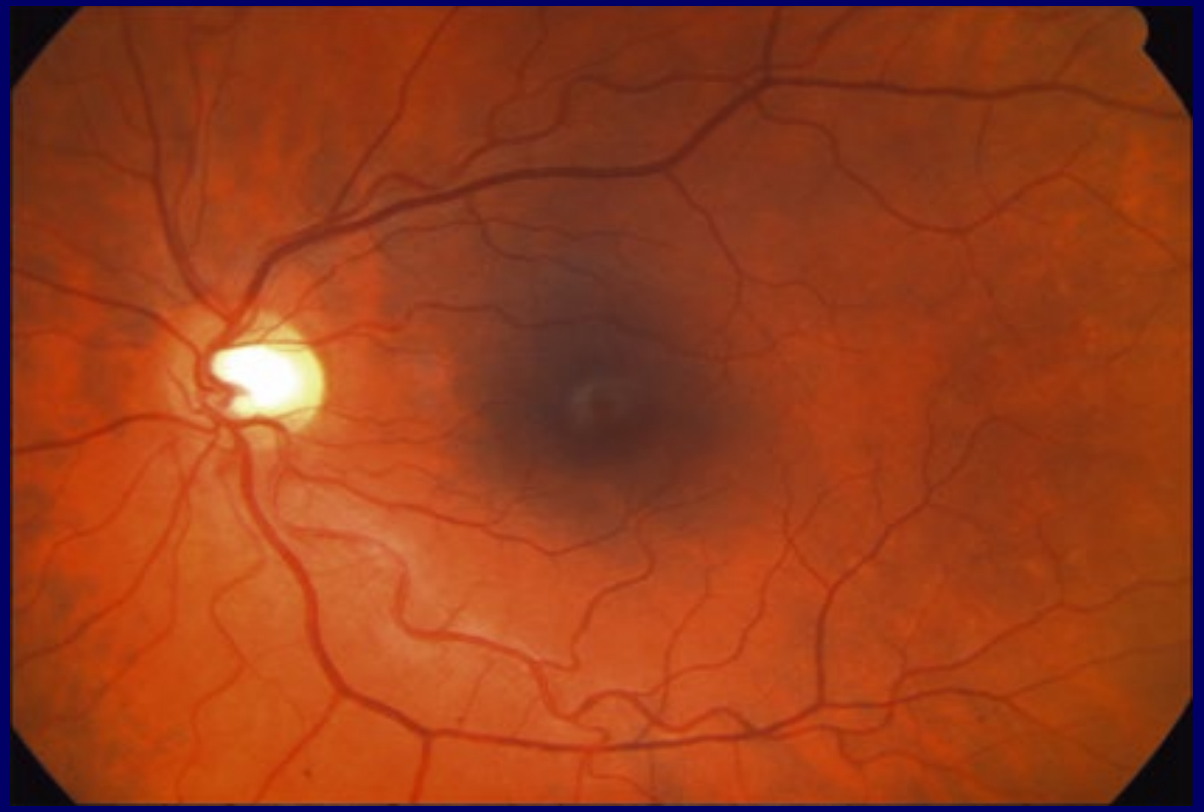
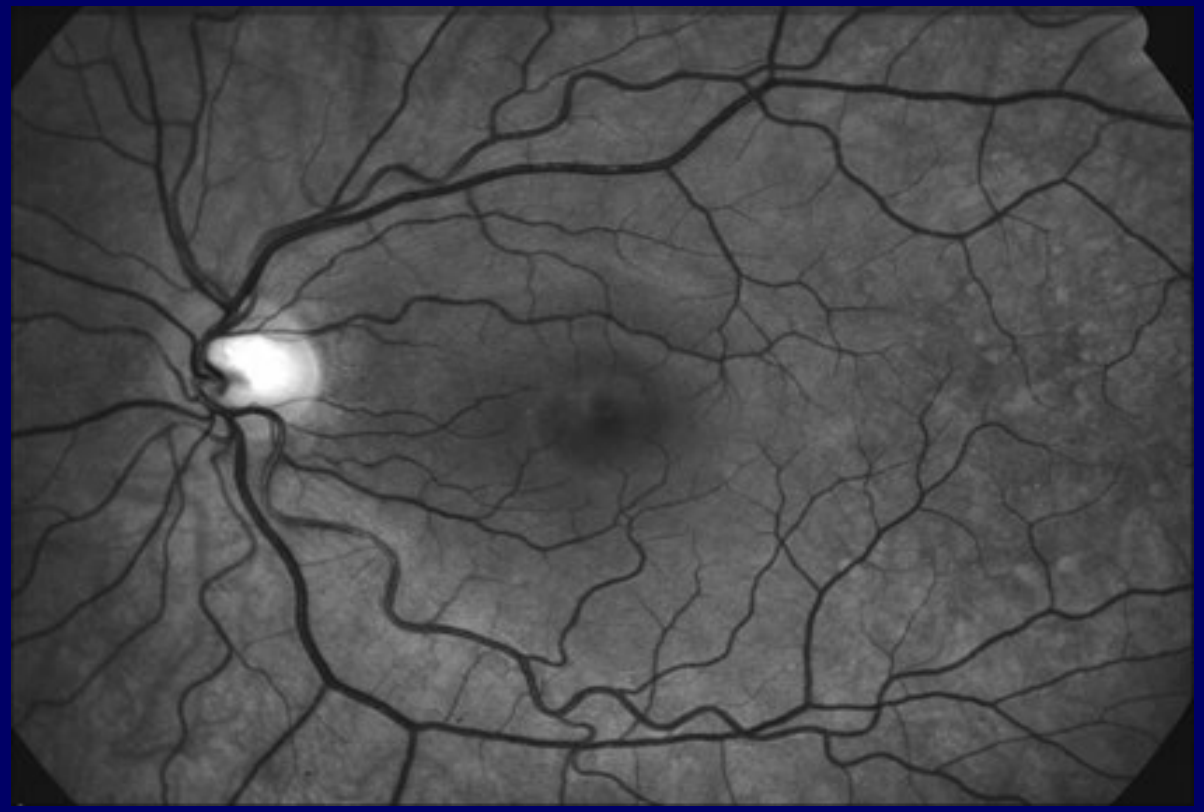
- Apellis
- Boehringer



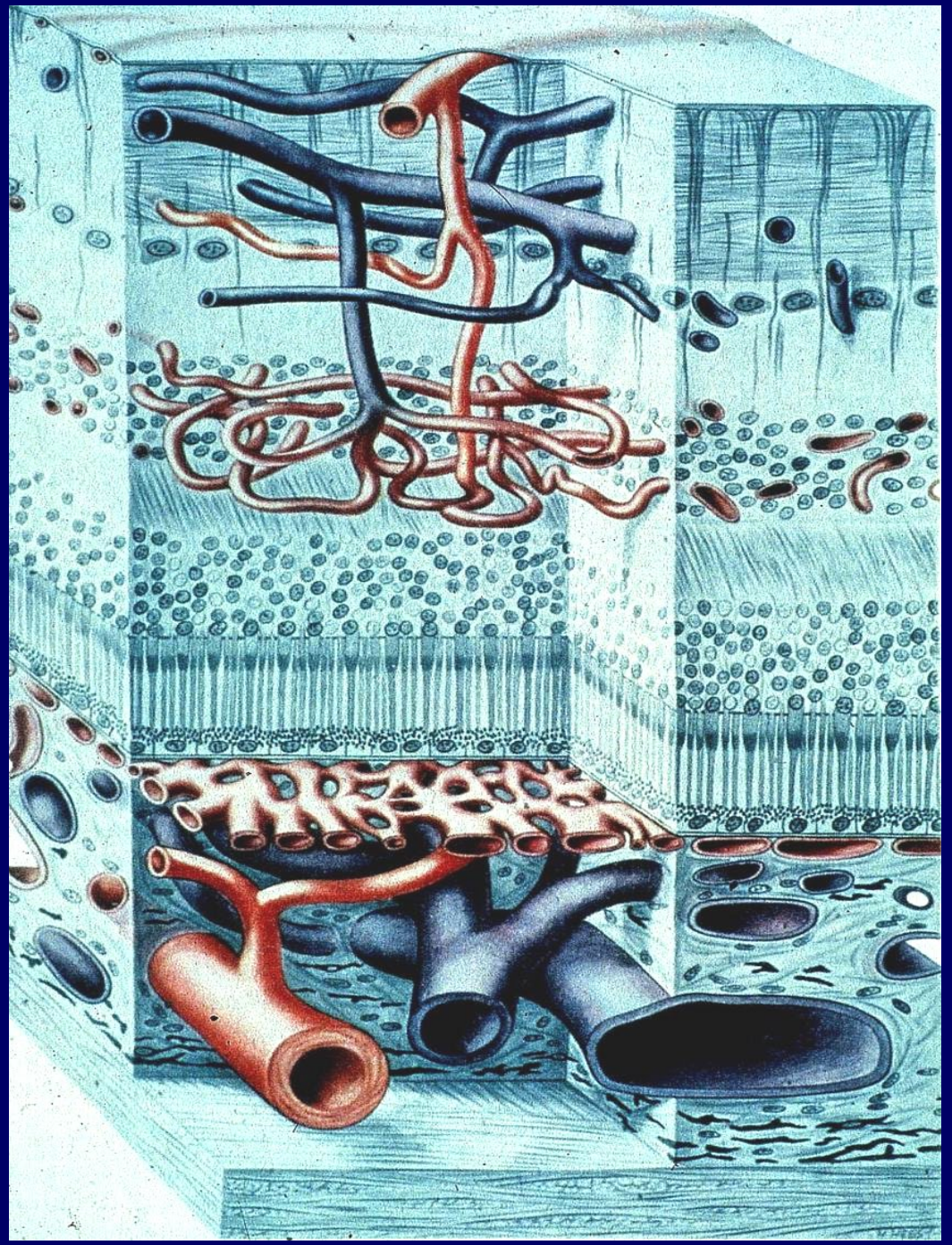

Pupil
Cornea
Iris
Sclera
Uvea
Lens
Vitreous
Retina
Optic
Nerve
Choroid
Macula

Gezonde retina



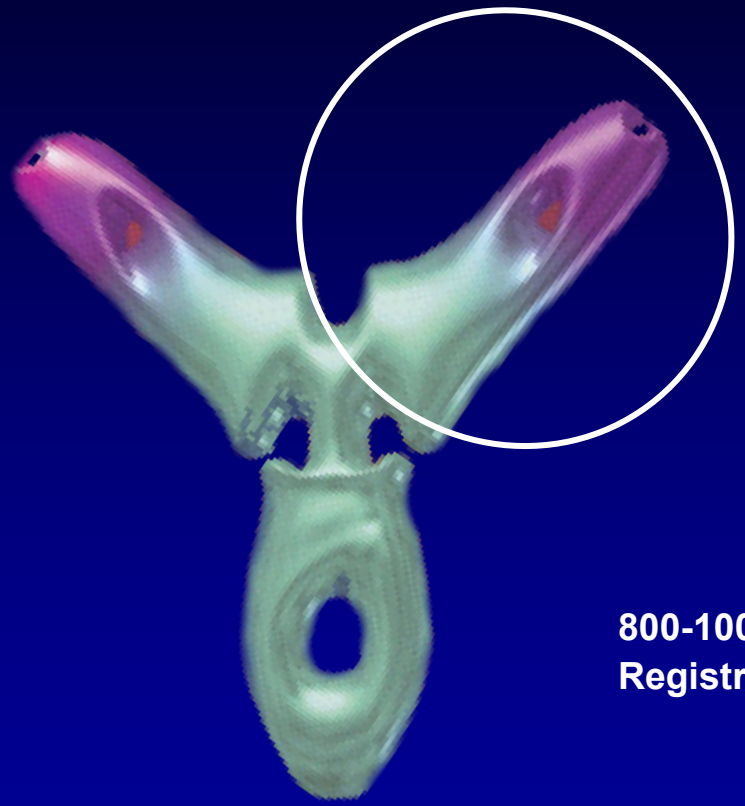


Anatomie Retina



VEGF remmers

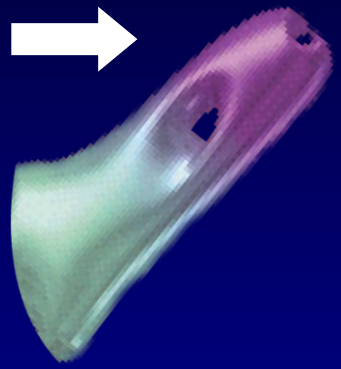
Avastin/bevacizumab



rhu Mab
150 kilodaltons

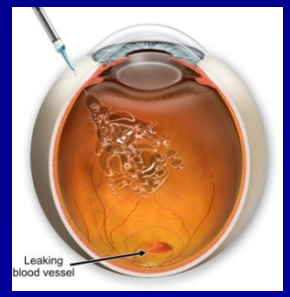
20-50 euros
Off-label

Lucentis/ ranibizumab



rhu Fab V2
48 kilodaltons

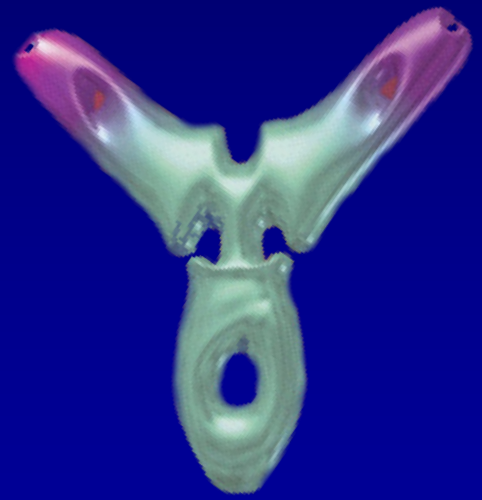
800-1000 euros
Registration for AMD, DME and RVO

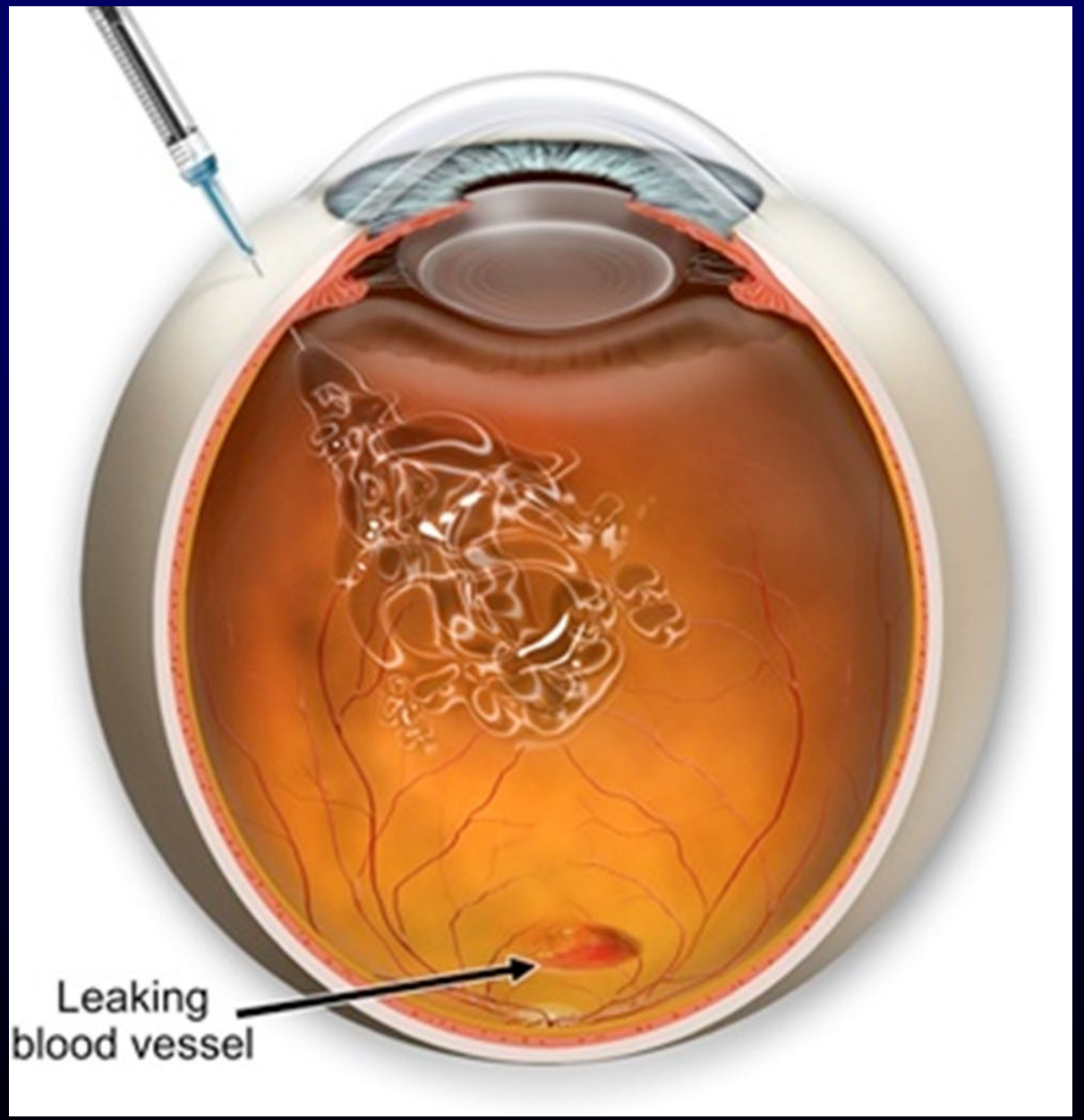


Aflibercept/eylea

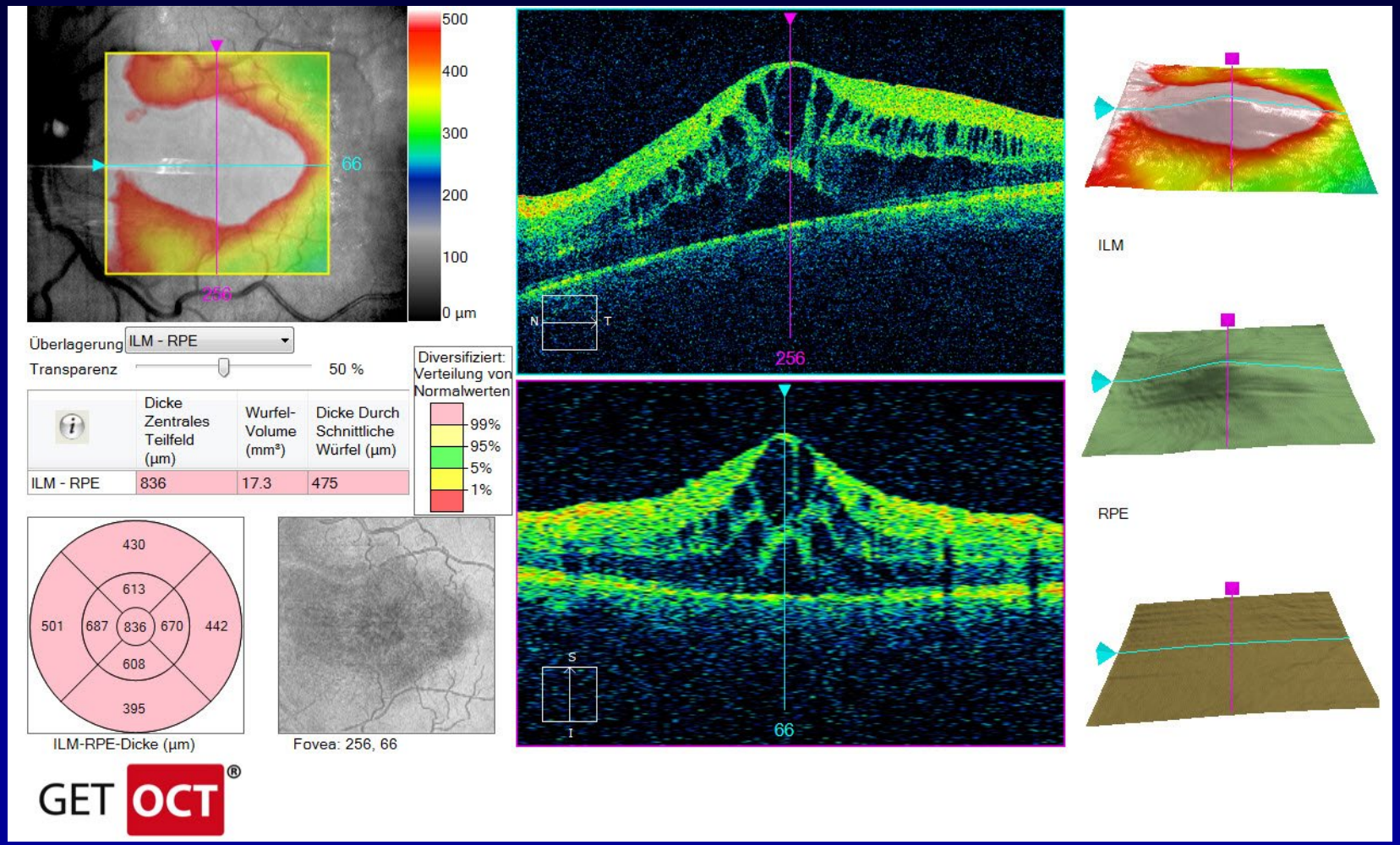
rhu Mab
150 kilodaltons

600-1000 euros
Registration for AMD in 2012,
DME en RVO 2013-2014




Leaking
blood vessel

Diabetic Macular Edema



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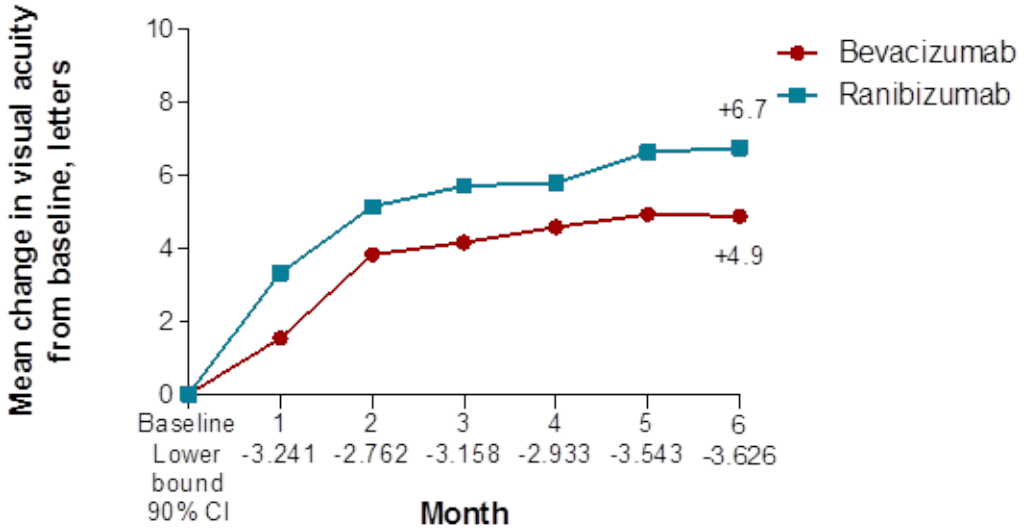
The BRDME study

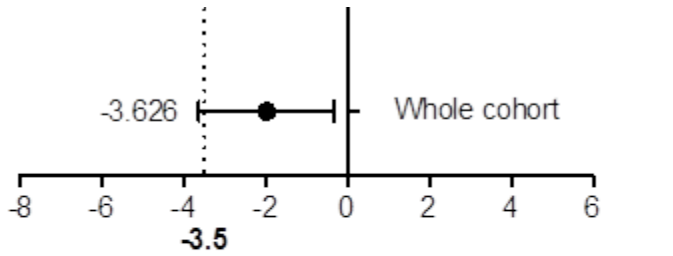
Results – primary outcome

- Mean VA gain (± standard deviation)
  - 4.9±6.7 letters with bevacizumab
  - 6.7±8.7 letters with ranibizumab

} 1.8 letters

- Non-inferiority: the lower boundary of the two-sided 90% BI was -3.626 letters





Lower bound two-sided 90% Confidence Interval
← Favours ranibizumab

Results – Subgroup Analysis

Baseline VA ≤69 letters (n=79):

- Mean VA gain
  - 6.7±7.0 letters bevacizumab
  - 10.4±10.0 letters ranibizumab.

} 3.7 letters

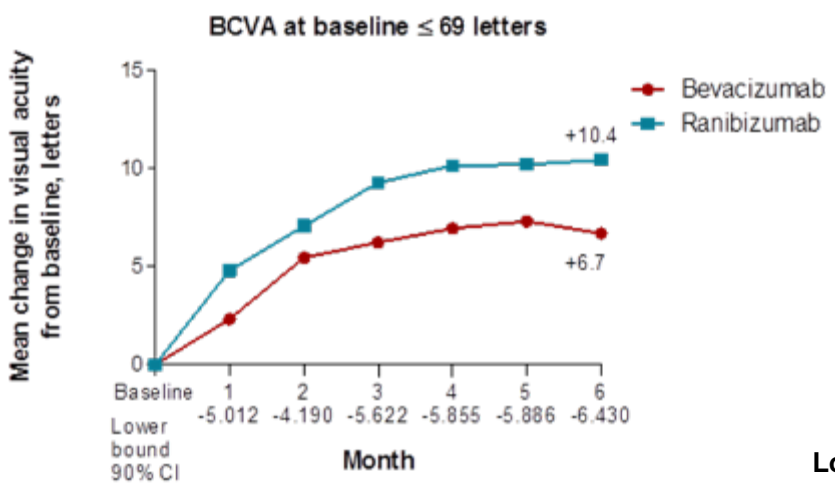
- Lower boundary of two-sided 90% BI: -6.430

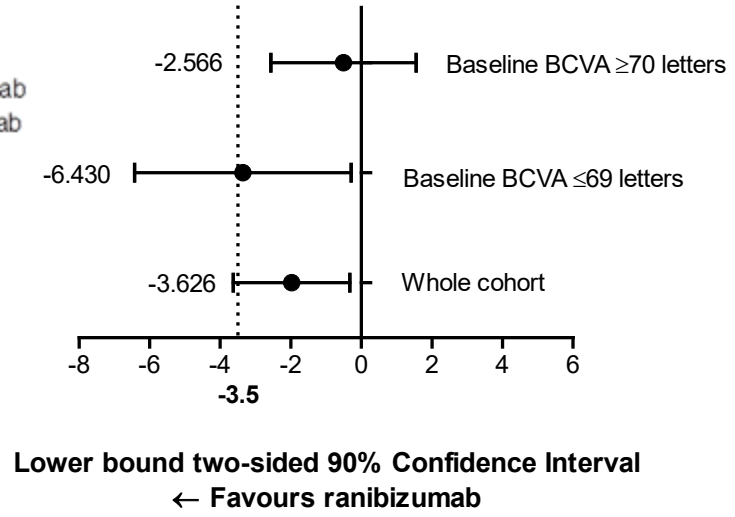
Baseline VA ≥70 letters (n=87):

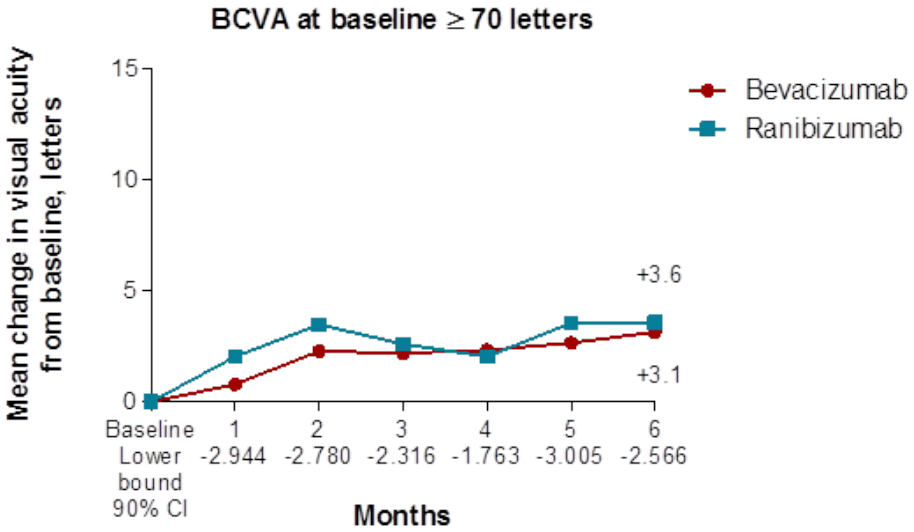
- Mean VA gain
  - 3.1±3.6 letters bevacizumab
  - 3.6±5.7 letters ranibizumab.

} 0.5 letters

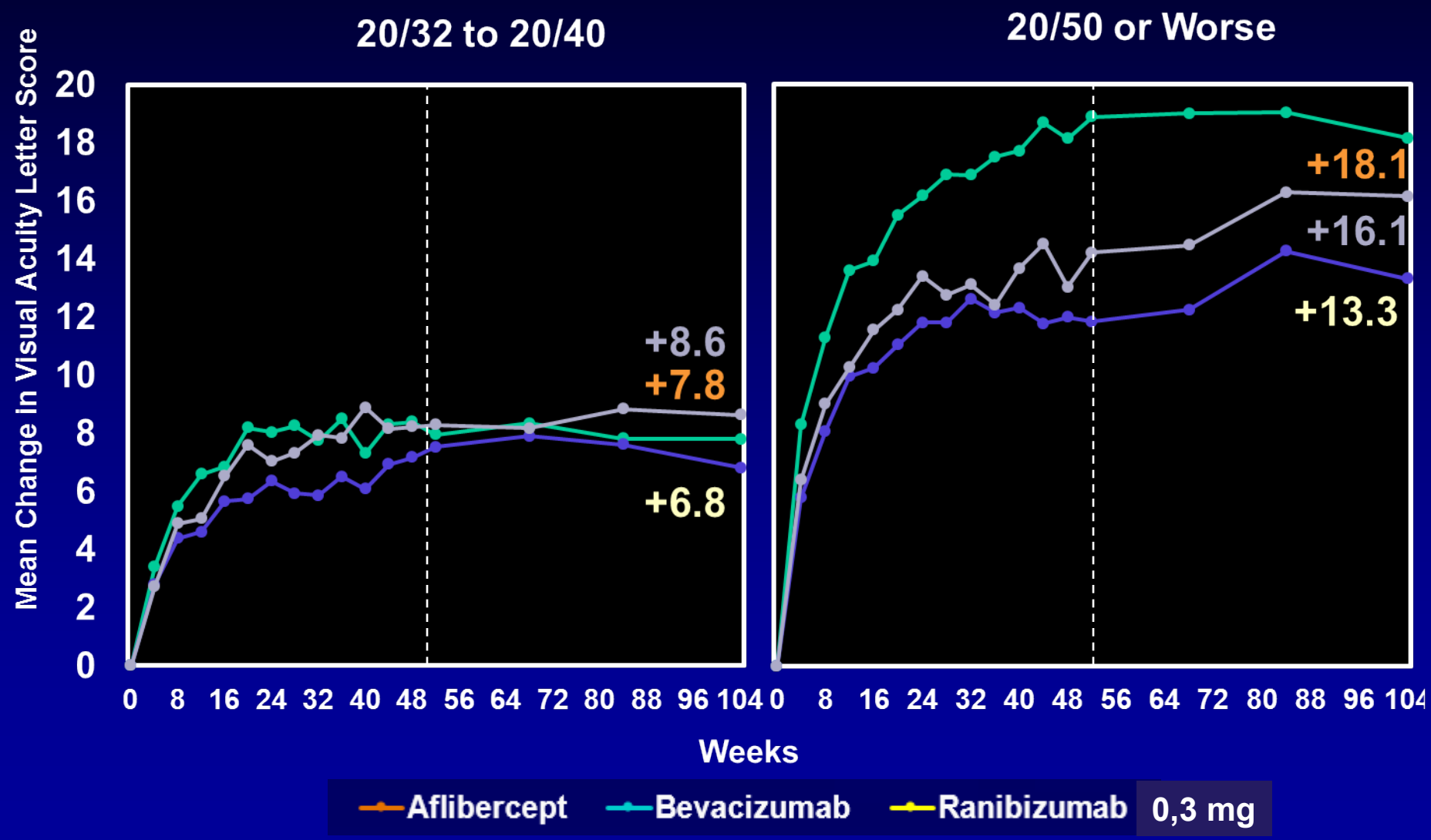
- Lower boundary of two-sided 90% BI: -2.566





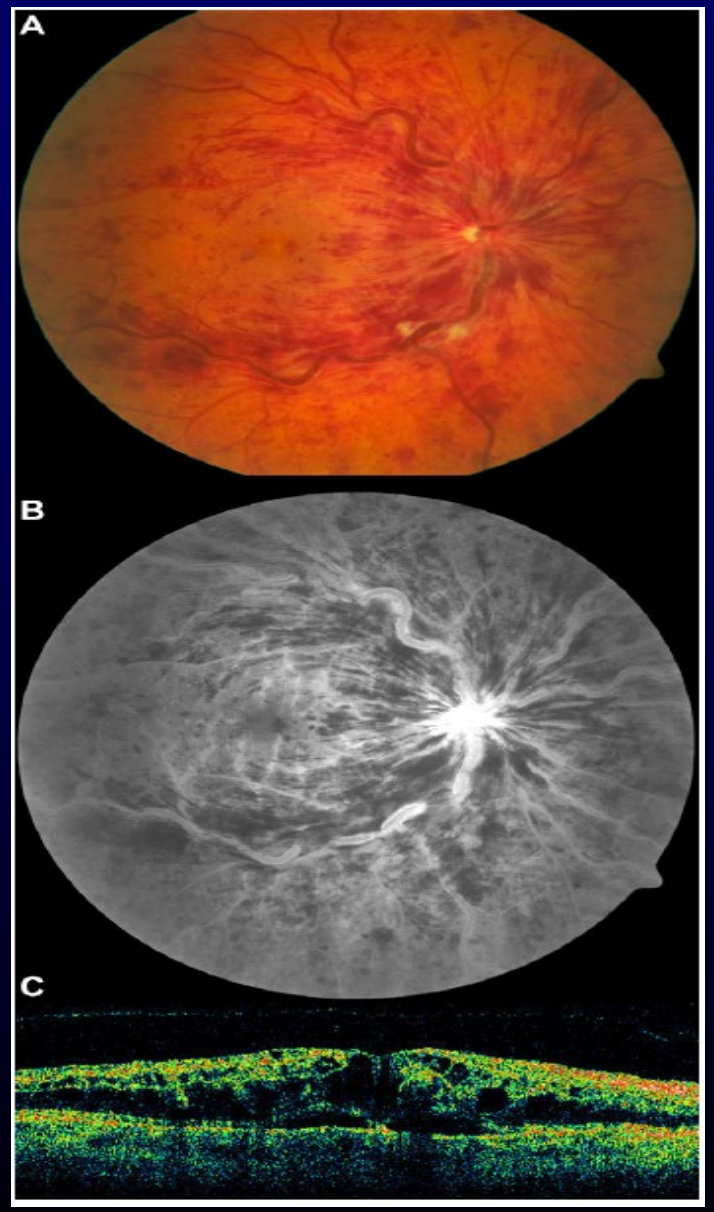


DRCRnet Protocol T: Mean Change in Visual Acuity Over 2 Years *By Baseline Visual Acuity Subgroup*



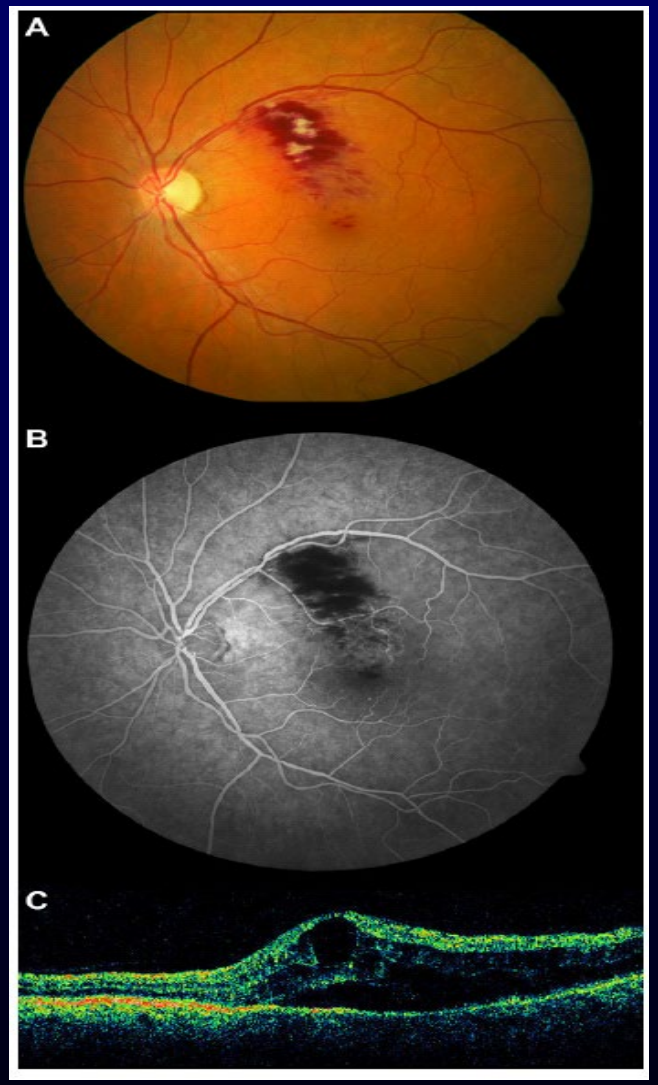
Central retinal vein occlusion

- Prevalence 0.1-0.4%
- Most patients 60-70, any age possible, 10% <50 years
- Ocular risk factors
  - Glaucoma and ocular hypertension-30-70%
- Systemic risk factors
  - Cardiovascular >50 years-OR 3-5
  - No clear association with hereditary thrombophilic syndromes or other risk factors for DVT
- Causes of CRVO
  - Steep venous pressure gradient
  - Atherosclerosis
  - Secundary EC proliferation and thrombosis

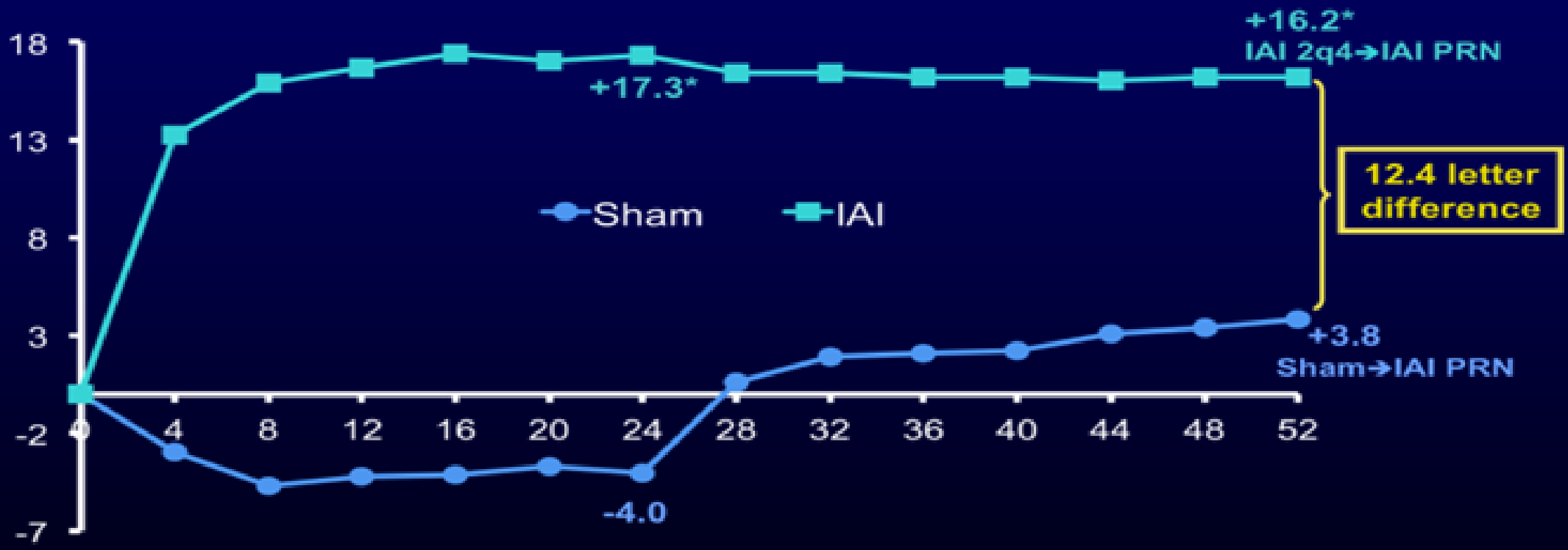


BRVO

- Prevalence 0.6-1.1%
- Ocular risk factors
  - None
- Systemic risk factors
  - Systemic hypertension
- Causes of BRVO
  - Atherosclerosis
  - Venous obstruction at arteriovenous crossing
  - Secondary EC proliferation and thrombosis
- Subtypes
  - Major BRVO
  - Macular BRVO



Effect van VEGF remmers bij macula oedeem bij retinale veneuze occlusie-CRVO



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Comparing the efficacy of bevacizumab to ranibizumab in patients with retinal vein occlusion. The BRVO study.

Prof. Dr. R.O. Schlingemann
r.o.schlingemann@amsterdamumc.nl

Methods

- A comparative, randomized, double-masked, multicenter, non-inferiority trial.

- From June 2012 – February 2018, 277 patients randomized:
  - 1.25 mg bevacizumab, n = 139
  - 0.5 mg ranibizumab, n = 138

- 6 monthly injections

Outcomes

- *Primary outcome*:
  - Change in visual acuity from baseline to 6 months.
  - Non-inferiority margin is 4 letters.

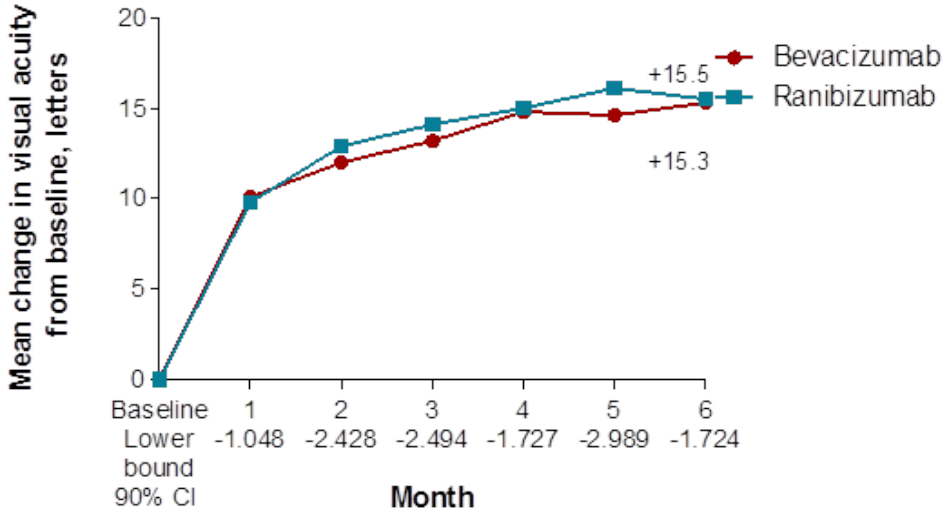
- *Secundary outcome*:
  - Change in central area thickness from baseline to 6 months.

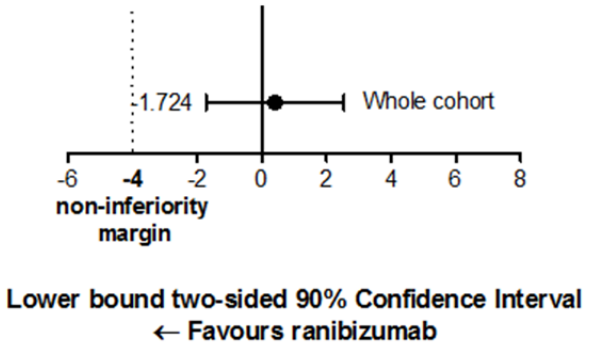
Results – visual acuity

- Mean gain in visual acuity (± standard deviation)
  - 15.3±13.0 letters in bevacizumab
  - 15.5±13.3 letters in ranibizumab

} difference: 0.2 letters

- Non-inferiority: lower bound of the two-sided 90% CI was -1.724 letters.





Results – visual acuity in subgroups

Baseline visual acuity ≤62 letters (n=134):

- Mean gain in visual acuity
  - 22.6±12.1 letters bevacizumab
  - 21.0±16.2 letters ranibizumab.

} 1.6 letters

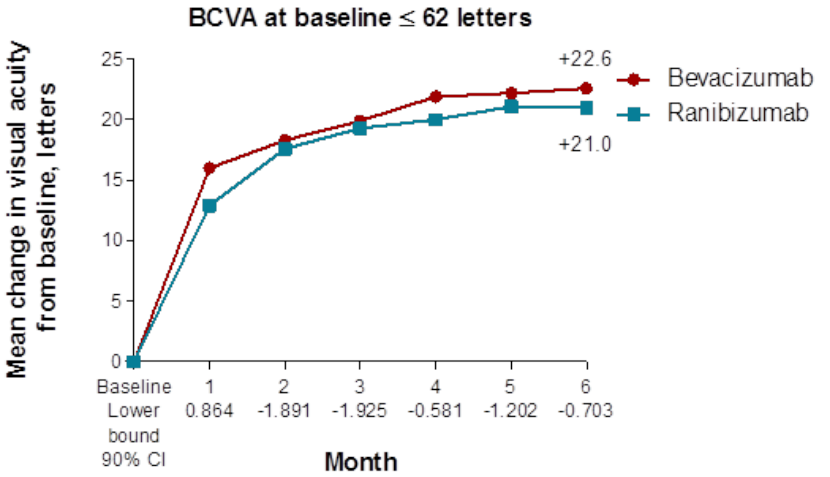
- Non-inferiority: lower bound of the 90% CI -0.703

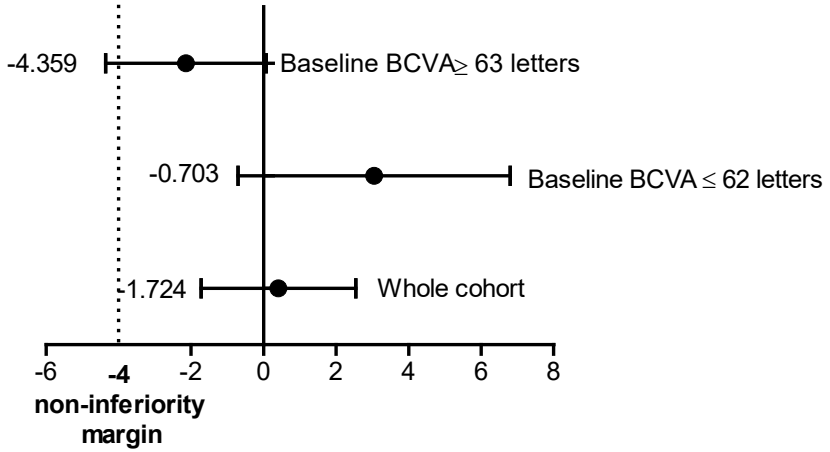
Baseline visual acuity ≥63 letters (n=143):

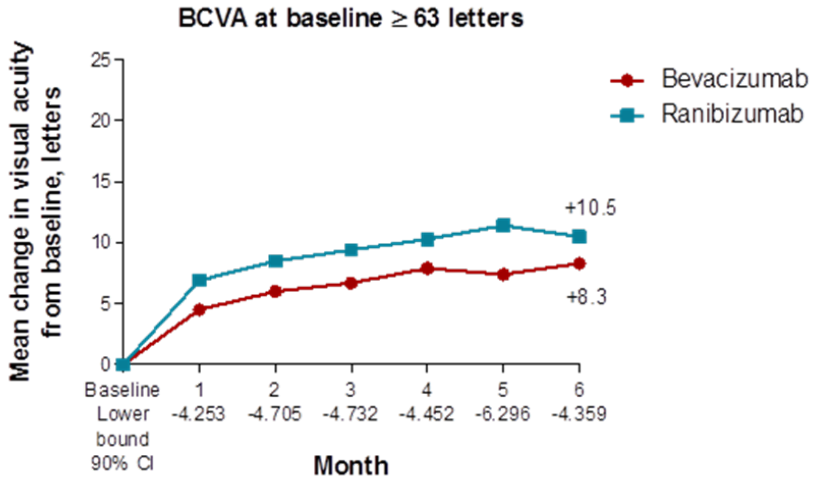
- Mean gain in visual acuity
  - 8.3±9.5 letters bevacizumab
  - 10.5±7.0 letters ranibizumab.

} 2.2 letters

- Non-inferiority: lower bound of the 90% CI -4.359







Lower bound two-sided 90% Confidence Interval
← Favours ranibizumab

Conclusion

- 1.25 mg Bevacizumab is non-inferior to 0.5 mg ranibizumab in the treatment of macular edema due to retinal vein occlusion.

- Anatomical and safety outcomes did not differ between treatment groups.

- **Recommendation:** 1.25 mg bevacizumab is an effective alternative to 0.5 mg ranibizumab in the treatment of RVO.

Zijn de resultaten inmiddels opgenomen in richtlijnen?

Standpunt Werkgroep Medische Retina Nederlands Oogheelkundig Gezelschap

- Start : 3 x Avastin every 4 weeks
- Examinations at baseline and at 3rd injection : VA / OCT / IOP
- Follow up:
  - 1-If improved OCT and VA: 1x-2x avastin every 4 weeks, repeat untill flat OCT and stable VA
  - 2-If increasing or persistent oedema, switch to eylea / lucentis, 2x every 4 weeks, if response, follow 1
  - 3-If stable VA and flat OCT, treat and extend by increasing interval by 2-4 weeks, i.e. 6, 8,10,12, 16 and 20 weeks, followed by observation.
  - 4-If persistent diffuse edema-consider steroids
  - 5-If persistent or recurrent focal edema-consider (ICG-guided) laser
  - If VA < 0.05 consider observation only, with rubeosis checks
- Visit clinic at 4 months and subsequently every 8 months

(Hoe) wordt het nieuwe middel nu ingezet in de praktijk voor de nieuwe indicatie(s)?

Onderzoek	Patiëntgroep	Jaarlijks aantal injecties	Jaarlijks aantal injecties dat potentiëel met bevacizumab gedaan kan worden	Jaarlijkse potentiële kostenbesparing	Jaarlijkse besparing na toepassing 90% implementatiegraad
Comparing the effectiveness and costs of bevacizumab to ranibizumab in patients with RVO (The BRVO study)	Retinal vein occlusion	100.000	90.000 (10% switch naar aflibercept of ranibizumab vanwege betere resultaten op OCT).	€54 mln.	€ 49 mln.
Comparing the effectiveness and costs of bevacizumab to ranibizumab in patients with DME (The BRDME Study)	Diabetic macular edema	100.000	50.000 (bij pat. met een slechtere startvisus start met aflibercept of ranibizumab)	€30 mln.	€ 27 mln.
Comparing the effectiveness and costs of bevacizumab to ranibizumab in patients with AMD (COSD/BRAMD).	Exudative age-related macular degeneration	230.000	Grofweg 160.000 (30% switch naar aflibercept of ranibizumab vanwege betere resultaten op OCT)	€96 mln.	€ 86 mln.
Totaal		**430.000 injecties**	**300.000 injecties**	**€180 mln.**	**€ 162 mln.**

Ter afsluiting

- Wordt het middel vergoed voor de nieuwe indicaties?
  - Ja, maar niet als DGM
- Is het middel geregistreerd voor de nieuwe indicaties?
  - Nee
- Wat zou hierin makkelijker, beter kunnen?
  - Financiering van studies waar kans op financieel voordeel maatschappij heel groot is anders regelen

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