CATT Tales: 15 Years of Science, Politics, and Persistence

J. Donald M. Gass Award Lecture, Retina Society 2020

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Disclosures

- Dr. Maguire has received payments from Genentech for service on Data and Safety Monitoring Committees
- Dr. Martin has no financial interests to disclose

Summary

- CATT overcame many obstacles before we ever enrolled a patient
- CATT and 5 other large clinical trials established the equivalence of bevacizumab and ranibizumab for improving VA and for safety
  - Use of bevacizumab has reduced total cost of care and increased availability of anti-VEGF treatment to many patients worldwide
- Review of CATT images and VA data resulted in many publications that have improved our understanding of treatment effects and led to modifications to treatment approach
- Many remaining unanswered questions including what is the optimal treatment approach beyond 2 years, why does VA decrease long term and how can it be prevented, and what are the long-term effects of continuous treatment

CATT Timeline

- In July 2005, ranibizumab clinical trial results (MARINA) presented at national meeting
- Single case report of bevacizumab to treat neovascular AMD reported at same meeting
  - Over the next year, bevacizumab became standard of care with more than 500K injections given worldwide without any RCT data to support its use
- Need for a head-to head trial was obvious. CATT developed in Fall 2005, submitted to NEI in January 2006, and funded on June 10, 2006, before the cost of ranibizumab was ever known
- Ranibizumab FDA approved June 30, 2006 and $2000 price established – only then that the trial took on a whole new dimension

Reaction by Pharmaceutical Industry

- "CATT, opens 'a Pandora's box' for the drug industry by taking testing out of the hands of the companies, changing the rules of development and potentially undermining a blockbuster long before it comes off patent."
- "CATT is one of the top seven 'harbingers of change' … likely to affect the evolution of the pharmaceutical sector."
- If CATT "shows Avastin to be as safe and effective for AMD as Lucentis, it may pave the way for an increasing number of payers to take comparative drug studies out of the hands of the pharmaceutical companies"
- CATT "may create a disincentive for companies to study such areas" => leading to unintended consequences
- The NEI-sponsored trial signals a new level of activism in the US by the single largest payer body, the Centers for Medicare and Medicaid Services (CMS).
- The NEI, spurred to action on the advice of an independent Medicare advisory panel, is stepping forward in this highly unusual way because of the disparity in cost between the two drugs

CATT Hurdles

- At $50 for bevacizumab and $2000 for ranibizumab, the potential cost savings to CMS if drugs equivalent was more than $3 Billion a year – would assume then that obtaining additional federal support for conducting a comparative effectiveness study would be easy
- It was not

CATT Hurdles

- How do you pay for an expensive drug in a trial using public money when there is no pharma company partner ($25M for ranibizumab)?
- How do you balance co-pays of $400 for ranibizumab and $10 for bevacizumab? (encourages differential drop out)
- How do you mask the drug at the Clinic level?
- How do you eliminate identification of the drug on Medicare Summary Notice (would unmask the patient)?
- Who supplies bevacizumab and how is it distributed?
- How do you do any of this when there is no public infrastructure anywhere to support it?

CATT Hurdles

- CMS told us they did not have the authority to do many of the things we needed and in fact said ”You need an act of Congress to do what you want to do.”
- NIH had no policies or precedent anywhere to navigate these issues
- FDA had strict guidelines and we were held to the same standard (entirely appropriate) as any pharma company in terms of IND and how drug was supplied
  - Had to establish shelf life and have quality programs in place for bevacizumab
- Most immediate issue was covering the cost of the ranibizumab

Policy Changes

1) Drug Cost: On July 9, 2007, the Revised Medicare Clinical Trial Policy was published that allowed CMS coverage of Lucentis in the CATT

2) Co-Pays: Legal review determined that the NEI can pay the co-pay and NEI committed to do so when no supplemental insurance available.

3) Masking: Worked closely with CMS staff to develop AMD Demonstration Project that would have facilitated payment and masking of study drugs. Approved by CMS but not granted final approval by OGC.

Policy Changes

4) Medicare Improvements for Patients and Providers Act of 2008 (HR6331) became law on July 15, 2008

- Contained the following amendment:

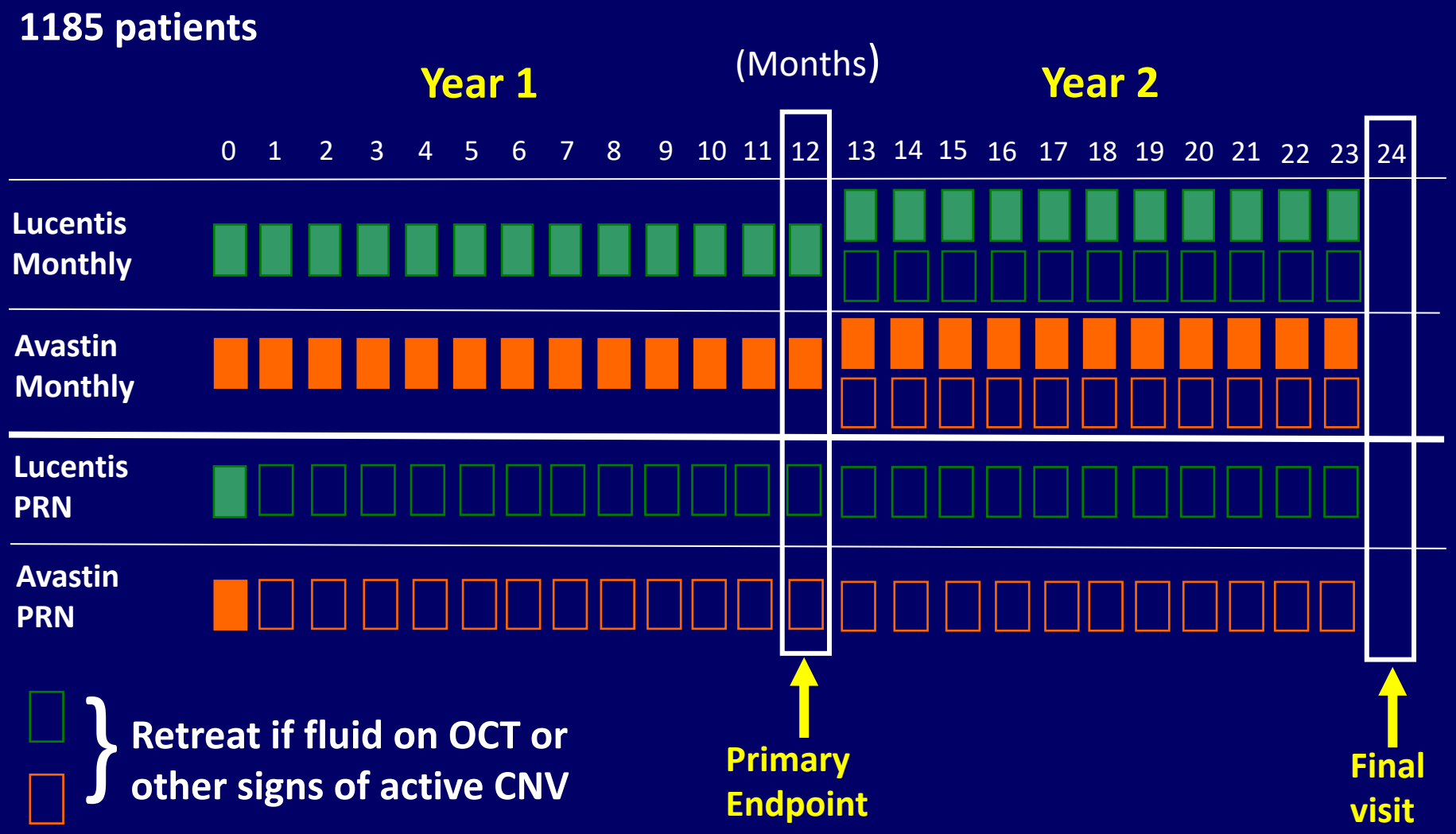
SEC. 184. COST-SHARING FOR CLINICAL TRIALS.

Section 1833 of the Social Security Act (42 U.S.C. 1395l), as amended by section 151(a), is amended by adding at the end the following new subsection:

`(w) Methods of Payment- The Secretary may develop alternative methods of payment for items and services provided under clinical trials and comparative effectiveness studies sponsored or supported by an agency of the Department of Health and Human Services, as determined by the Secretary, to those that would otherwise apply under this section, to the extent such alternative methods are necessary to preserve the scientific validity of such trials or studies, such as in the case where masking the identity of interventions from patients and investigators is necessary to comply with the particular trial or study design.'

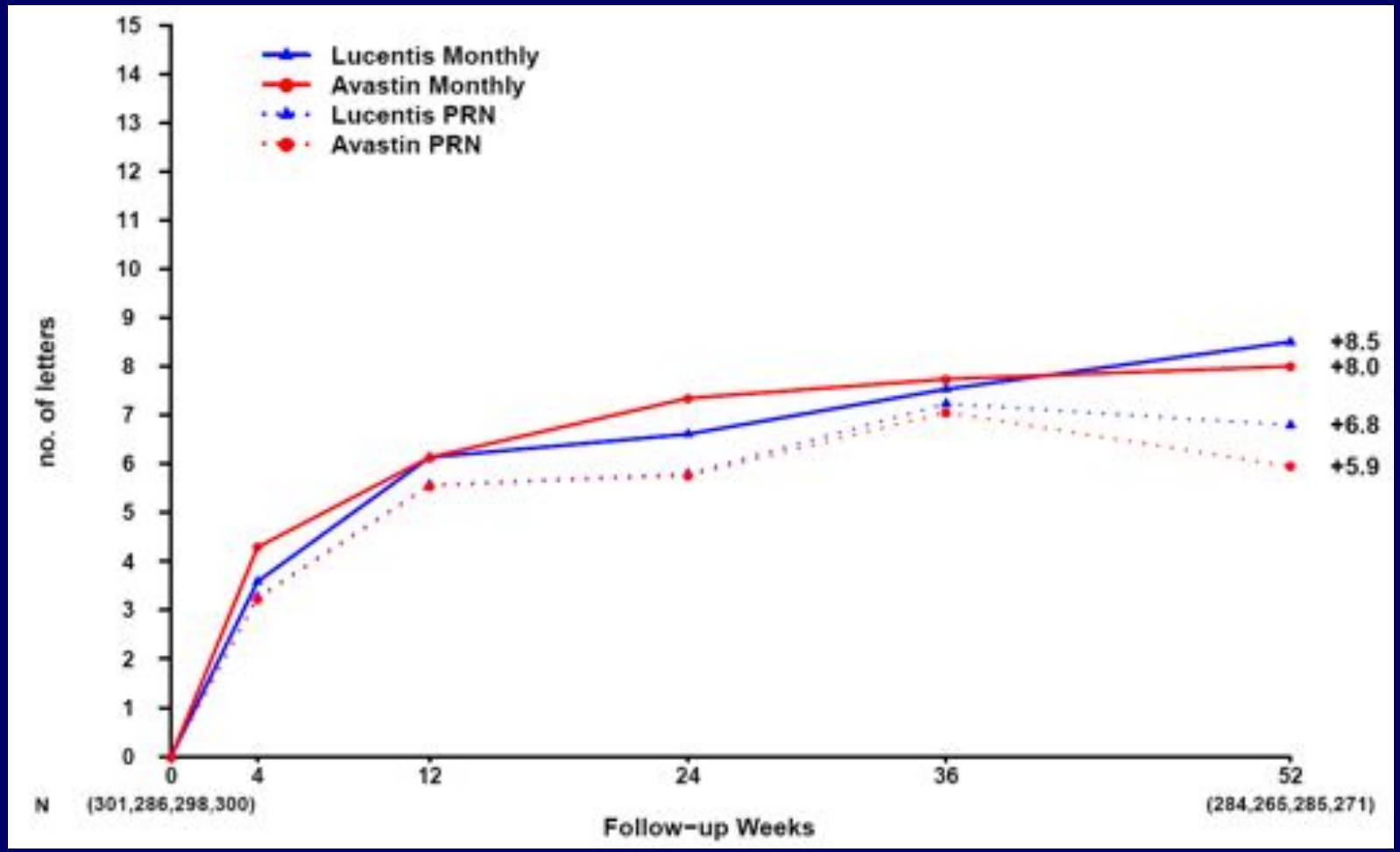
CATT - The Clinical Trial

CATT Treatment

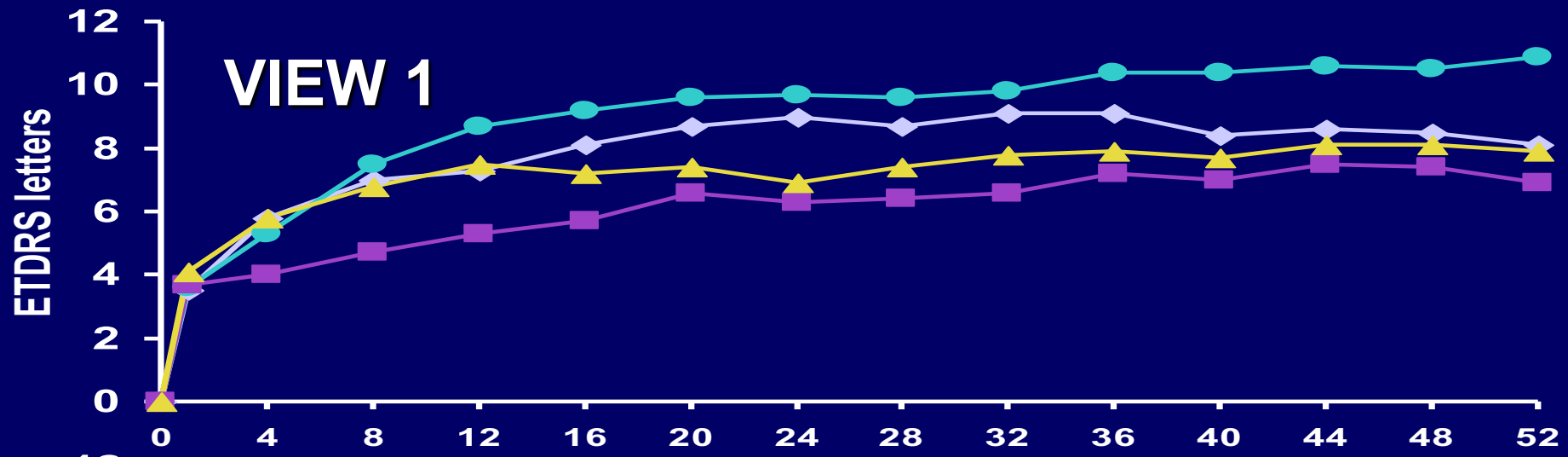


Drug Equivalence

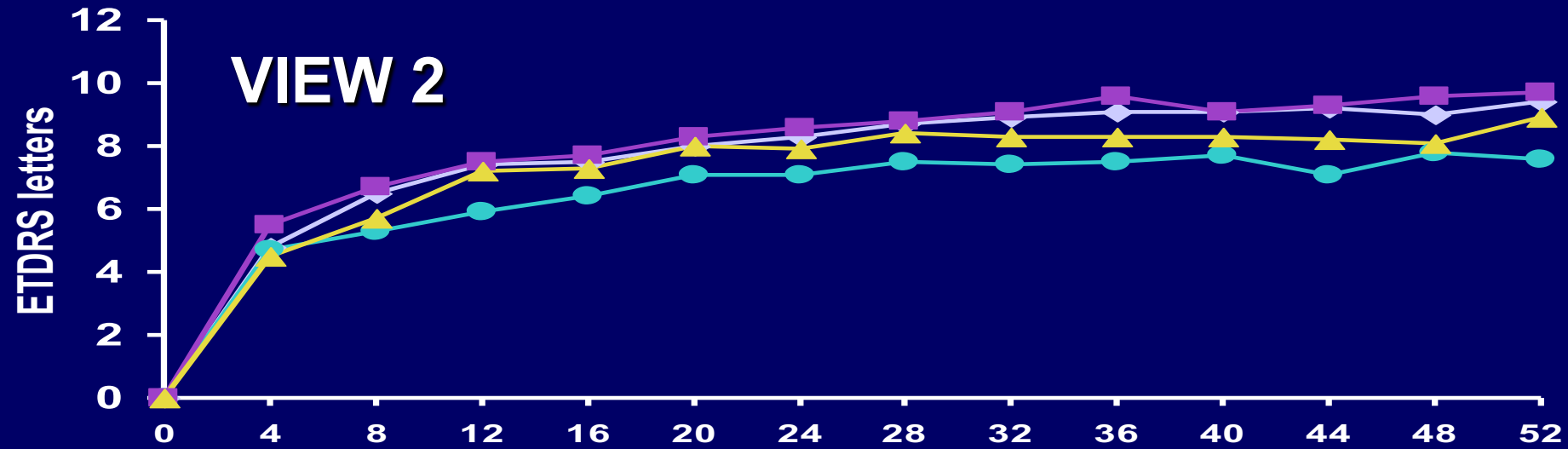
- Ranibizumab and bevacizumab equivalent for visual acuity at 1 Year



VIEW 1 & 2 (Aflibercept)
Mean Change in Visual Acuity to 1 year



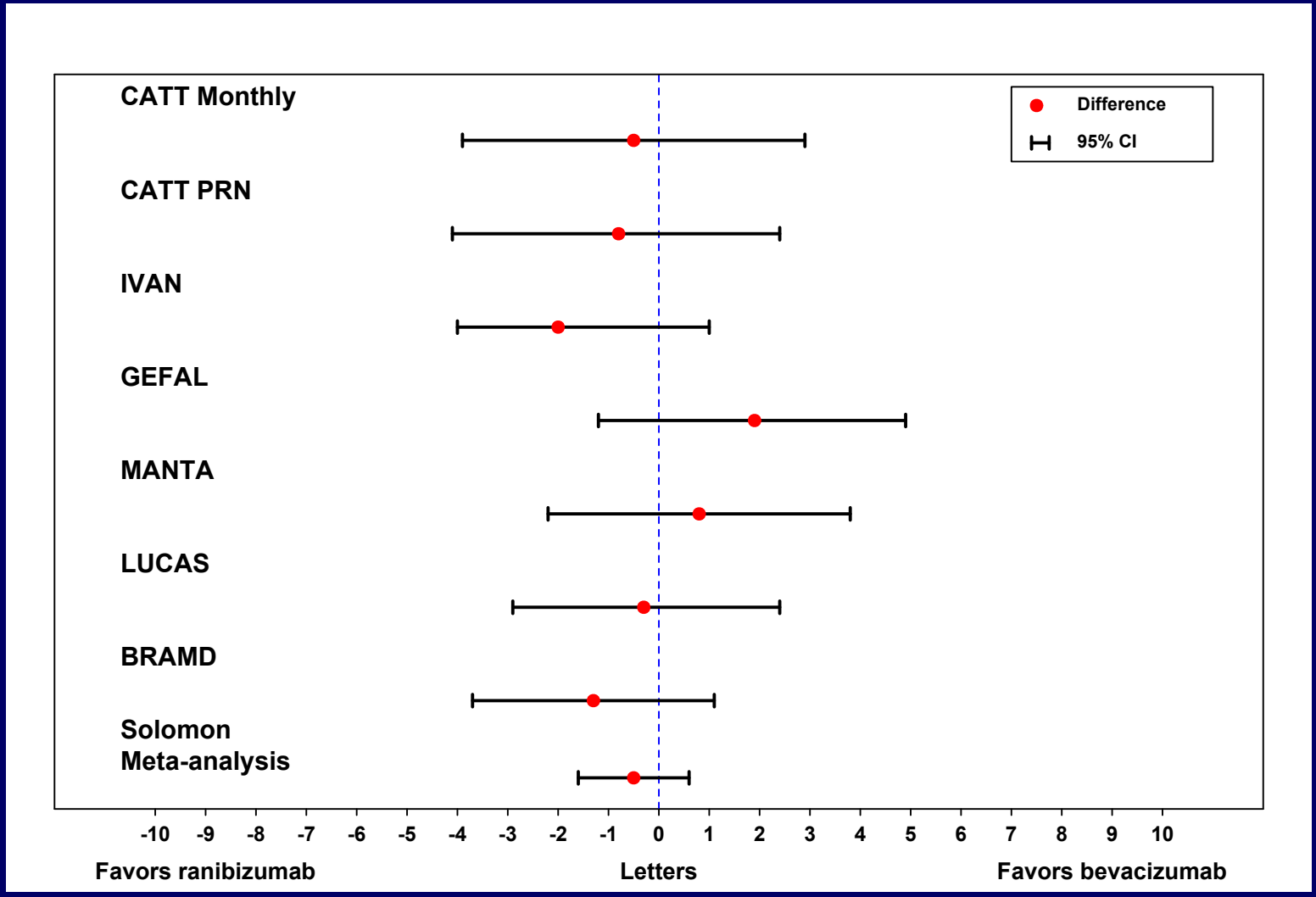
10.9* 2q4 (n=304)
8.1 Rq4 (n=304)
7.9† 2q8 (n=301)
6.9† 0.5q4 (n=301)



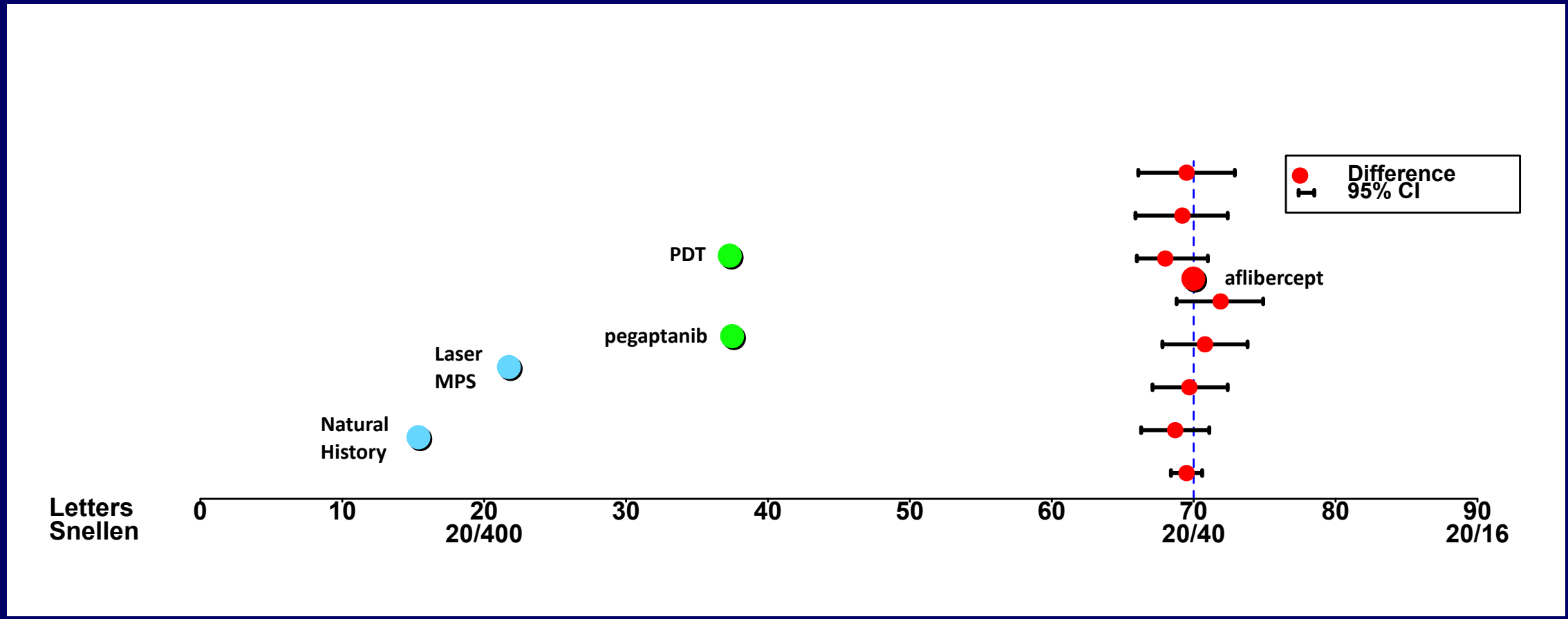
9.7† 0.5q4 (n=296)
9.4 Rq4 (n=291)
8.9† 2q8 (n=306)
7.6† 2q4 (n=309)

*P = 0.0054
†P = NS
vs. Rq4

Difference in VA Between Drugs



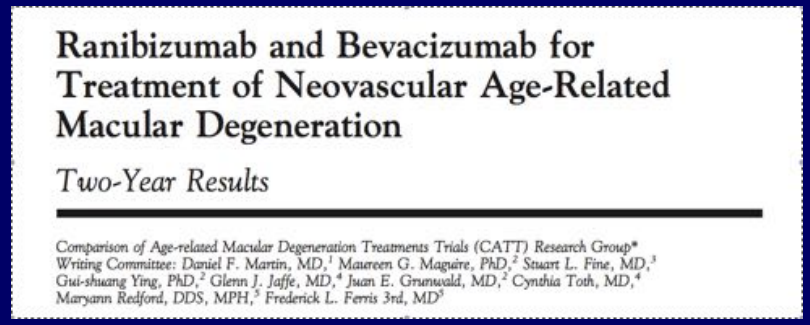
Difference in VA Between Drugs



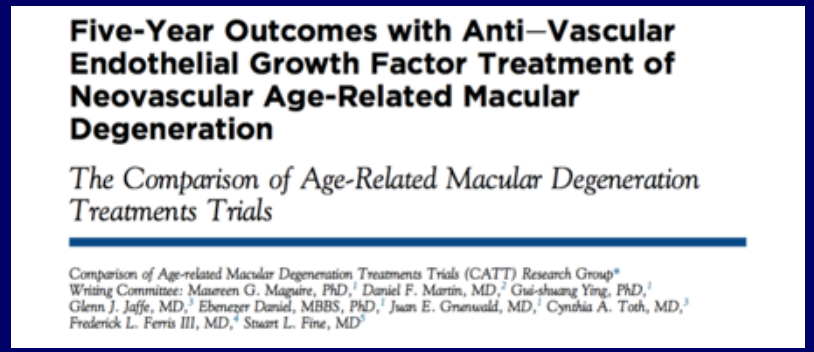
CATT Publications

(2010)

(2011)



(2012)



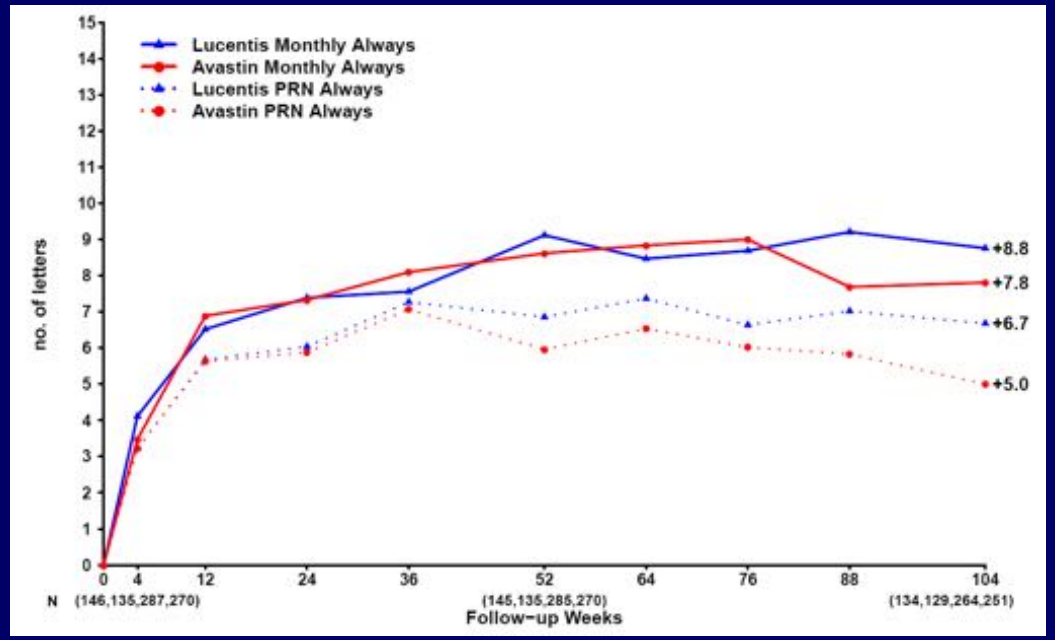
(2016)

- 60 published CATT papers, editorials and commentaries to date

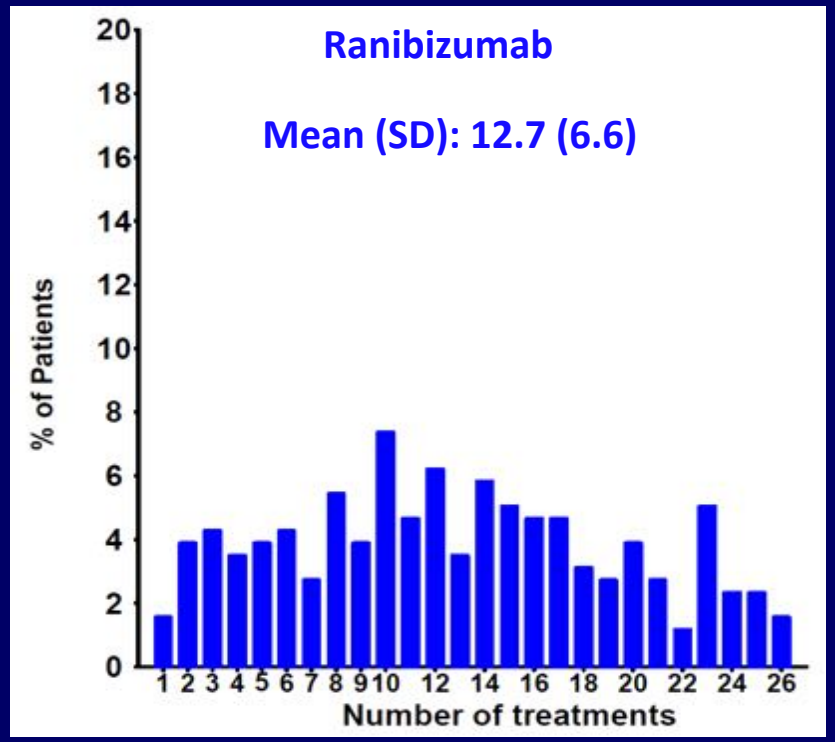
CATT Secondary Analyses

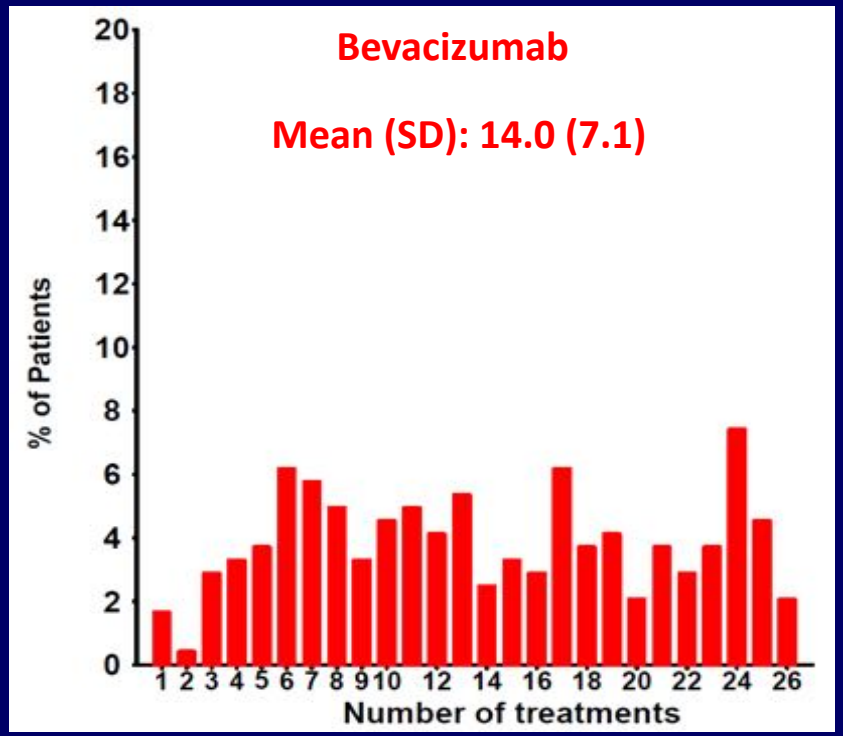
PRN Dosing

- Results in excellent VA outcomes but 2 letters less gain than monthly dosing in CATT, IVAN, and HARBOR
  - 20/40 vs 20/40+2
- 10 fewer intravitreal injections over 2 years



Predictors of Number of Injections

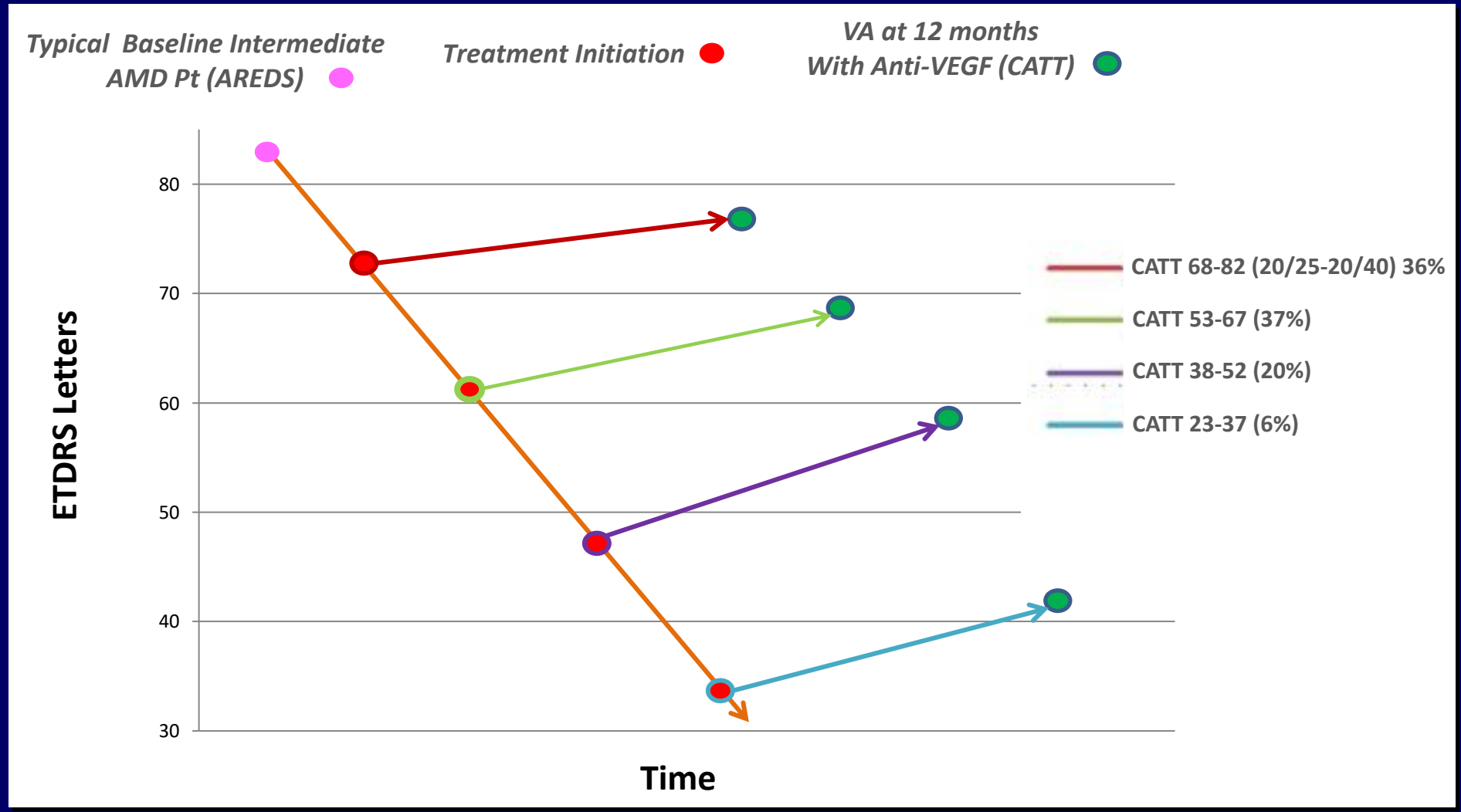




- No anatomical or genetic variables found that explain wide variability in number of injections required to control disease activity

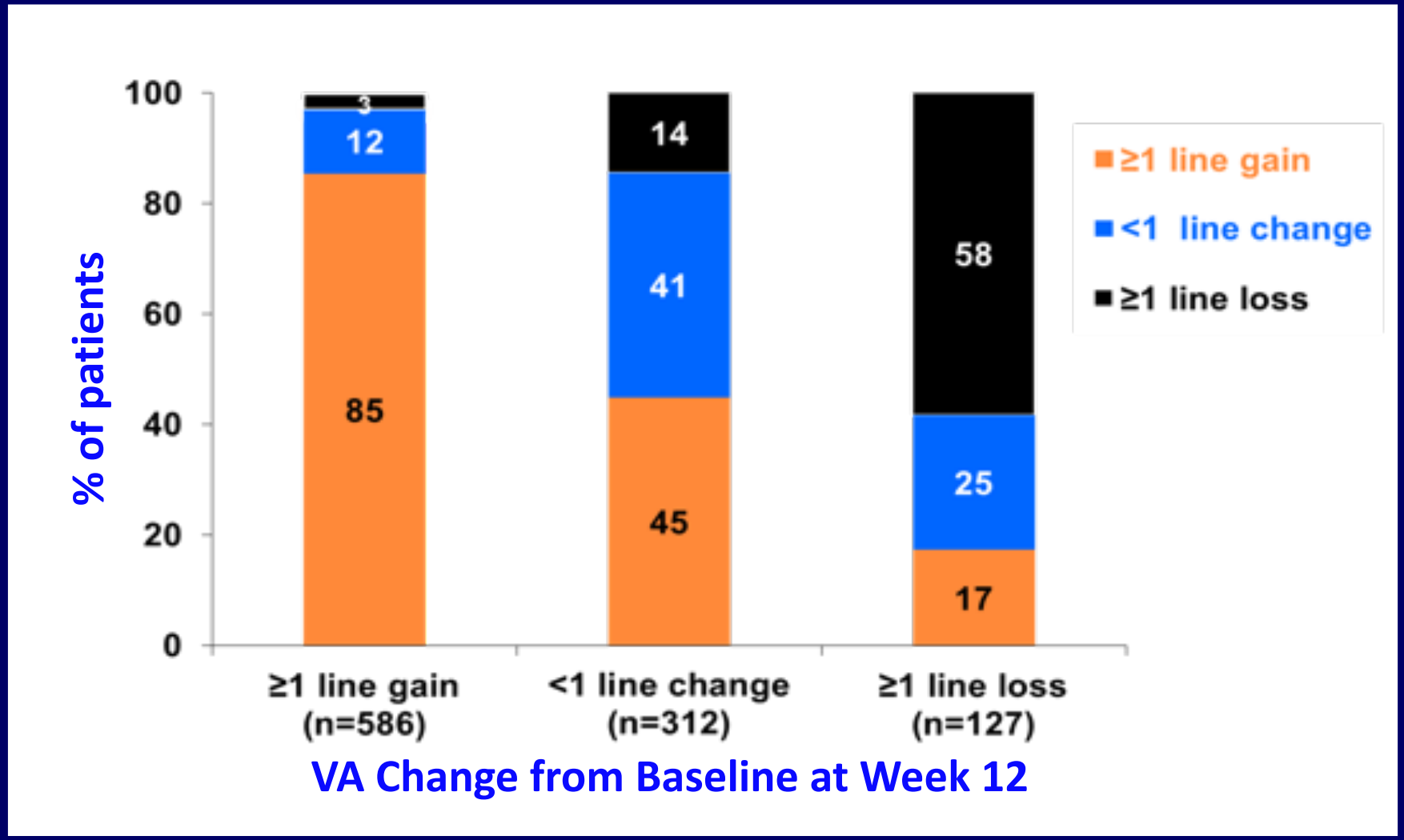
Predictors of VA Outcome

- Better VA at baseline predicts better VA at 1 Year



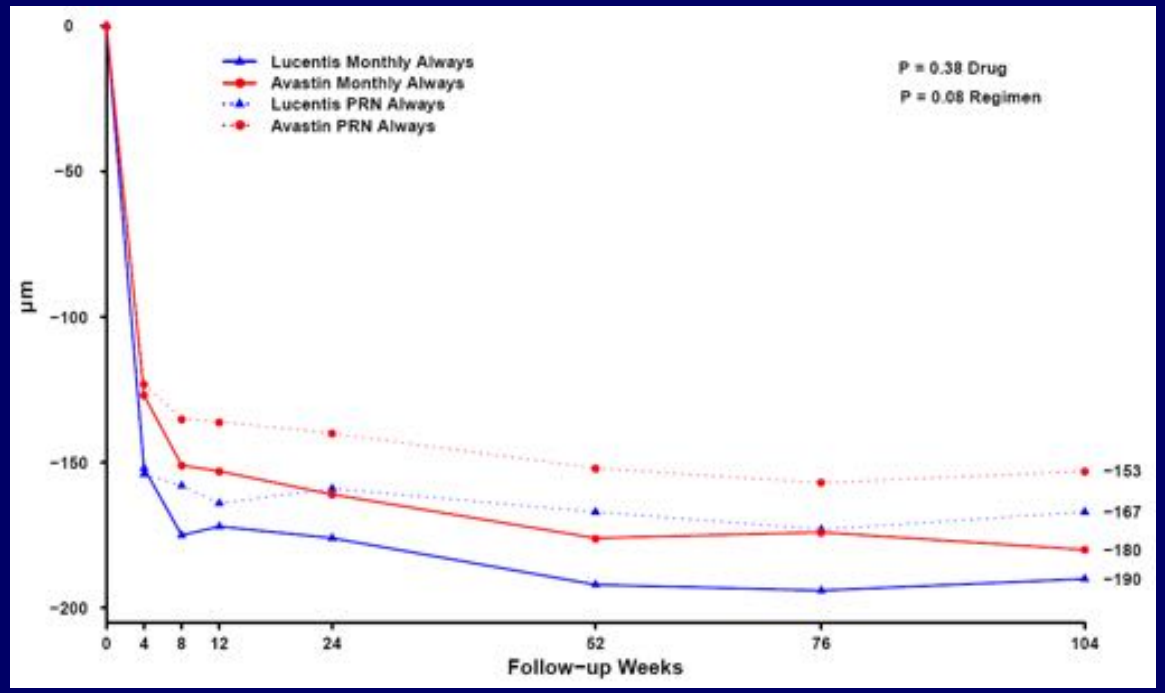
Predictors of VA Outcome

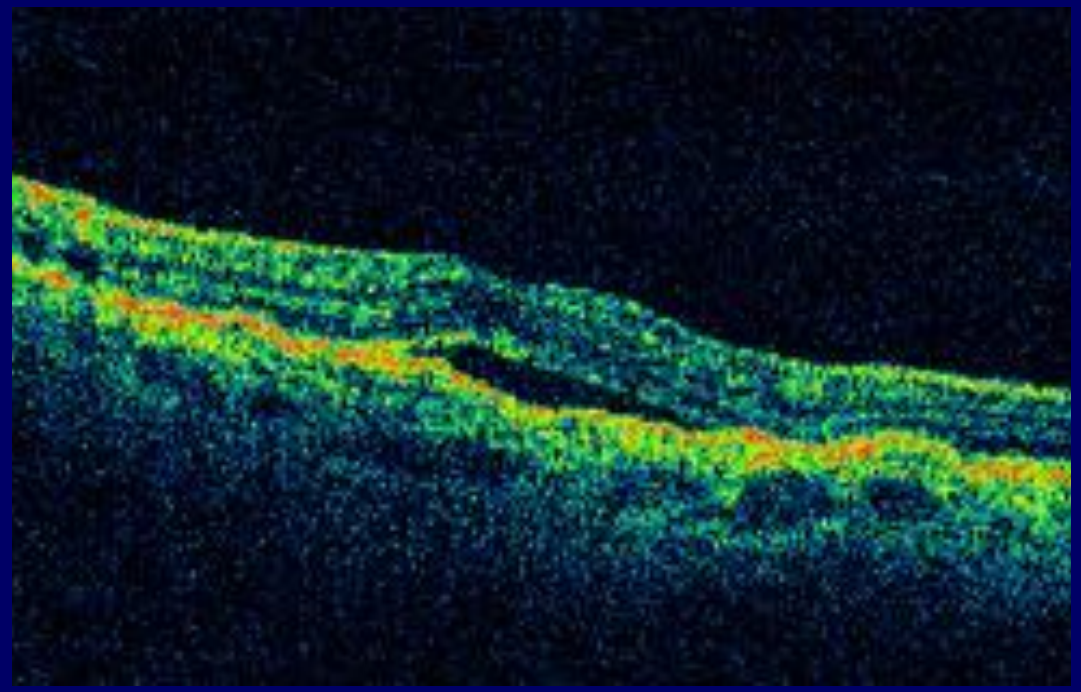
- VA response at week 12 is by the strongest predictor of VA at 1 Yr



Impact of Fluid on Vision

- Treatment results in immediate & profound reduction of fluid in most eyes
- Small amount of residual fluid remains on OCT in >80% of cases

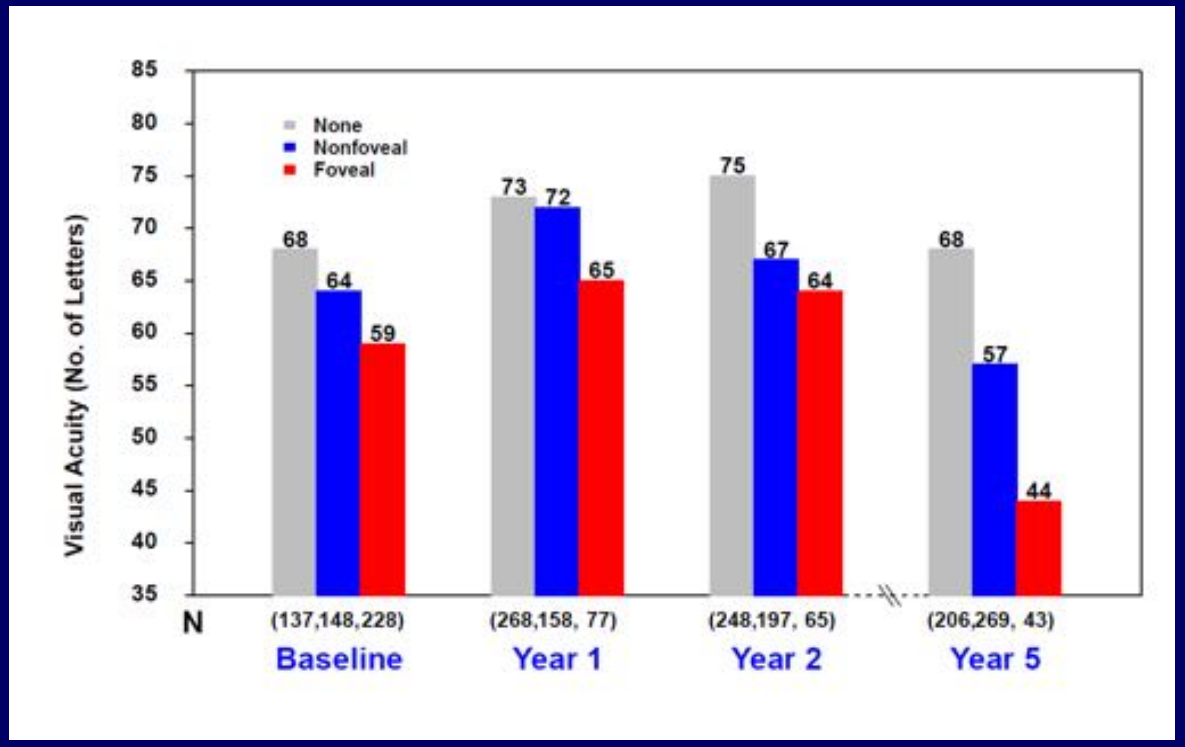




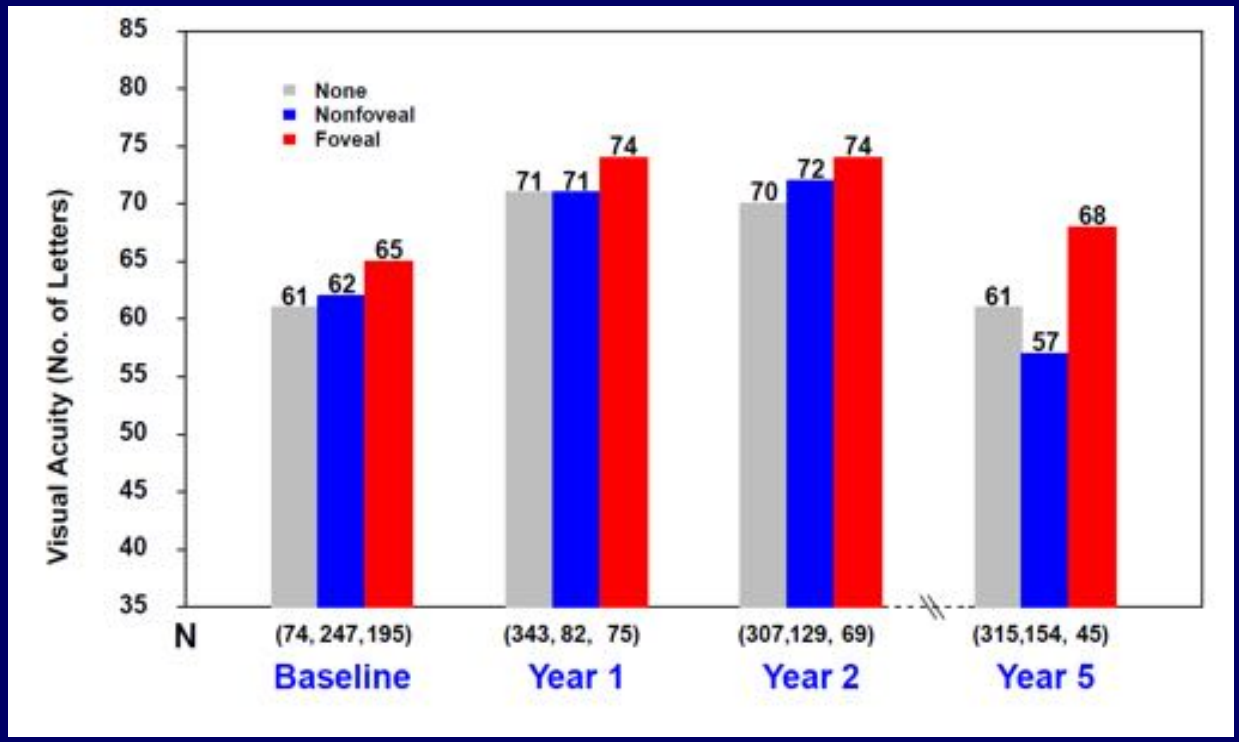
Impact of Fluid on Vision

- Small amounts of residual fluid have minimal adverse effect on VA unless intraretinal and in center of fovea

Intraretinal Fluid

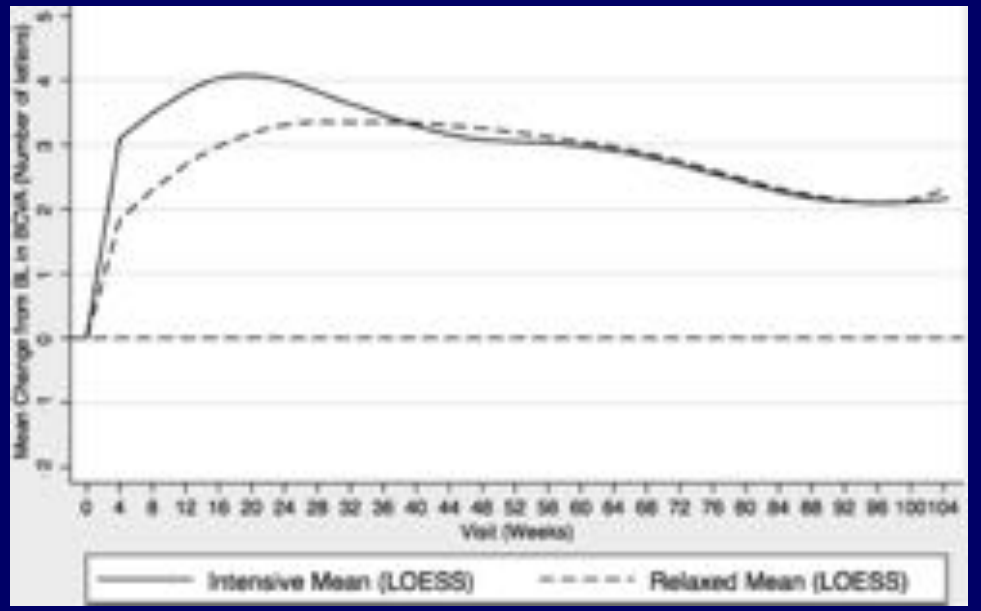


Subretinal Fluid



Impact of Subretinal Fluid on Vision

- Finding of better or no reduction in VA with presence of subretinal fluid (SRF) replicated in IVAN, HARBOR, and VIEW
- FLUID Study
  - 349 patients with newly Dx nAMD randomly assigned to:
    - Intensive Tx – elimination of all fluid
    - Relaxed Tx – treat all IRF but tolerate up to 200 um of SRF at foveal center
    - Ranibizumab T&E
  - No difference in VA at 24 months



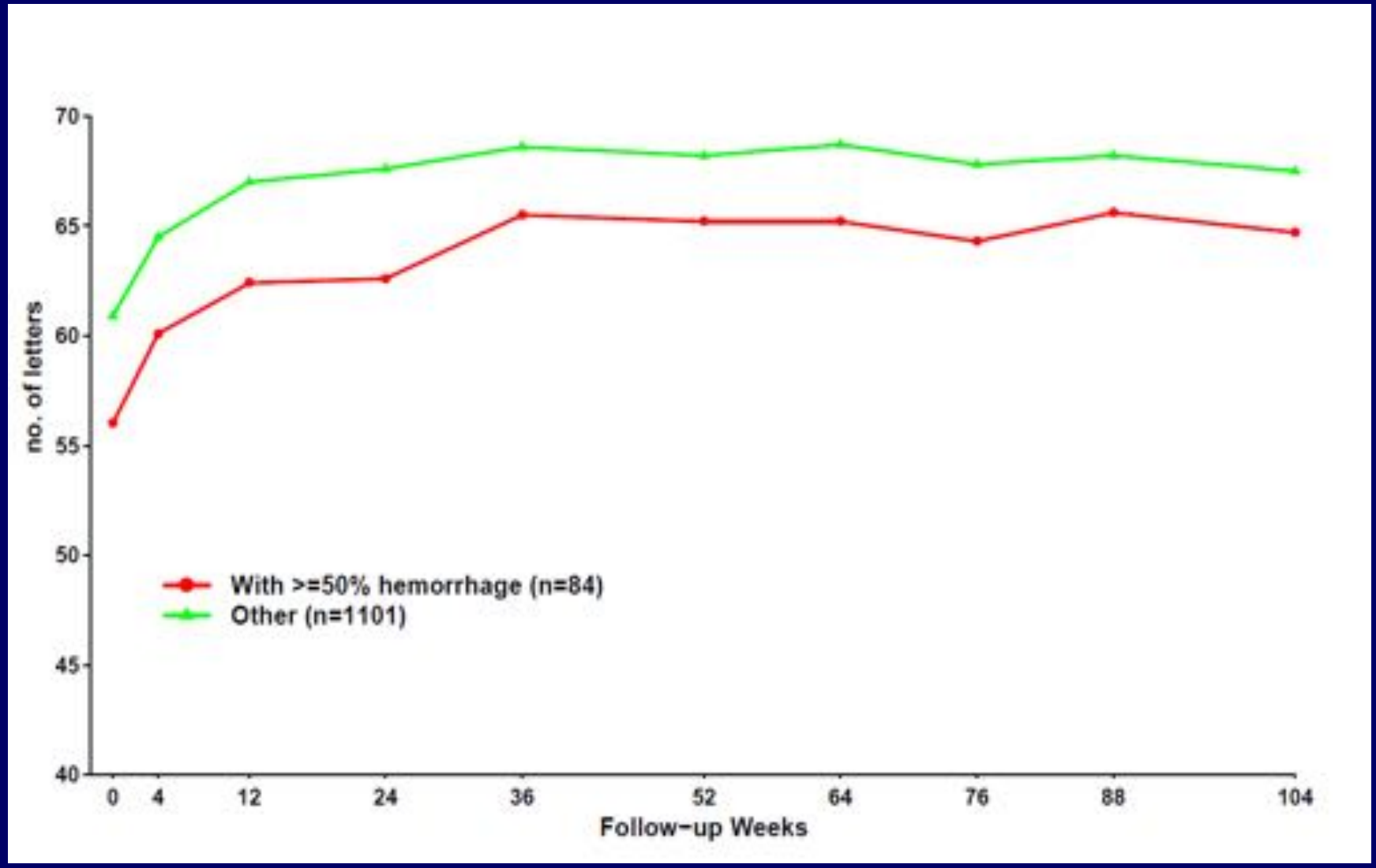
Subretinal Hemorrhage

- Patients with significant subretinal hemorrhage do very well with anti-VEGF therapy alone

Baseline

1 Year

Mean Visual Acuity Over Time
By Subretinal Hemorrhage Status at Baseline

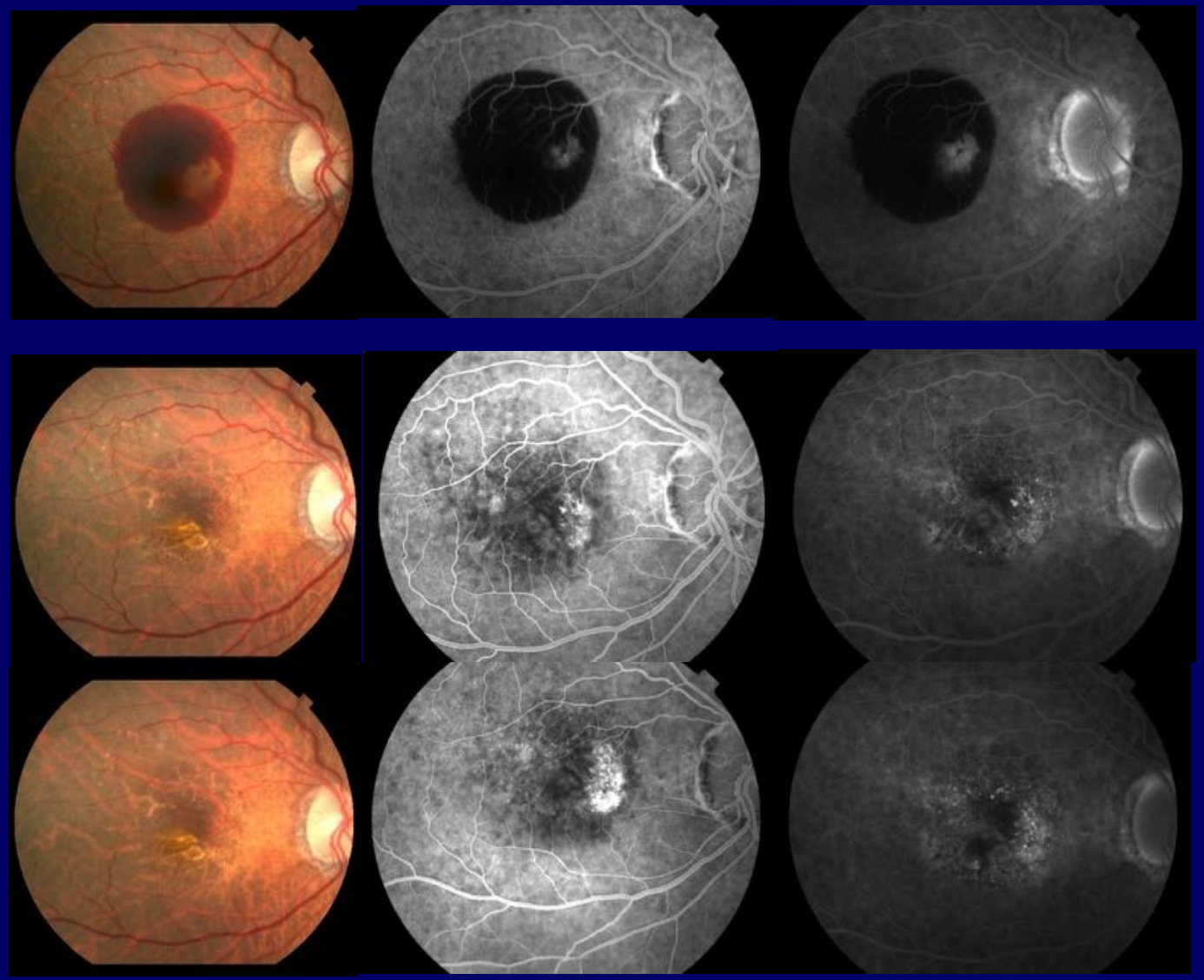


Subretinal Hemorrhage

Baseline
(20/50)

1 Year
(20/40)

2 Years
(20/25)

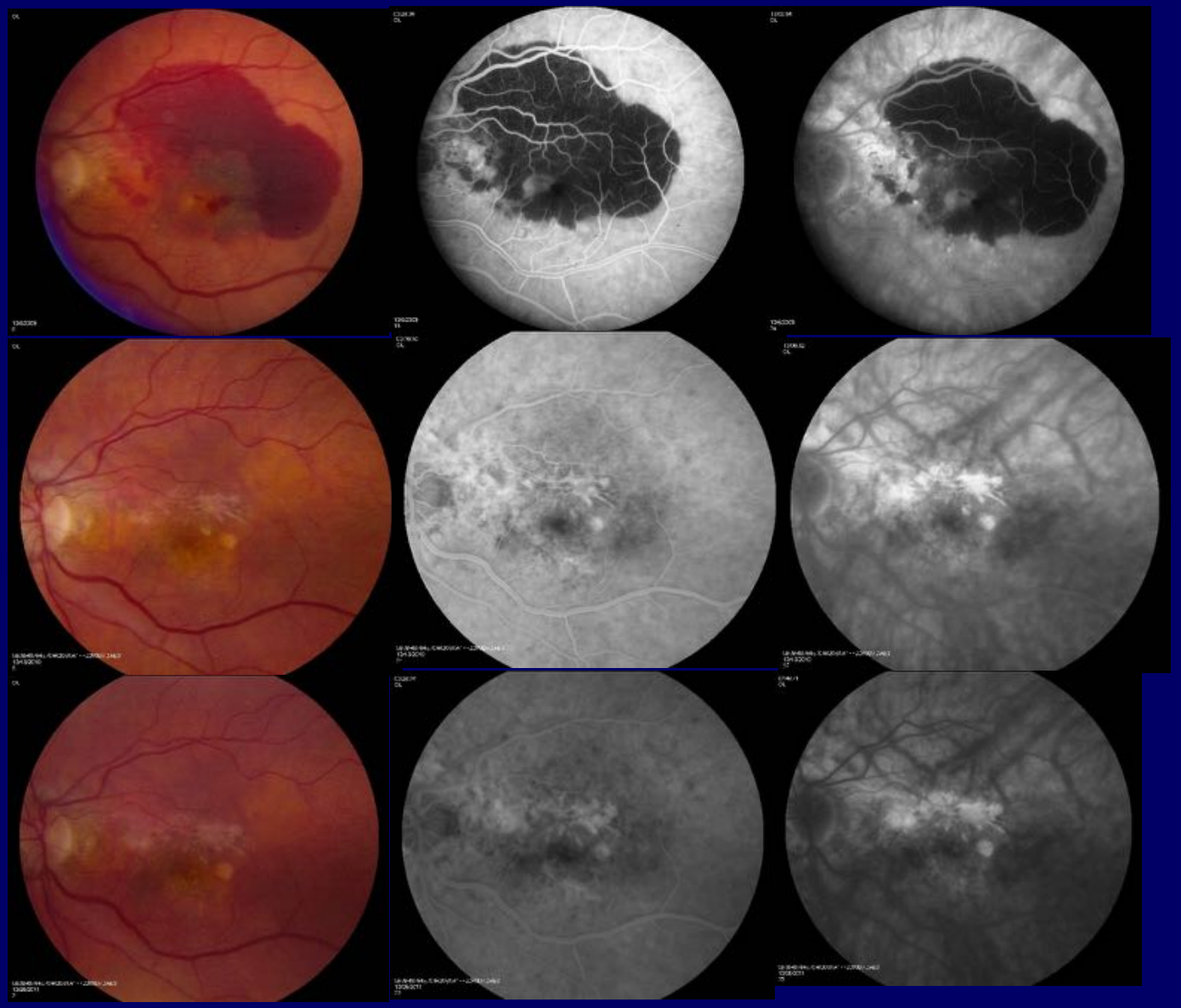


Subretinal Hemorrhage

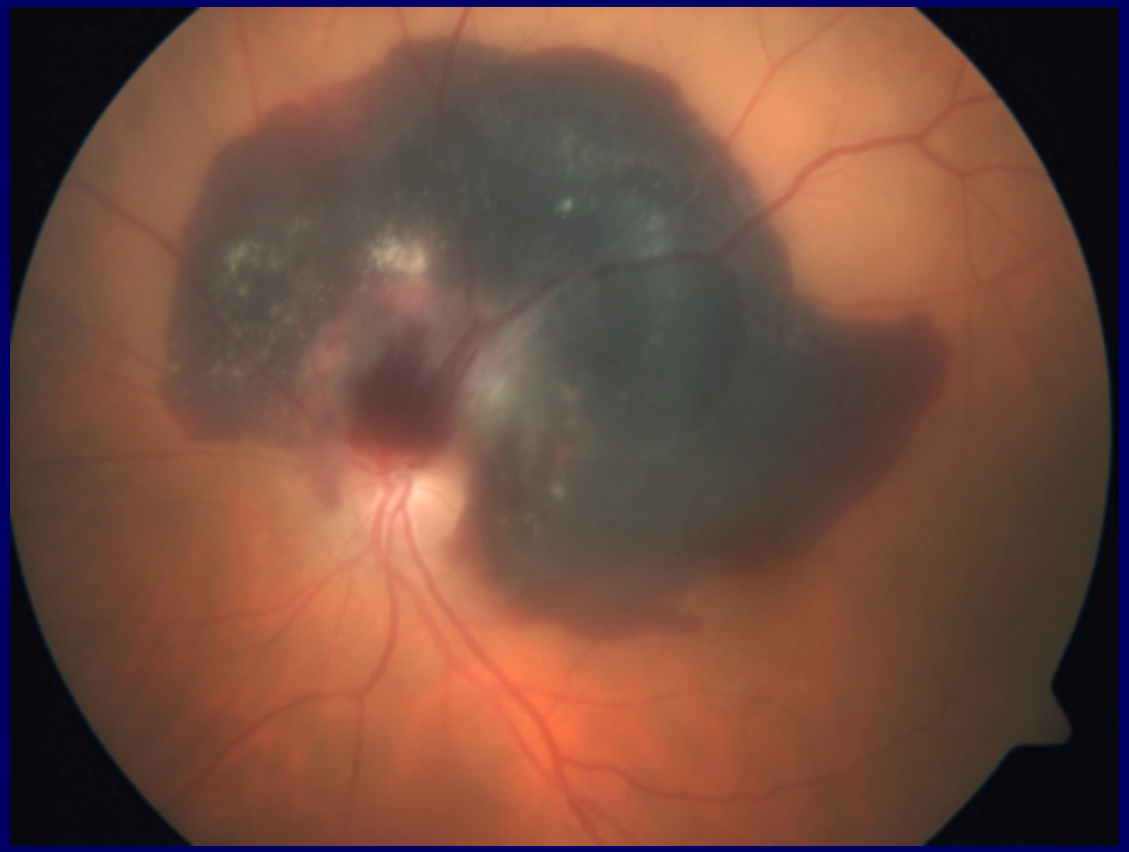
Baseline
(20/100)

1 Year
(20/50)

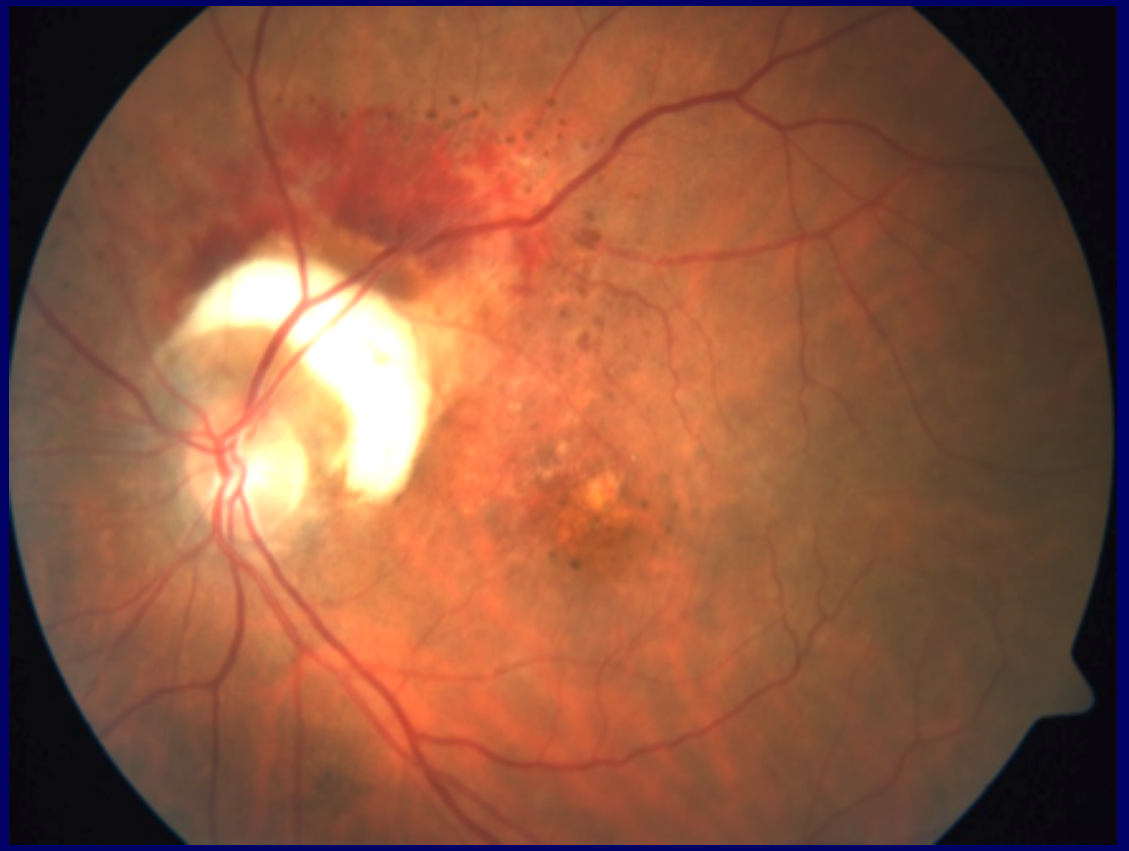
2 Years
(20/40)



SRH Treated with Monthly Bevacizumab

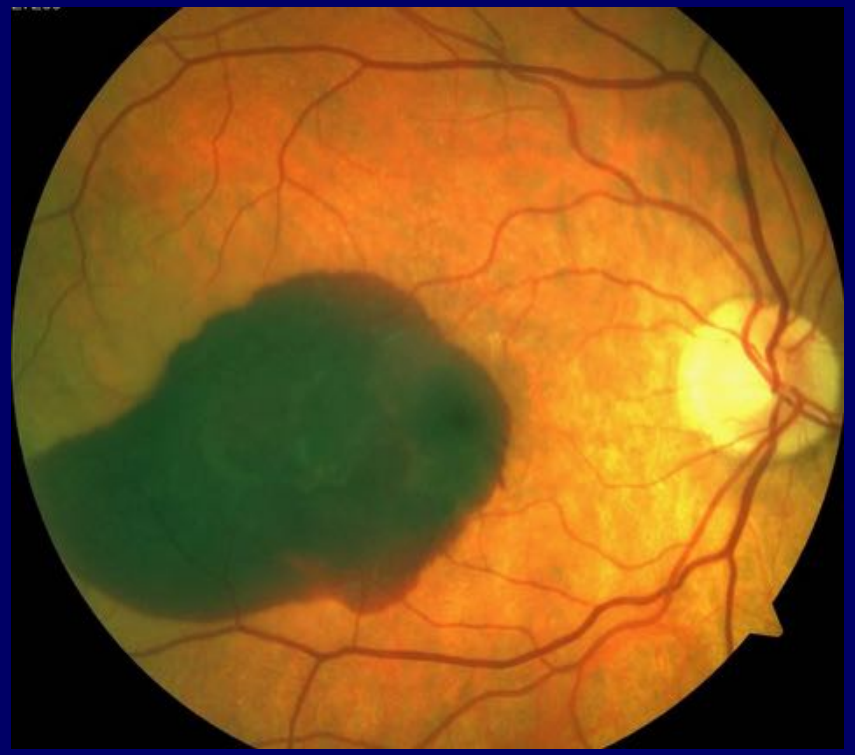


CF 3 ft
(baseline)

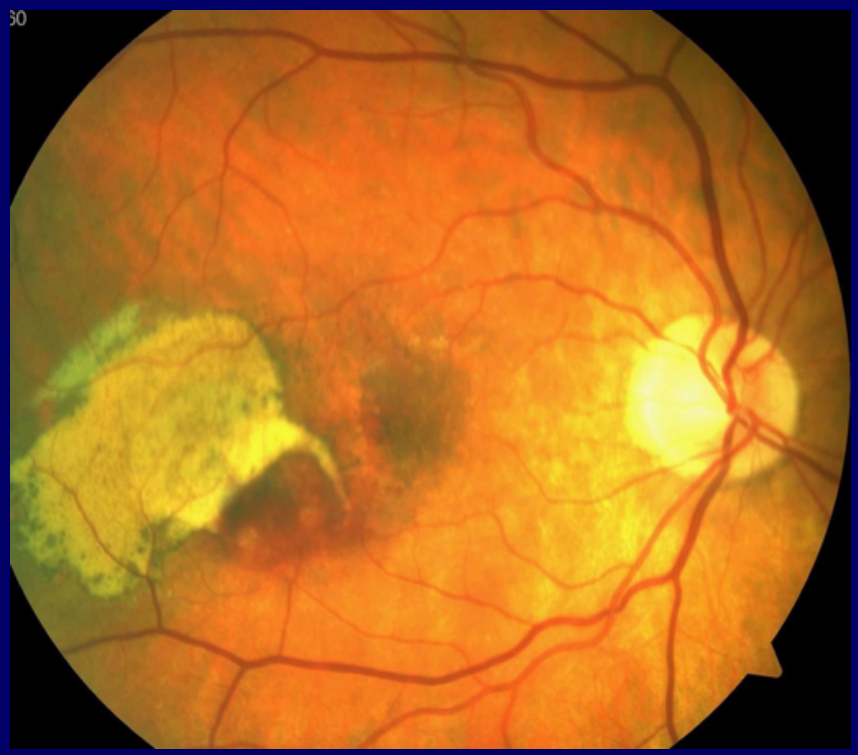


20/40
(after 4 monthly injections)

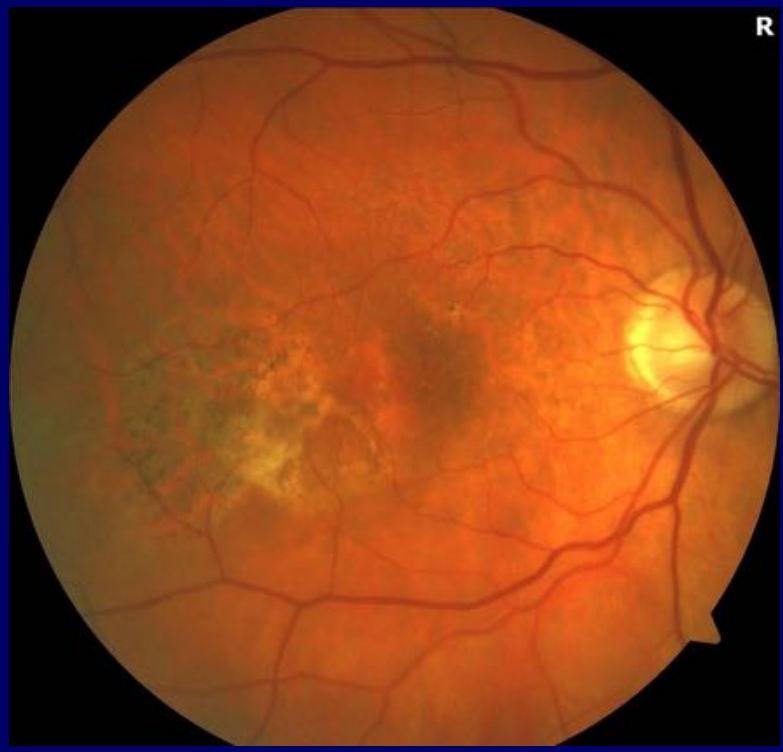
SRH Treated with Monthly Anti-VEGF



20/400
(baseline)



20/80
(3 months)

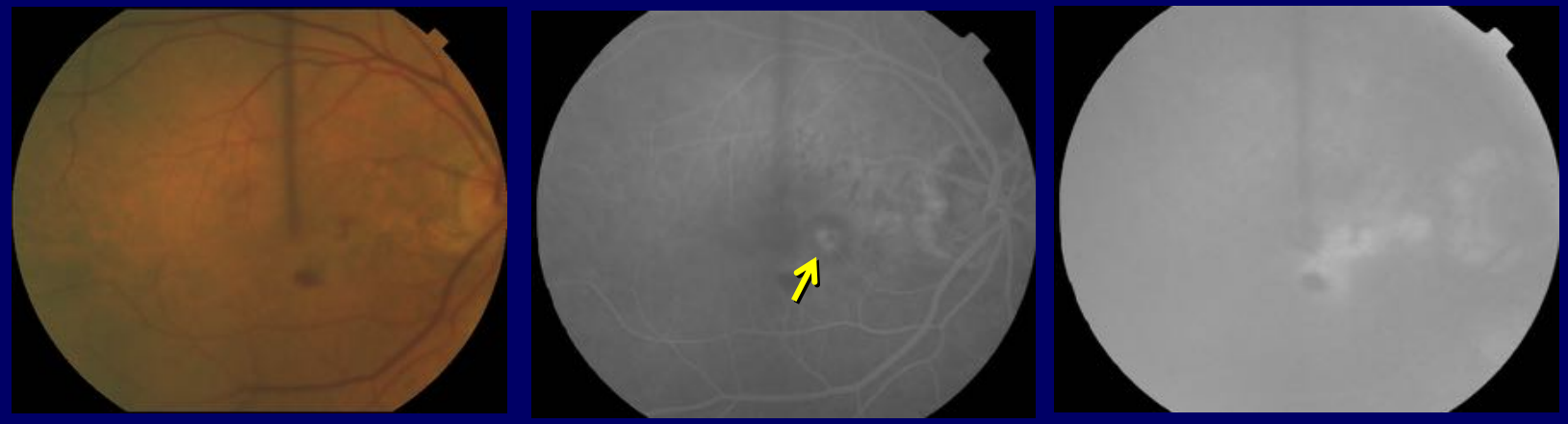


20/30
(1 year)

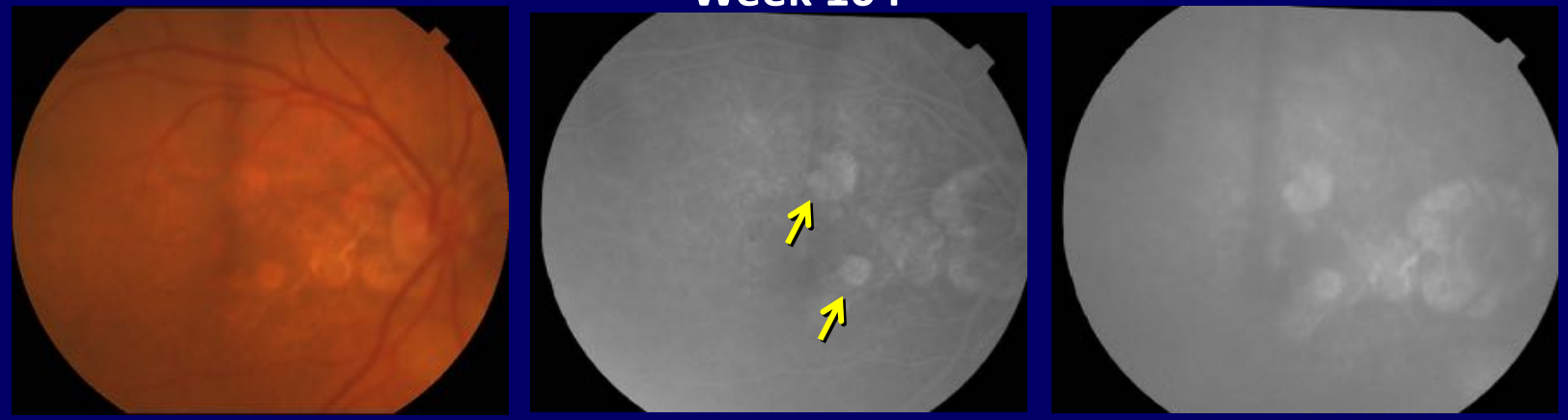
Macular (Geographic) Atrophy

- Macular (geographic) atrophy more common in monthly treated eyes than PRN treated eyes at 2 Years

Baseline



Week 104



Macular (Geographic) Atrophy

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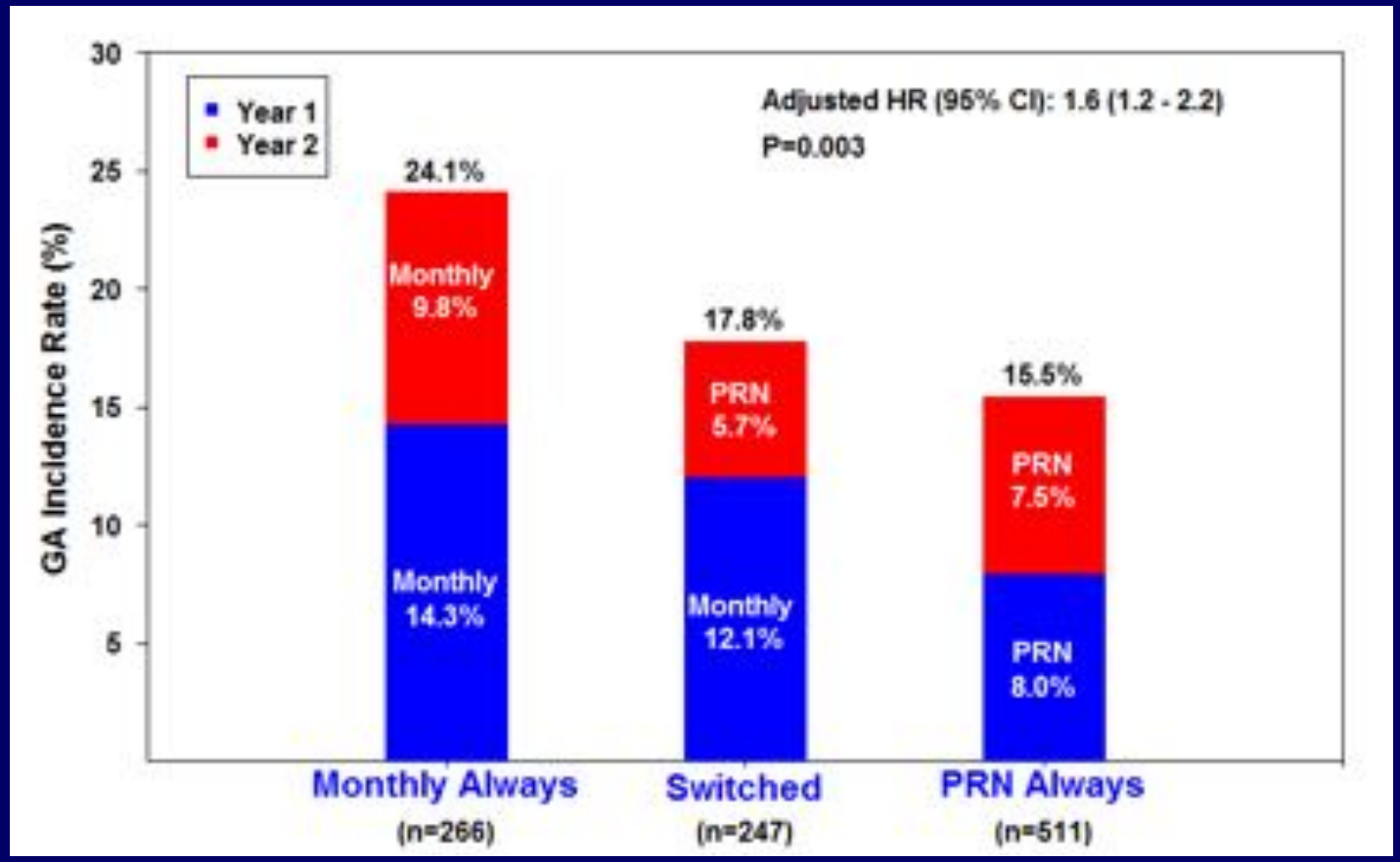
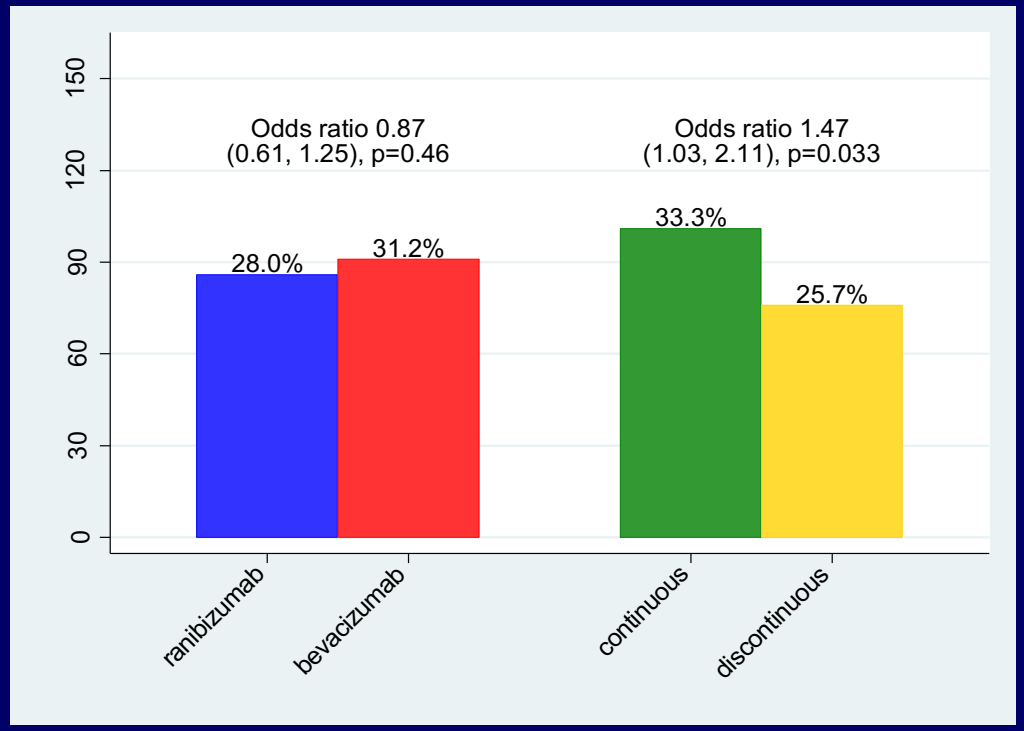


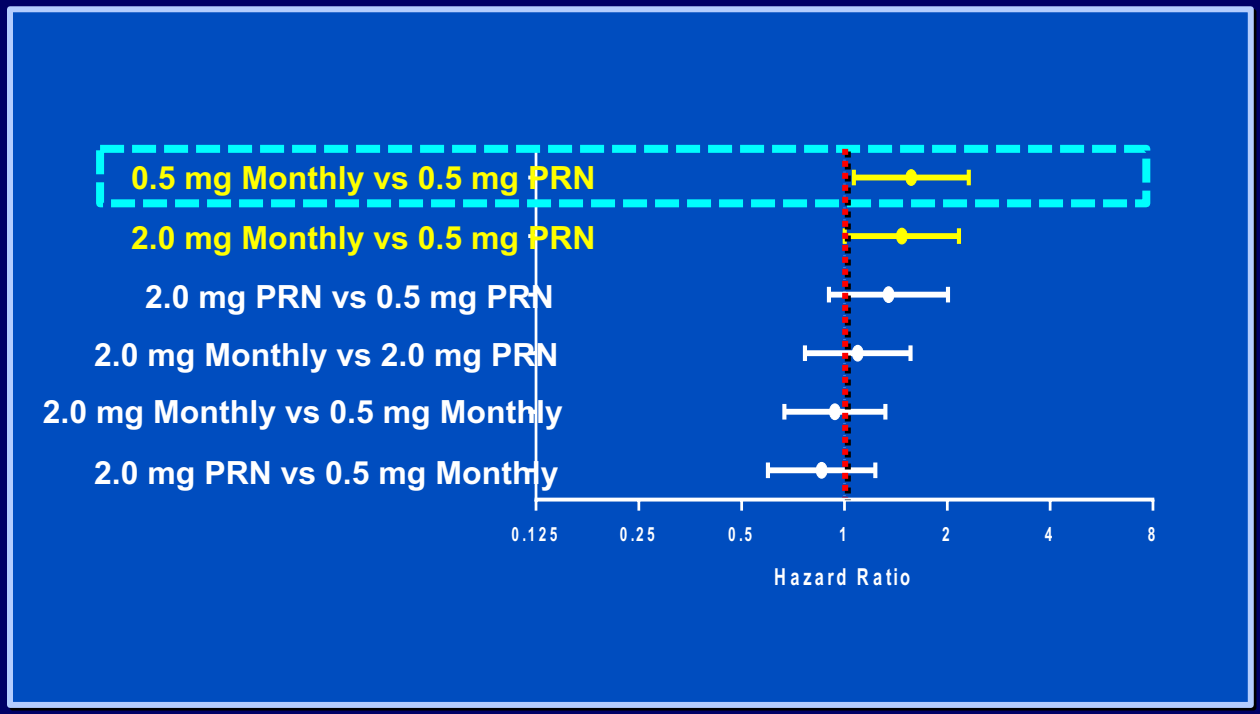
Macular (Geographic) Atrophy

- Macular (geographic) atrophy more common in monthly treated eyes than PRN treated eyes at 2 Years

IVAN



HARBOR



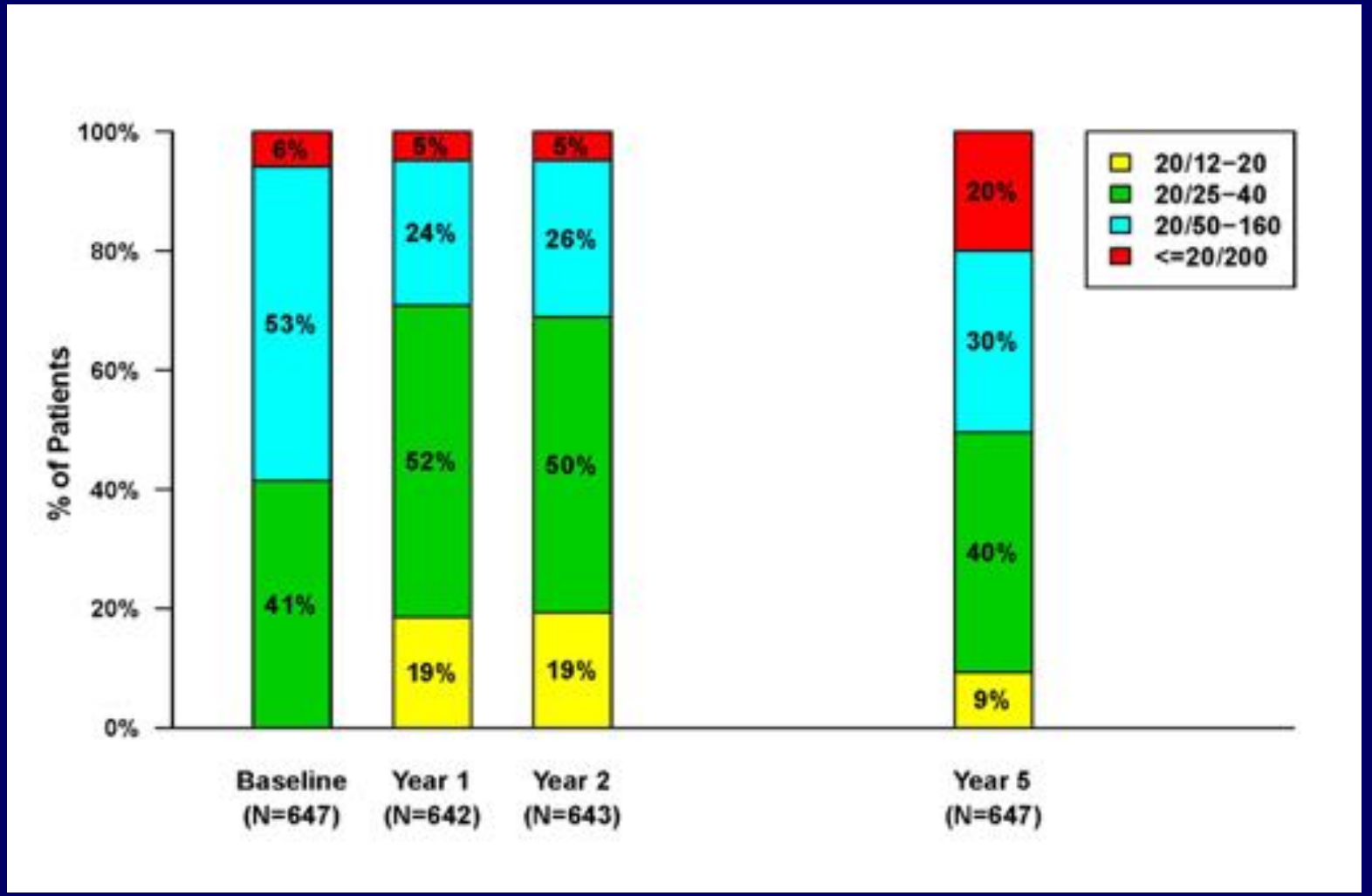
The CATT Follow-up Study

CATT Follow-Up Study

- All CATT participants alive at the end of the 2-year clinical trial were targeted for the CATT Follow-Up Study ≈ 5.5 years
- 71% of eligible returned N=647
  - Age: Mean = 83 yrs
  - Visits for AMD care over 3.5 years: Mean = 25 SD = 13
- After clinical trial, most patients were treated with a drug or dosing strategy that was different from original CATT assignment
  - Ability to assess drugs or treatment groups effects compromised

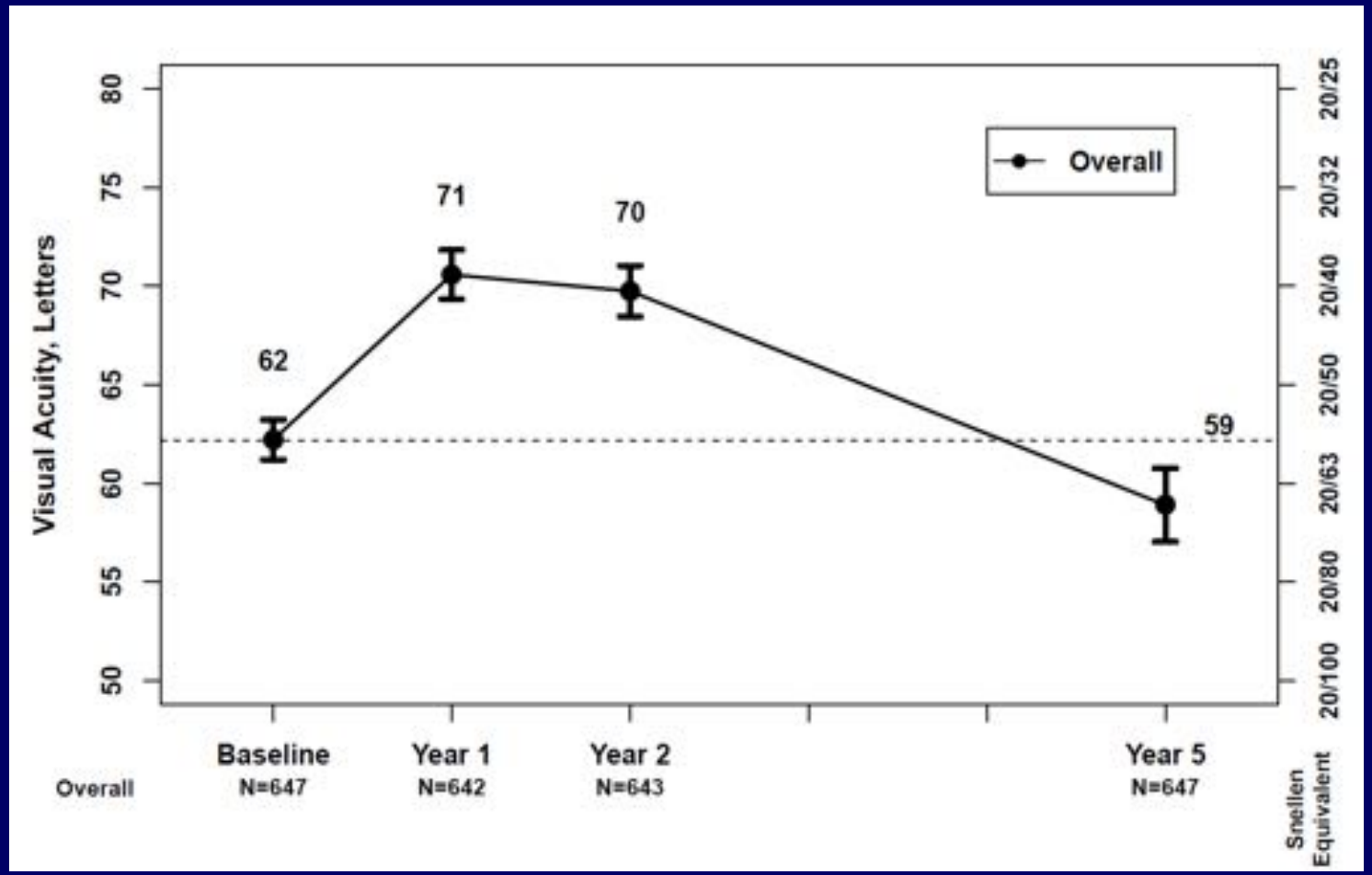
Visual Acuity Over 5 Years

- 50% of patients are 20/40 or better at 5 Years



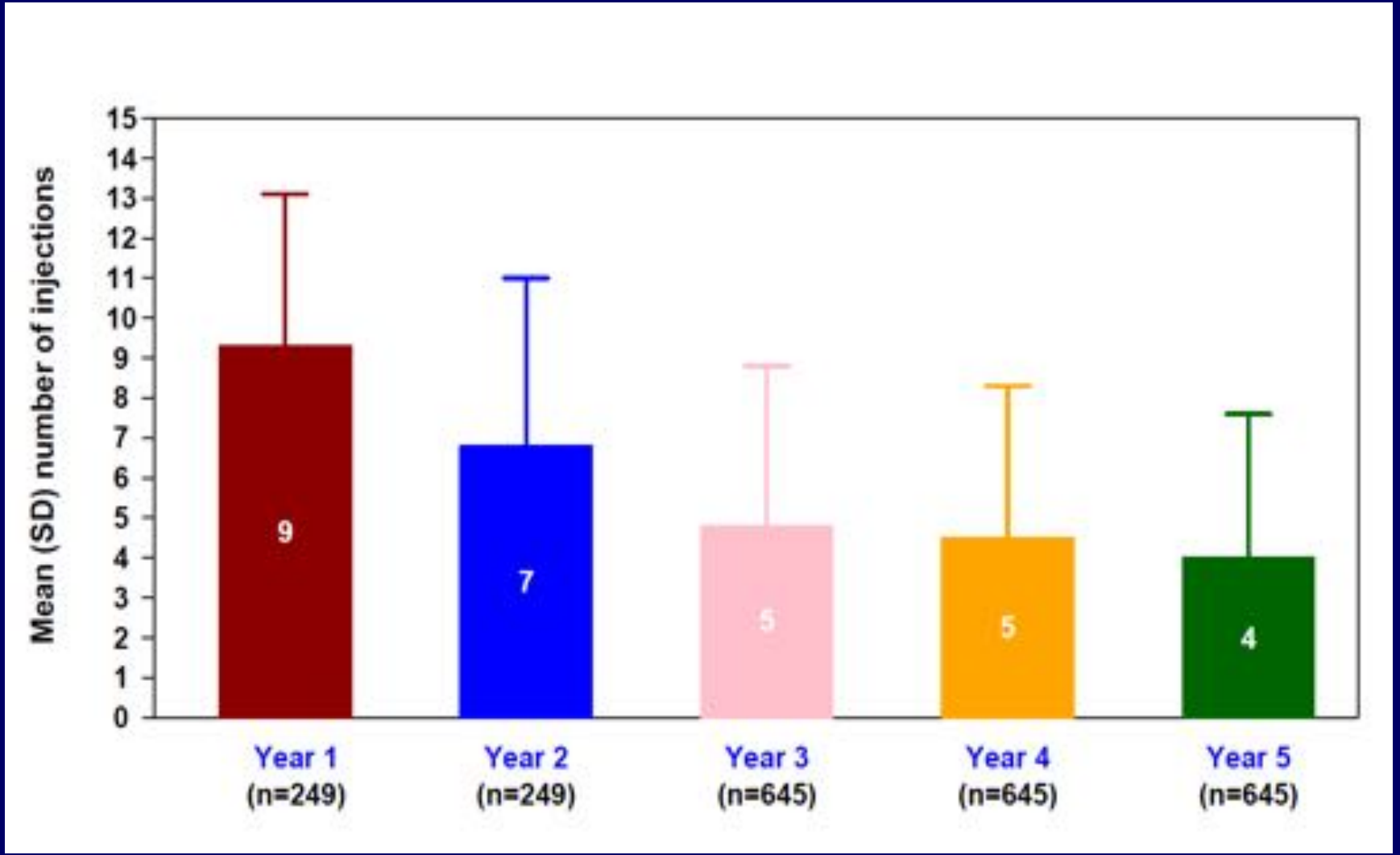
Visual Acuity Over 5 Years

- Visual acuity gains in first 2 years not sustained with mean 11 letter loss between Year 2 and Year 5

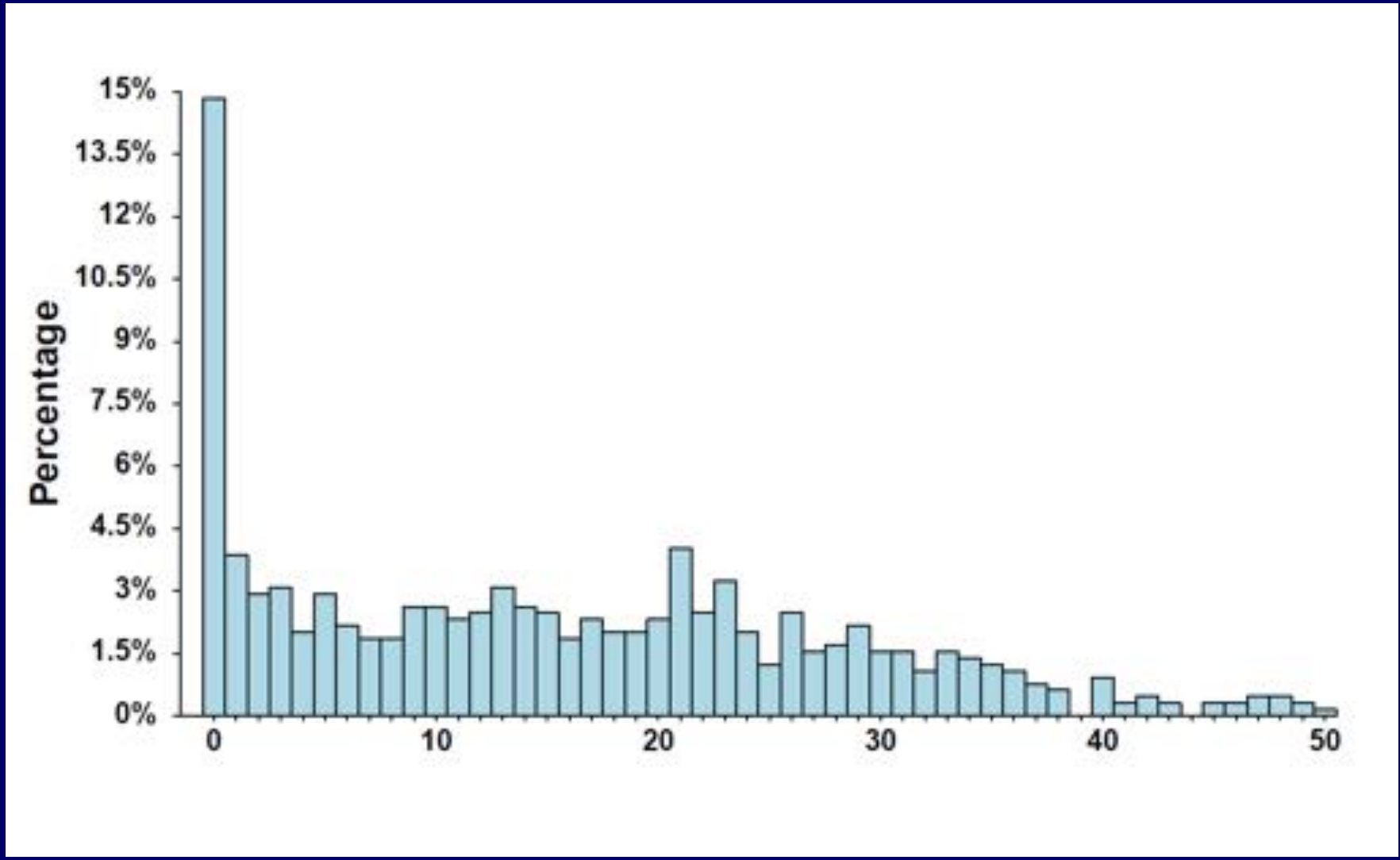


Mean Number of Injections

(PRN Only Group for Year 1 and Year 2)



Number of Injections after Year 2

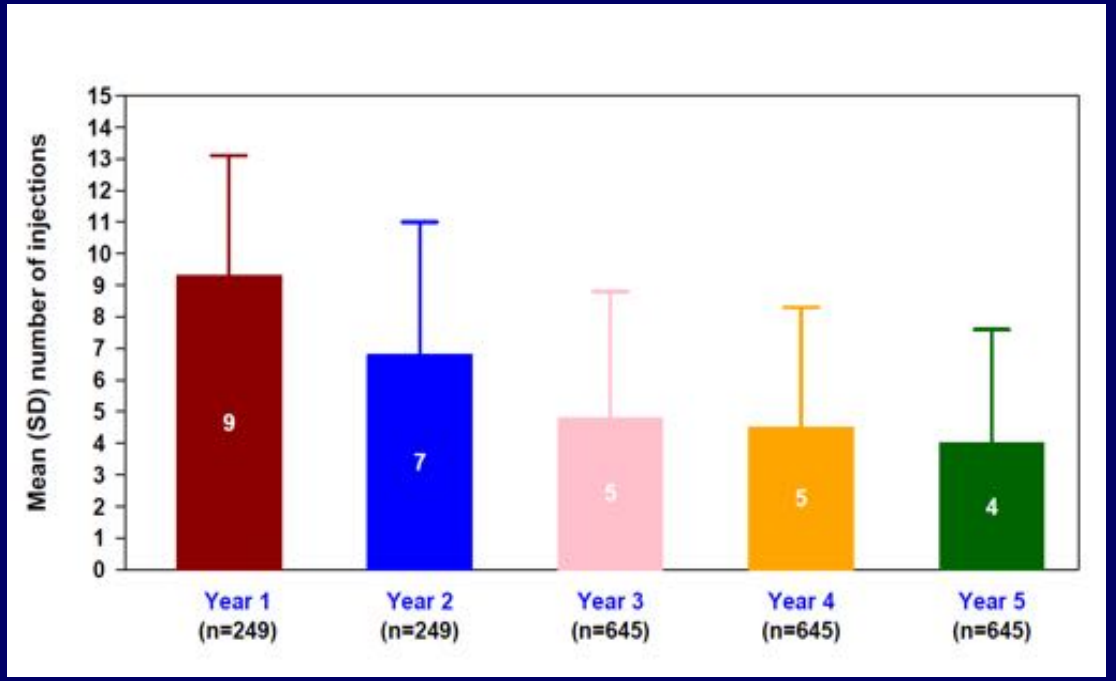


Reasons for Fewer Injections

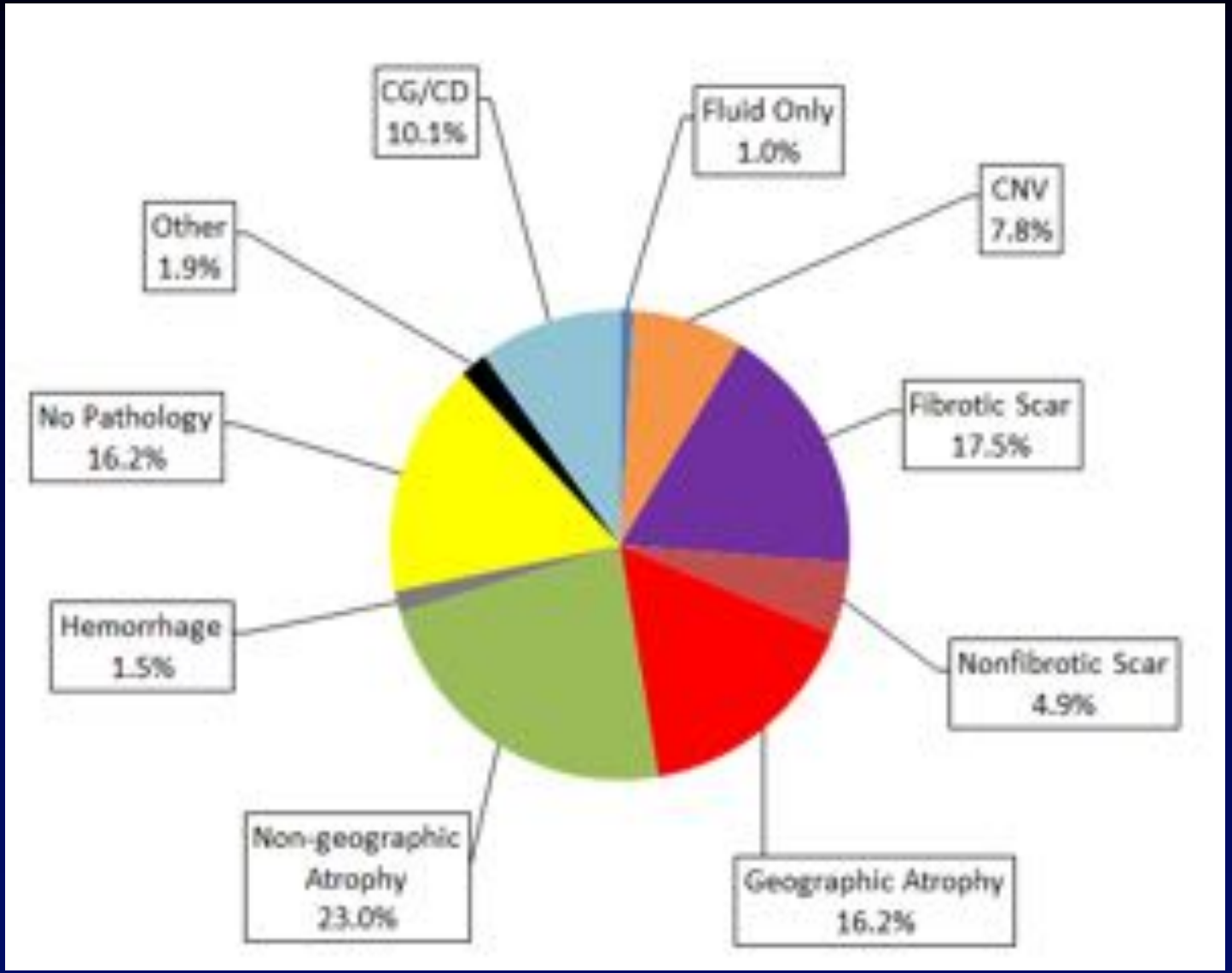
- No fluid or CNV activity detected by ophthalmologist
- Fluid not judged to be meaningful (e.g. retinal degeneration overlying an area of GA or persistent subRPE fluid eccentric to the center)

90%

- Development of GA
- Prolonged periods illness
- Confinement to assisted living facility
- Inability to participate in exam
- Desire to stop treatment

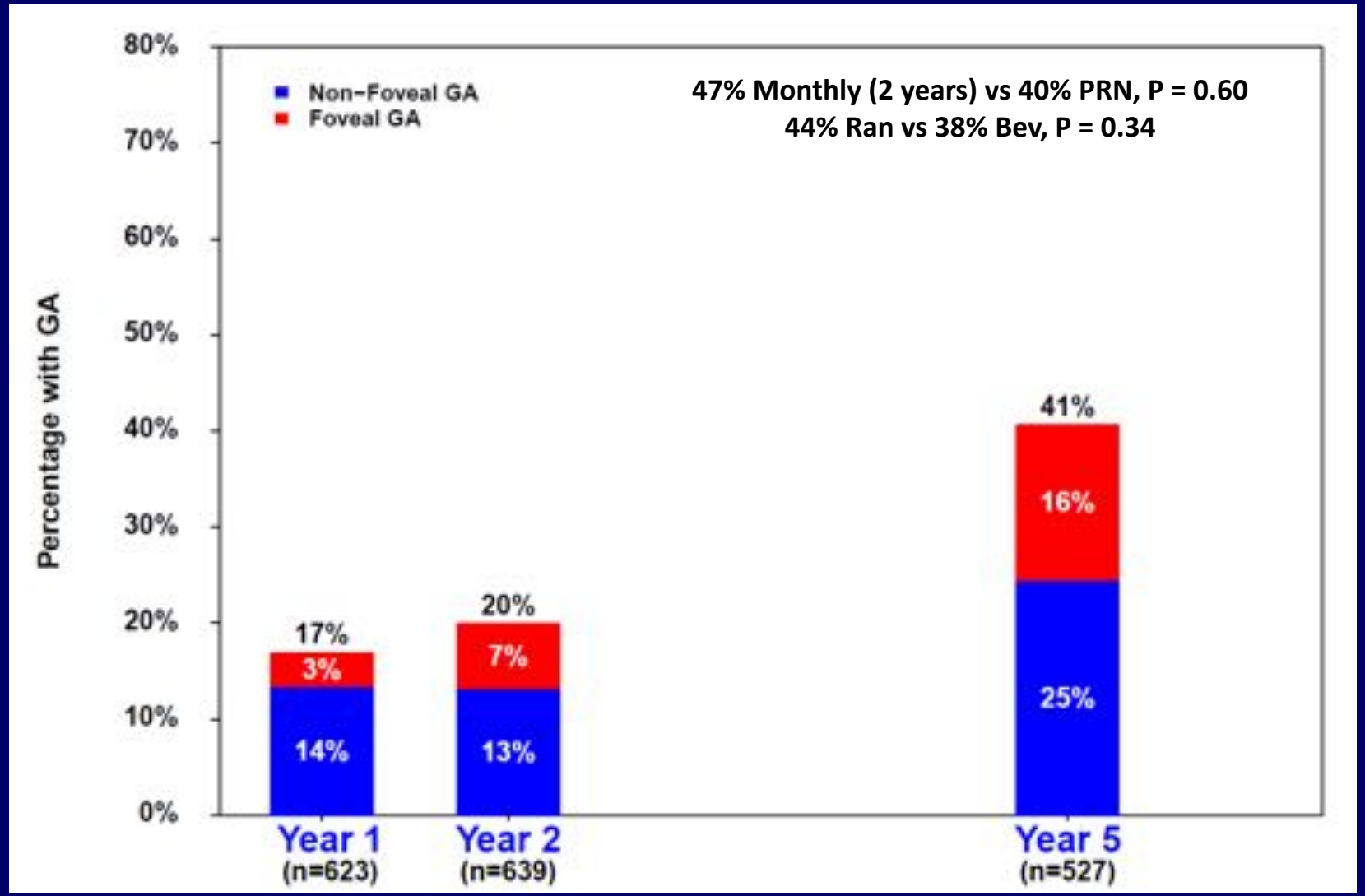


Pathology in the Foveal Center – Year 5



Foveal and Non-Foveal GA

5-Year Cohort

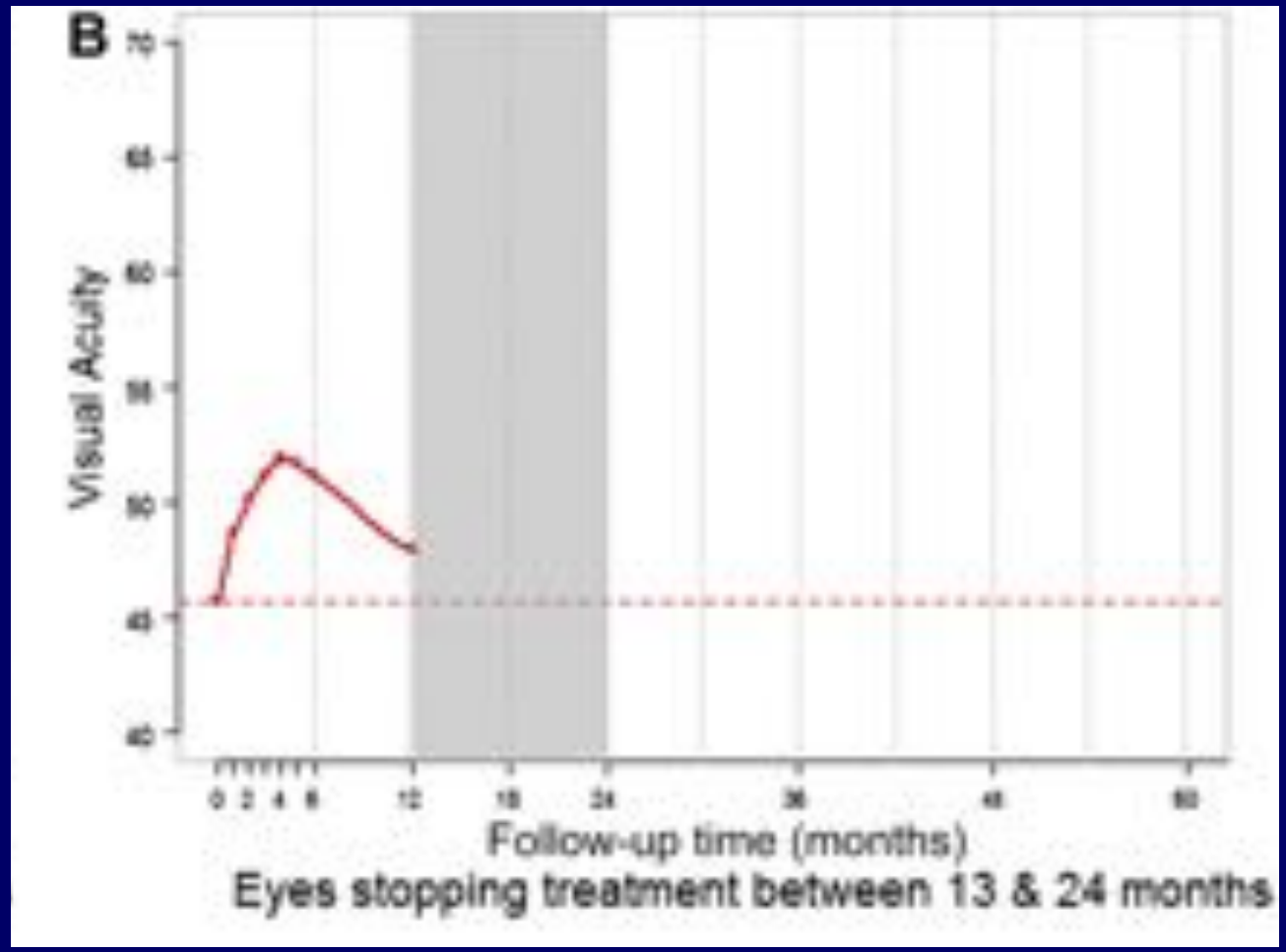


Who Stops Treatment/Visits?

- Fight Retinal Blindness (FRB) database (Australia, NZ, and Switzerland)
  - "Real World" observational study
  - 1212 eyes with nAMD treated with anti-VEGF
  - Treatment initiation at least 5 years earlier (2007-2010)
  - Dropout occurred steadily during follow-up
  - By 5 years 55% dropped out

Gillies, Campain, Barthelmes, et al. Ophthalmology 2015;122:1837-1845

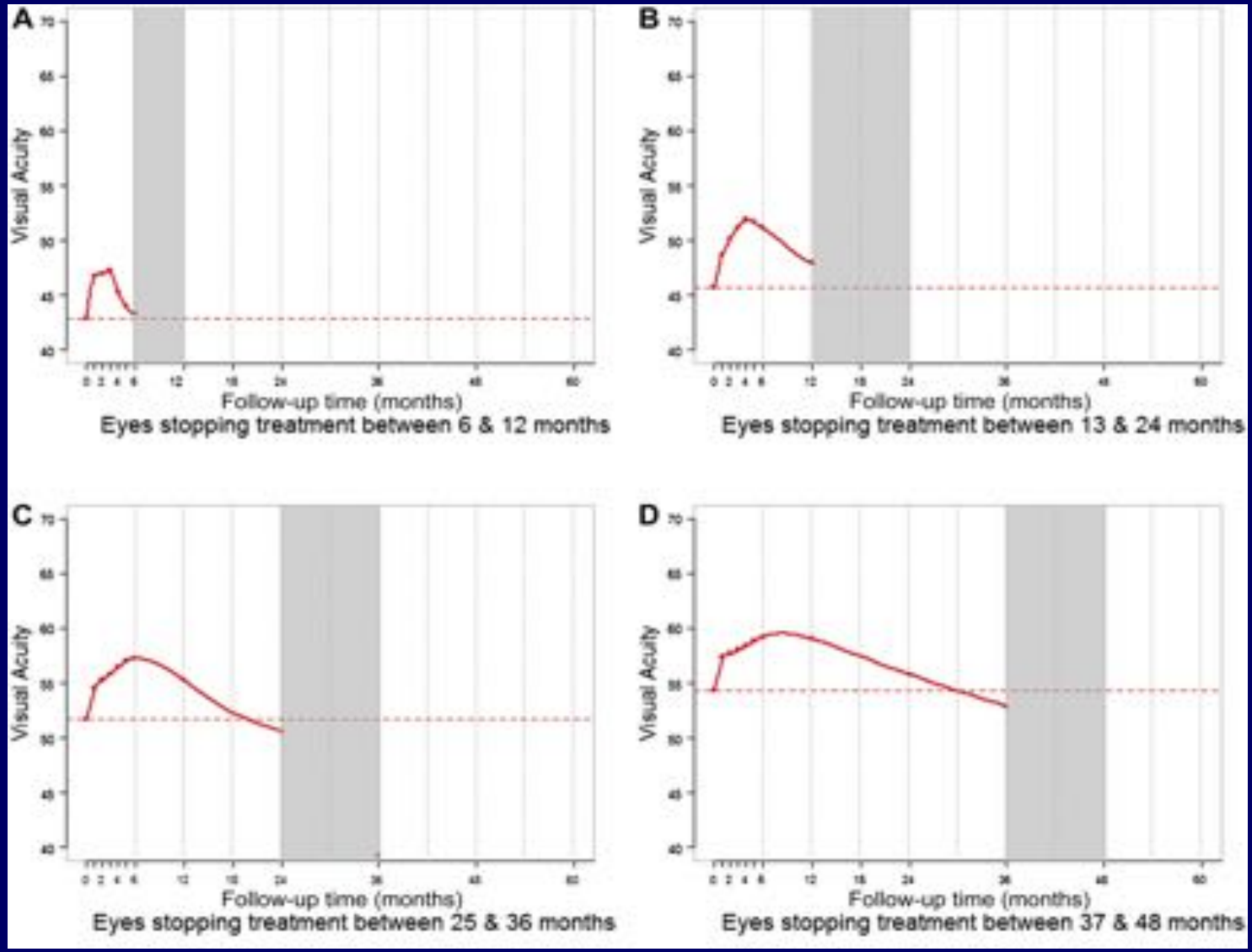
Patients Who Stopped Treatment



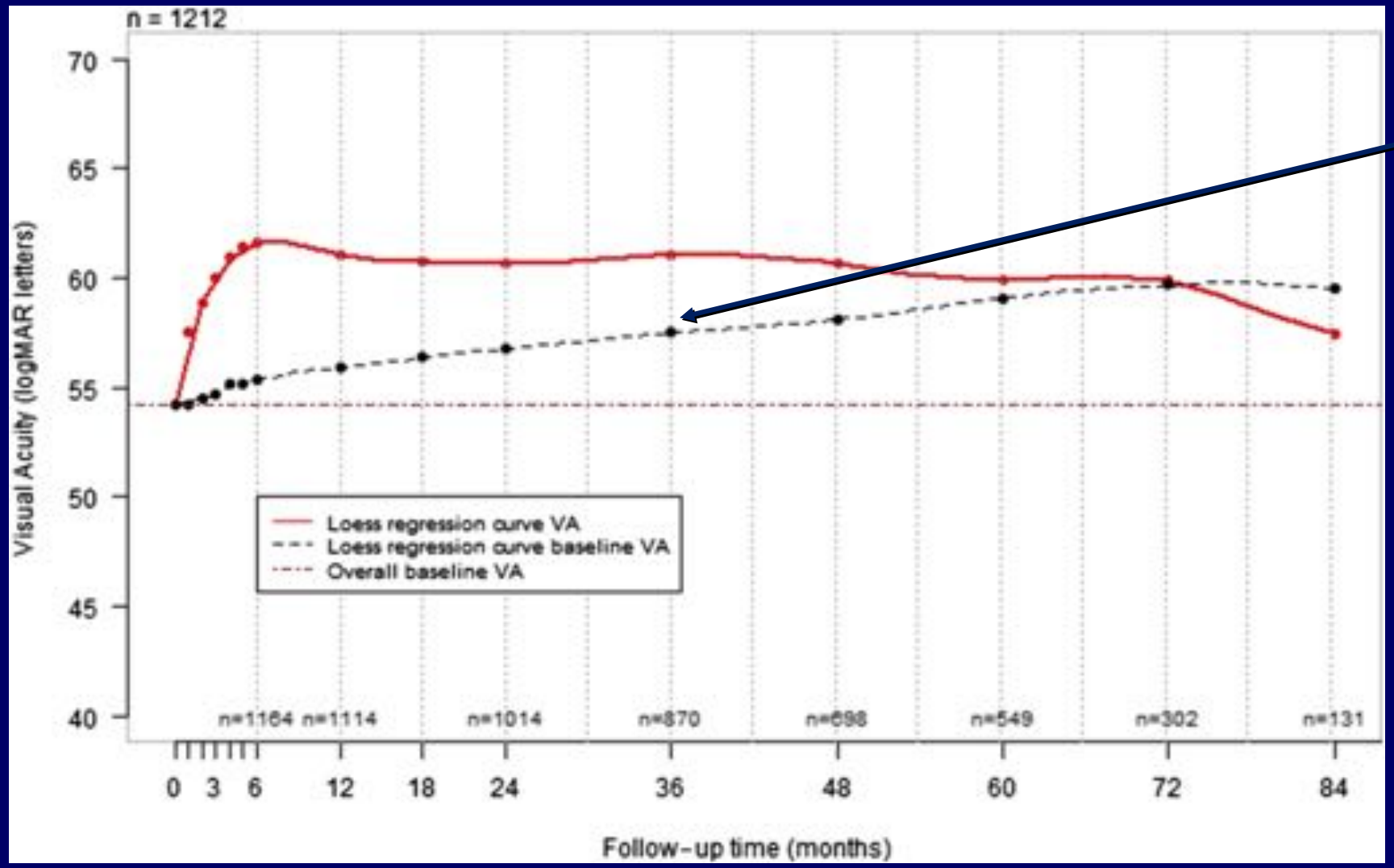
- Stopped between 13 and 24 months:
  - BL VA = 45 (20/125) vs 55 (20/80) for all
  - VA decreased before stopping

Gillies, Campain, Barthelmes, et al. Ophthalmology 2015;122:1837-1845

Pattern Repeats for Other Groups Stopping



Patients Who Stopped Rx/Follow-up



Baseline VA of those seen at follow-up

Those who stayed under treatment had better Baseline VA

Gillies, Campain, Barthelmes, et al. Ophthalmology 2015;122:1837-1845

Follow-up Studies with Dropouts

- In every long-term study of AMD treatment, mean VA of those patients who drop out is worse than those who continue participation (CATT, HORIZON, FRB!)
- CATT results, and results of other studies, are overly optimistic – those who do not return have worse vision

Summary

- CATT overcame many obstacles before we ever enrolled a patient
- CATT and 5 other large clinical trials established the equivalence of bevacizumab and ranibizumab for improving VA and for safety
  - Use of bevacizumab has reduced total cost of care and increased availability of anti-VEGF treatment to many patients worldwide
- Review of CATT images and VA data resulted in many publications that have improved our understanding of treatment effects and led to modifications to treatment approach
- Many remaining unanswered questions including what is the optimal treatment approach beyond 2 years, why does VA decrease long term and how can it be prevented, and what are the long-term effects of continuous treatment

CATT Research Group

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- Ebenezer Daniel MBBS PhD - Photo Reading Center (Penn)
- Frederick L. Ferris MD – NEI Advisor
- Maryann Redford DDS, MPH – NEI Project Officer
- 44 clinics, 250 ophthalmologists, and 150 coordinators who recruited, treated and followed our patients