Debate:

Is there a case for a REACTIVE anti-VEGF therapeutic regimen?

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Why consider reactive treatment ?

- There are several safety concerns associated with over-treating:
  - The risk of post-injection endophthalmitis is small but real
  - Occurrences of RPE/photoreceptor atrophy have been observed following ranibizumab and bevacizumab injections[1,2]
  - A significant temporary decrease in cone function has been observed in patients receiving bevacizumab injections[3]
- Reactive or PRN treatment regimens aim to alleviate the burden on patients, the physician and the system, as well as the financial costs associated with more frequent IVT injections

IVT, intravitreal; PRN, *pro re nata* (as needed); RPE, retinal pigment epithelium.

1. Berg K *et al. Ophthalmology* 2016; 123: 51–59. 2. Rosenfeld PJ. *Ophthalmology* 2011; 118: 523–530. 3. Pederson KB *et al. Retina* 2010; 30: 1025–1033.

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The most frequent adverse event associated with IVT injections is endophthalmitis

- **Endophthalmitis rates after IVT injections are low (~1 in 2000)[1], but this is compounded by repeated treatment[2]**
  - **The incidence of endophthalmitis may be as high as 1% when viewed over a 2-year course of treatment[3]**

IVT, intravitreal.

1. Fileta JB. *Ophthalmic Surg Lasers Imaging Retina* 2014; 45: 143-149. 2. Merani R, Hunyor AP. *Int J Retina Vitreous* 2015; 1: 9. 3. Schwartz SG, Flynn HW. *Curr Ophthalmol Rep* 2014; 2: 1–5.

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Intense IVT injection regimens severely affect quality of life

In a European survey of 131 retinal patients:

93% reported anxiety relating to their most recent injection

with

54% reporting anxiety ≥2 days prior

47% reported adverse physical effects, such as exhaustion, which was related either to the injection itself or to anxiety about the injection

42% desired fewer injections to achieve the same visual results

IVT, intravitreal.

Sivaprasad S, Oyetunde S. *Clin Ophthalmol* 2016; 10: 939–946.

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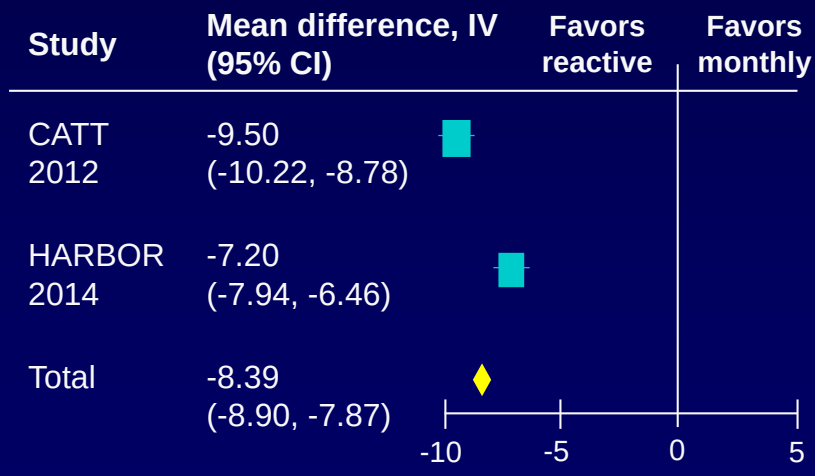
Reactive dosing regimens enable a reduction in the number of injections that patients receive

- **In a 12-month, phase III, open-label study of ranibizumab in patients with nAMD, patients were treated with a reactive injection schedule after three initial monthly injections[1]**
  - **Patients received 70% fewer injections versus fixed monthly dosing, with 80% of the treatment effect[2]**
  - **In the 9-month study period after loading, 20% of patients did not require any additional injections**

In a meta-analysis of 2-year head-to-head studies, reactive dosing enabled fewer injections[3]



CATT, Comparison of Age-Related Macular Degeneration Treatments Trials; CI, confidence interval; IV, independent variable; nAMD, neovascular age-related macular degeneration.

1. Holz FG *et al. Ophthalmology* 2011; 118: 663–671. 2. Stewart MW. *J Clin Med* 2015; 4: 1079–1101.
3. Schmucker CM *et al. PLoS One* 2015; 10: e0137866.

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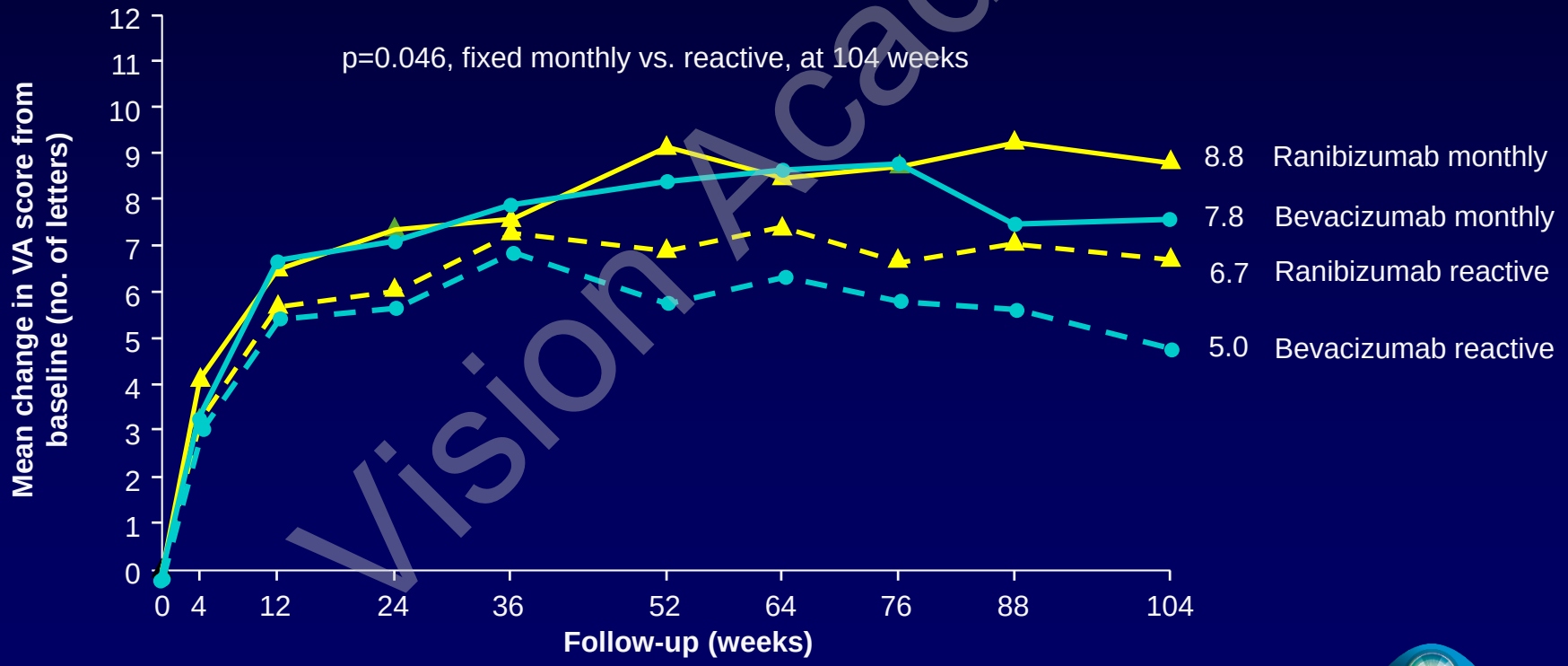
Reactive dosing regimens can provide similar efficacy to fixed monthly injections

- **The CATT non-inferiority study compared different dosing regimens of bevacizumab and ranibizumab in patients with nAMD[1]**
  - **VA outcomes were similar between reactive and fixed dosing regimens**



CATT, Comparison of Age-Related Macular Degeneration Treatments Trials; nAMD, neovascular age-related macular degeneration; VA, visual acuity.

Martin DF *et al. N Engl J Med* 2011; 364: 1897–1908.

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The efficacy of reactive and T&E regimens are not largely dissimilar

- **Retrospective comparisons of reactive and T&E regimens are inconclusive:**
  - **In nAMD, no strong differences in anatomical and functional improvements were observed[1]**
  - **Poor performance of reactive regimens in real-world studies has been attributed to a low mean number of injections and less-than-monthly visits; both common to T&E[2]**

nAMD, neovascular age-related macular degeneration; T&E, treat-and-extend; VA, visual acuity.

1. Garweg JG *et al. J Ocul Pharmacol Ther* 2017; 33: 773–778. 2. Mantel I. *Trans Vis Sci Technol* 2015; 4: 6.

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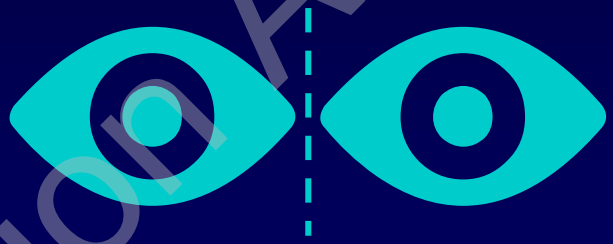
Additional considerations

In cases of bilateral disease, reactive therapy is cumbersome and complicated to implement



Summary

- Potential VA improvements must be balanced against the burden and complications of frequent IVT injections
- Reactive treatment regimens aim to reduce injection frequency without compromising VA outcomes
- Careful monitoring is crucial to prevent deterioration[1]
  - Maintenance of all monitoring sessions is essential

IVT, intravitreal; VA, visual acuity.

1. Haller JA. *Ophthalmology* 2013; 120: S3–7.

Optimal treatment regimen with anti-VEGF in AMD: proactive

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AMD, age-related macular degeneration; VEGF, vascular endothelial growth factor

Financial and other disclosures

I have the following financial interests or relationships to disclose	Disclosure code
Alcon	C,L,S
Allergan	C,L
Bayer	C,L,S
Boehringer Mannheim	C
Carl Zeiss Meditec	C,L
Heidelberg Engineering	C,L
Novartis Pharmaceuticals Corporation	C,L,S
Santen	C,L
Topcon	C,L

C, consultant; L, lecture fees; S, grant support

Anti-VEGF treatment regimens in AMD

PROACTIVE

- **Fixed dosing**
  - Monthly[1-3] or quarterly[4]
- **Treat-and-extend**[5]

REACTIVE

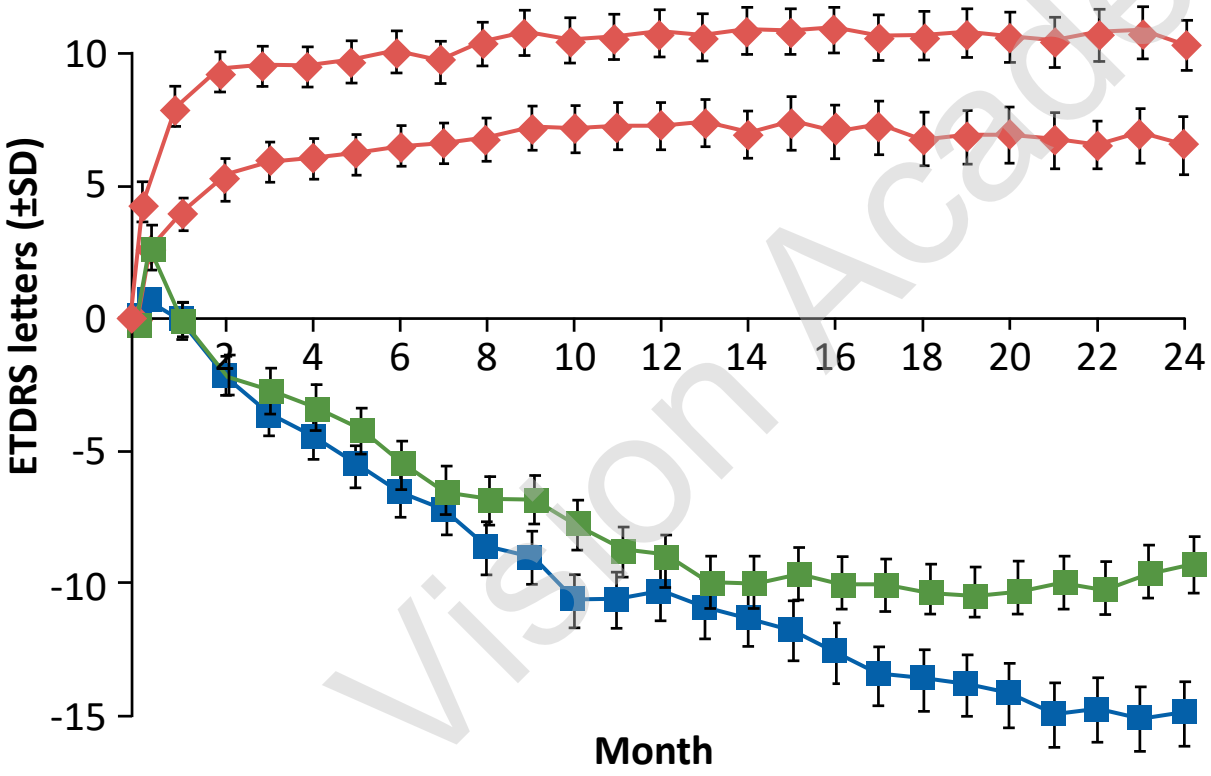
- ***Pro re nata* (PRN):** as needed
  - Monthly visits[3,6-7]
  - Extended visits[8-9]
  - Treat-to-target

AMD, age-related macular degeneration; VEGF, vascular endothelial growth factor

1. Brown DM *et al N Engl J Med*. 2006; 355: 1432–1444. 2. Rosenfeld PJ *et al. N Engl J Med*. 2006; 355: 1419–1431. 3. Martin DF *et al.* CATT Research Group. *N Engl J Med*. 2011; 364: 1897–1908. 4. Regillio CD *et al*. *Am J Ophthalmol*. 2008; 145: 239–248. 5. Mitchell P. Macular Degeneration Foundation. 2011. 6. Lalwani GA *et al*. *Am J Ophthalmol*. 2009; 148: 43–58.e1. 7. Holz FG *et al*. *Ophthalmology*. 2011; 118: 663–671. 8. Schmidt-Erfurth U *et al*. *Ophthalmology*. 2011; 118: 831–839. 9. Boyer DS *et al*. *Ophthalmology*. 2009; 116: 1731–1739

Optimal ≠ Perfect

MARINA and ANCHOR trials using fixed dosing regimens: gold standard of treating neovascular AMD



ANCHOR[1]
+10.7 ranibizumab 0.5mg

MARINA[2]
+6.6 ranibizumab 0.5mg

ANCHOR[1]
–9.8 verteporfin PDT

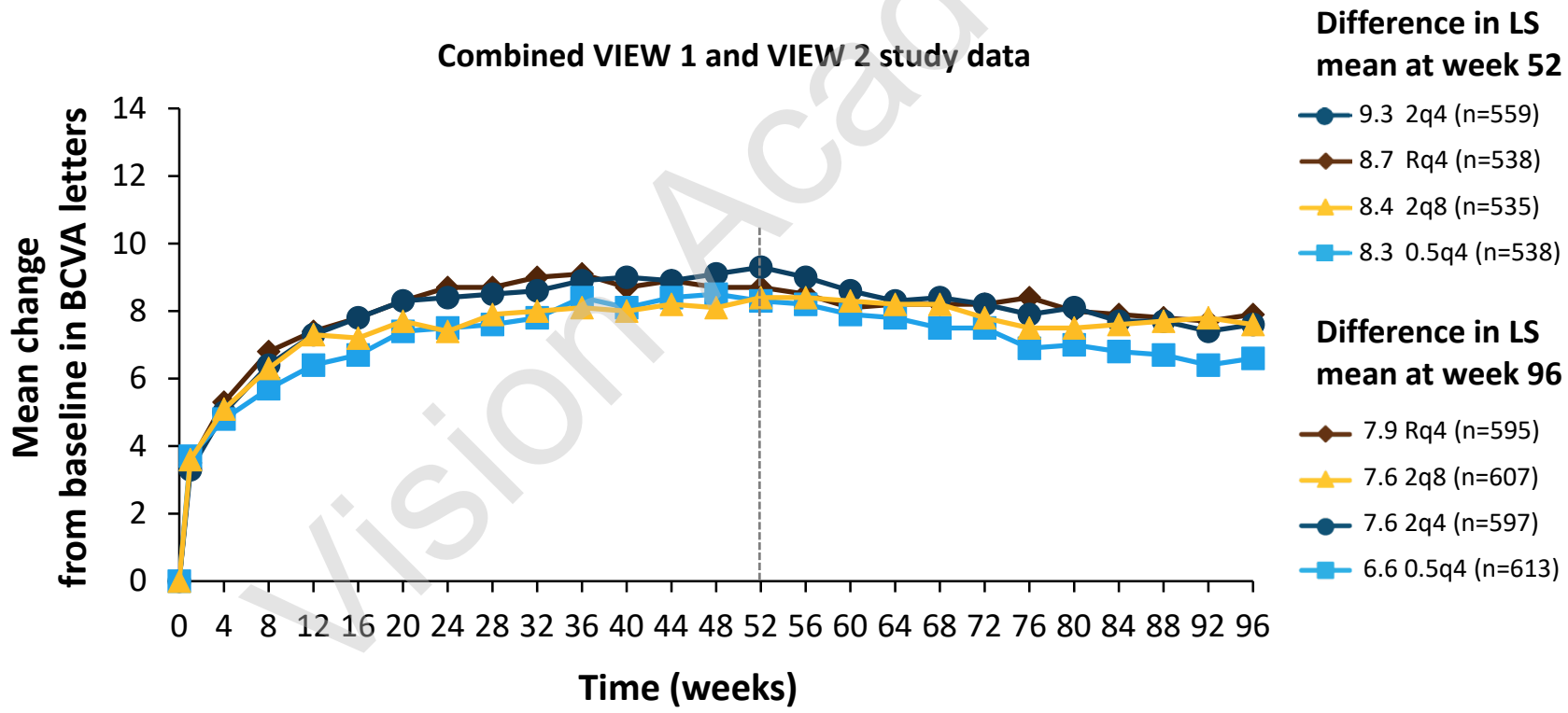
MARINA[2]
–14.9 sham

AMD, age-related macular degeneration; ETDRS, Early Treatment Diabetic Retinopathy Study; PDT, photodynamic therapy; SD, standard deviation

1. Brown DM *et al*. *Ophthalmology*. 2009;116:57-65;
2. Rosenfeld PJ *et al*. *N Engl J Med*. 2006;355:1419-1431.

VIEW: fixed dosing with aflibercept q8 achieved optimal results

- Aflibercept monotherapy improved visual acuity in the overall wet AMD population



AMD, age-related macular degeneration; BCVA, best corrected visual acuity; LOCF, last observation carried forward; LS, least square; Rq4, ranibizumab 0.5 mg every 4 weeks; 2q4, aflibercept 2 mg every 4 weeks; 0.5q4, aflibercept 0.5 mg every 4 weeks; 2q8, aflibercept 2 mg every 8 weeks.

Schmidt-Erfurth U *et al. Ophthalmology* 2014; 121: 193–201.

PRN re-treatment criteria:
ALL REQUIRED MONTHLY MONITORING!

PRONTO (n=40)

- **>5 letters VA loss** with OCT, evidence of fluid in the macula
- **>100 µm increase in CRT**
- New macular hemorrhage or new leakage on FA
- Persistent fluid on OCT, 1 month after previous injection
- Retreatment criteria in Year 2 amended to include any qualitative increase in the amount of fluid detected via OCT
- **Mean change from baseline in BCVA at 12 months: +9.3 letters**

SAILOR cohort I (n=2378)

- A 100 µm increase in CRT from the thinnest measurement recorded at any prior scheduled study visit
- Decreased VA >5 letters compared with any prior scheduled study visit
- **Mean change from baseline in BCVA at 12 months: +2.3 letters**

SUSTAIN (n=513)

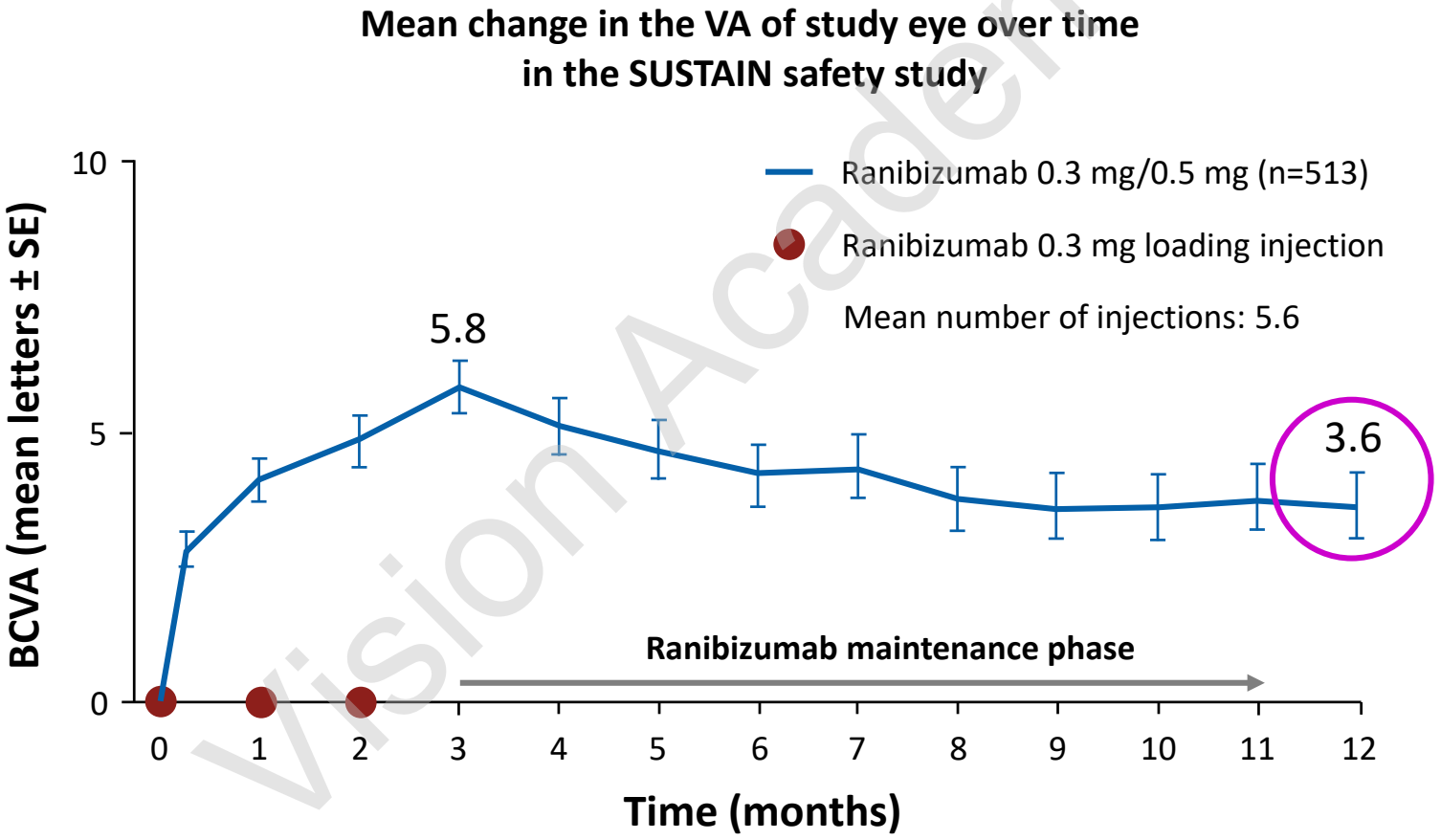
- Retreatment if either **>5 letters VA loss or >100 µm increase in CRT**
- **Option not to treat if VA ≥79 letters or CRT ≤225 µm or change** by <50 µm in CRT and <5 letters in BCVA after three consecutive treatments
- **Mean change from baseline in BCVA at 12 months: +3.6 letters**

MONT BLANC (n=255)

- A 100 µm increase in CRT from the thinnest measurement recorded at any prior scheduled study visit
- Evidence of subretinal fluid
- New subretinal hemorrhage
- Decreased VA >5 letters compared with VA score from the previous scheduled study visit
- **Mean change from baseline in BCVA at 12 months: +4.4 letters**

BCVA, best corrected visual acuity; CRT, central retinal thickness; FA, fluorescein angiography; OCT, optical coherence tomography; PRN, *pro re nata*; VA, visual acuity

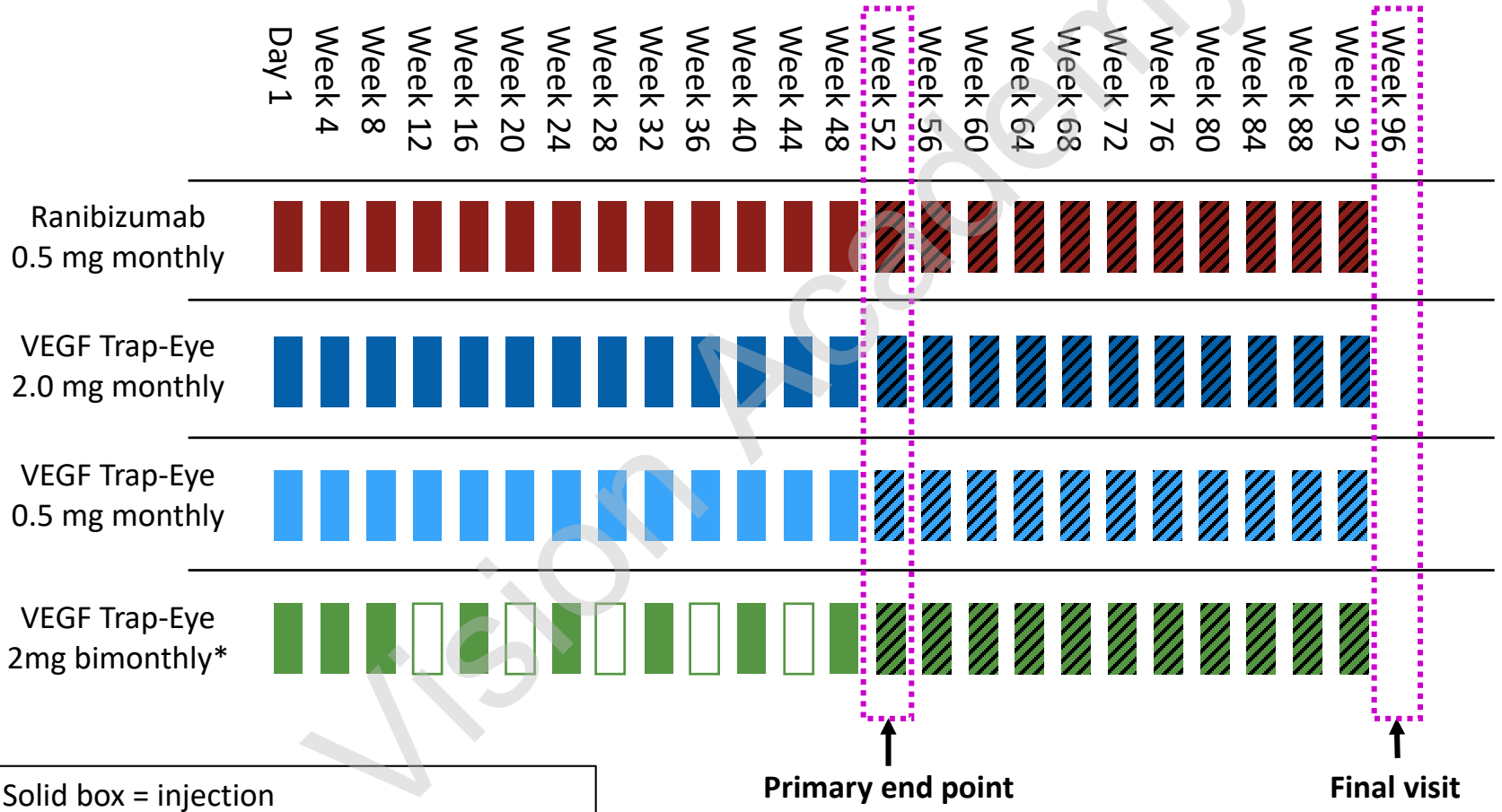
Modest VA improvements over 12 months with mean of 5.6 injections in SUSTAIN



BCVA, best corrected visual acuity; SE, standard error; VA, visual acuity

Holz FG *et al. Ophthalmology* 2011; 118: 663–71

VIEW studies (follow-up phase): ‘Capped PRN’ during second year

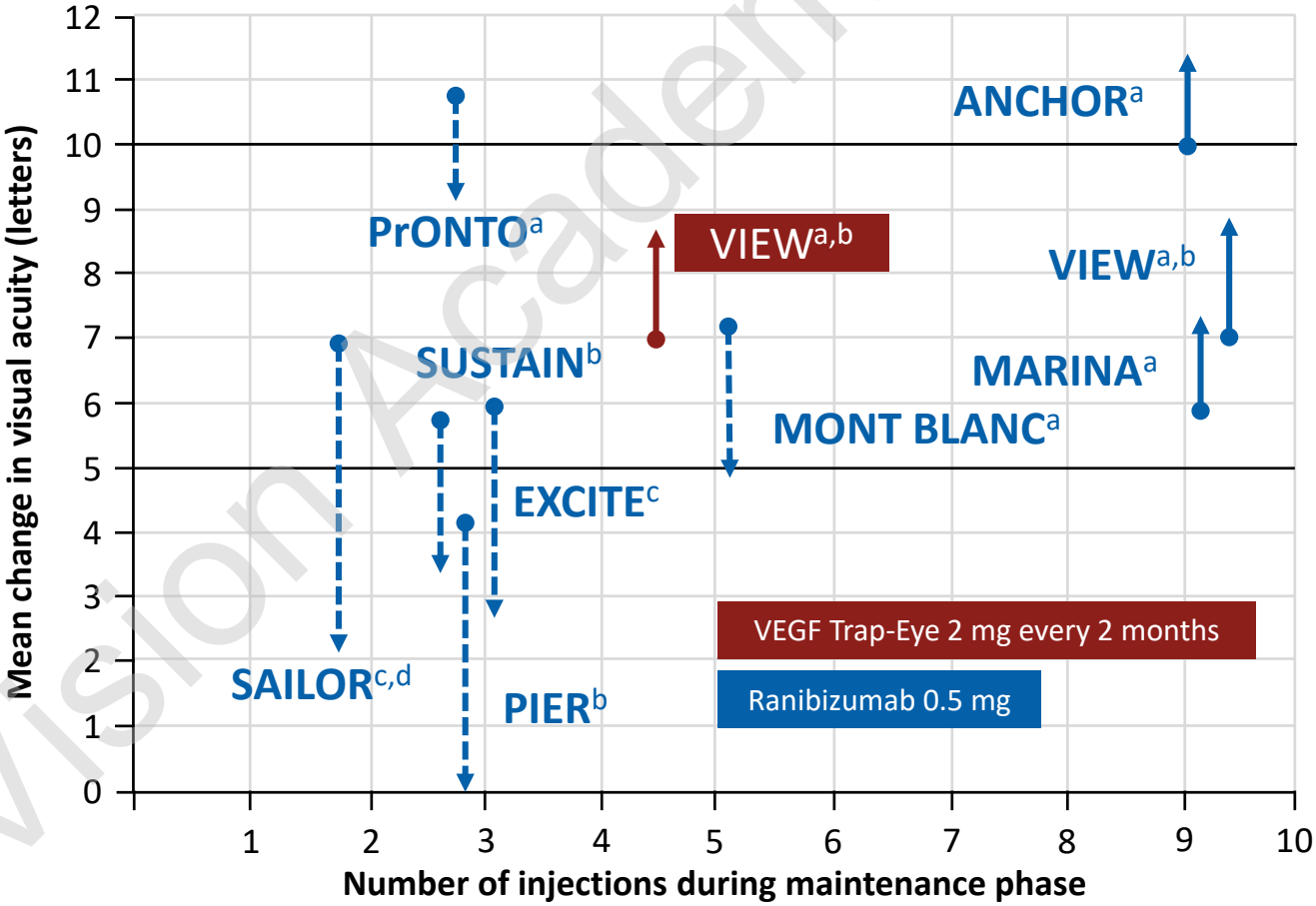


Solid box = injection
Outline = sham injection
Hatched box = modified quarterly dosing

*After three initial monthly doses.
PRN, *pro re nata*; VEGF, vascular endothelial growth factor

The simple fact is:
Visual outcomes correlate with NUMBER OF INJECTIONS

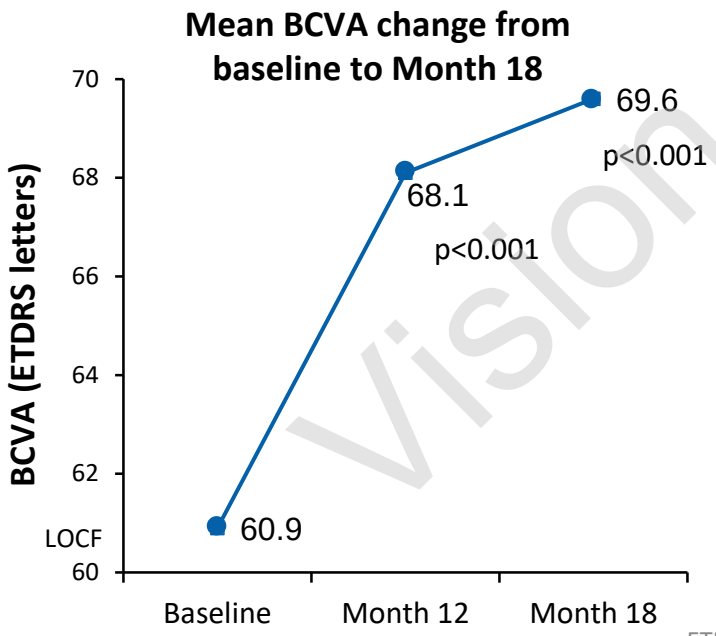
Better outcomes were observed with fixed dosing schedules after 3 initial monthly doses



[a]Monthly visits, [b]Integrated data, [c]Quarterly visits, [d]Cohort 1 ranibizumab-naïve.
VEGF, vascular endothelial growth factor
Lanzetta P *et al. Br J Ophthalmology* 2013; 97:1497-507

VA gains of >7 letters were maintained during T&E phase on aflibercept

- Retrospective study to assess real-life outcomes with aflibercept for the treatment of treatment-naïve neovascular AMD (n=85) in routine clinical practice in Sweden
- BCVA improved significantly in the first year where patients were treated as per the bimonthly licensed posology, and was sustained for 6 months after switching to a T&E regimen



By Month 12 — **+7.2 letters**, 7.7 injections

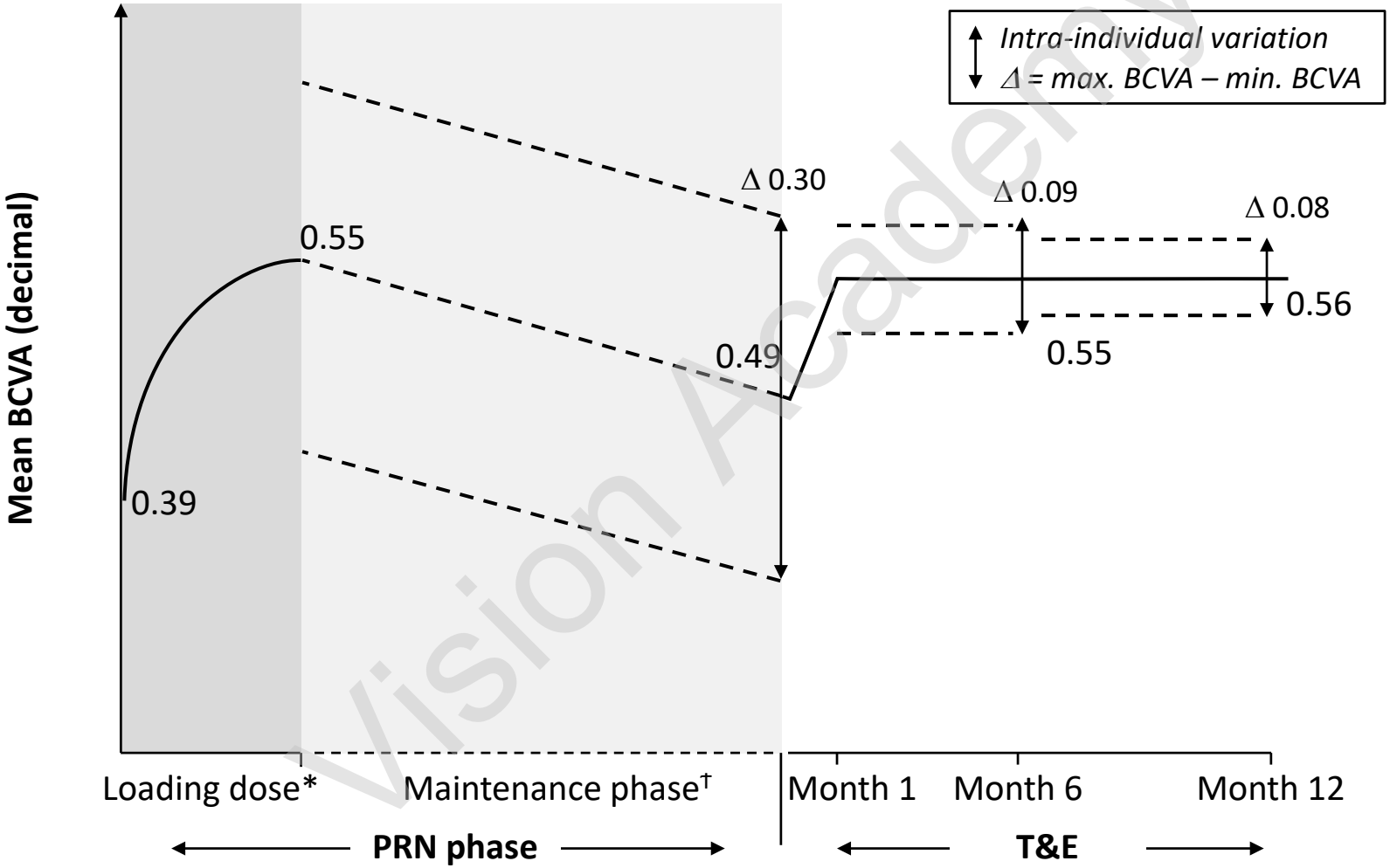
By Month 18 — **+8.7 letters**, 9.9 injections

Approximately 2 injections were administered in the final 6 months of the study while maintaining the 12-month VA gain of 7.2 letters

AMD, age-related macular degeneration; BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; T&E, treat-and-extend; VA, visual acuity

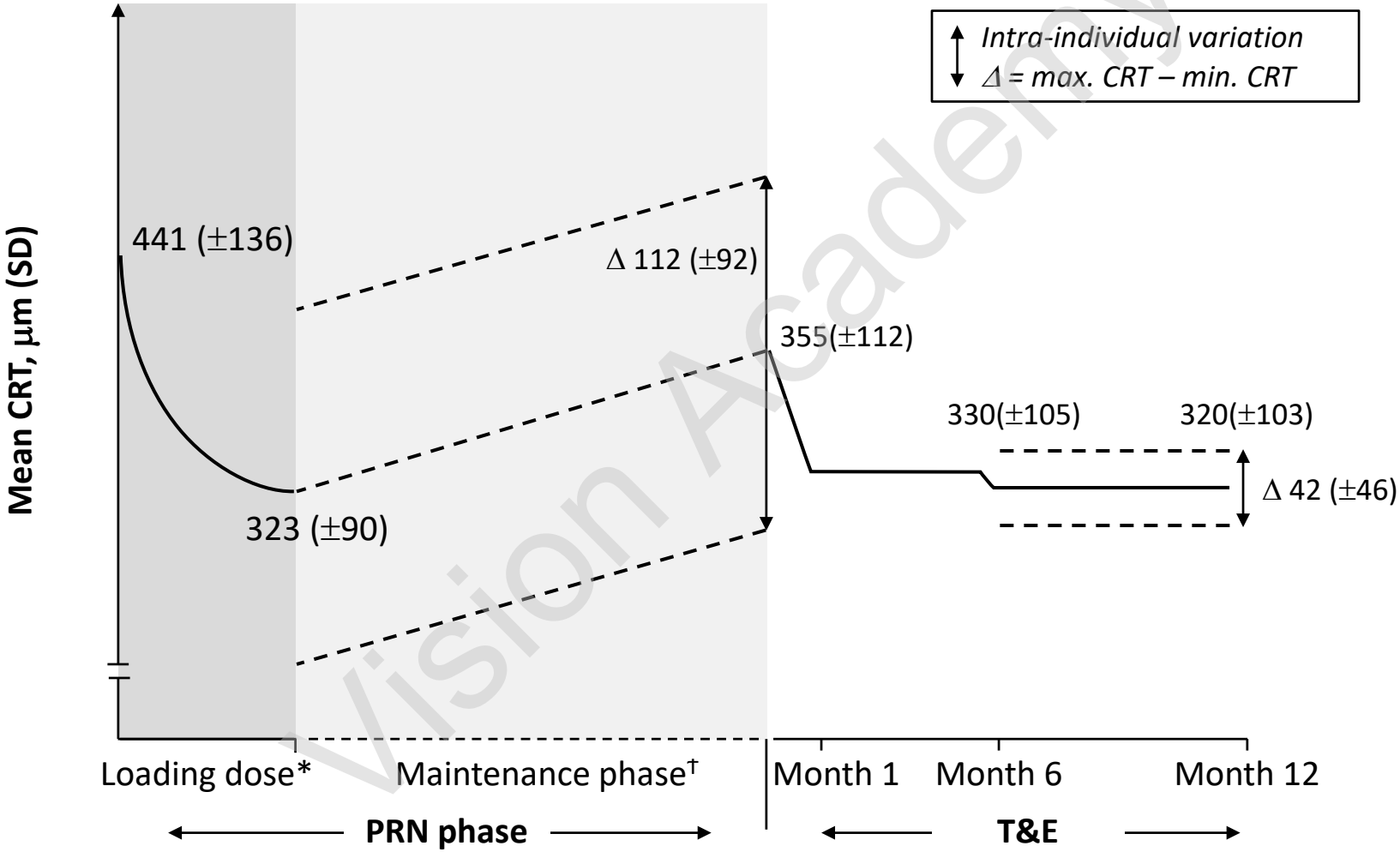
Epstein D *et al. Retina* 2016; 36: 1773-7

Visual gains greater with T&E compared to PRN, with less fluctuation in vision



*Three monthly injections at the 1st three visits; †Mean length of treatment during the PRN maintenance phase was 17 months (range 3–55 months)
BCVA, best corrected visual acuity; PRN, *pro re nata*; T&E, treat-and-extend
Hatz K and Prünte C. *Br J Ophthalmol* 2016; 100: 1341-5

Less fluid, more stable OCT thickness with T&E regimen compared to PRN

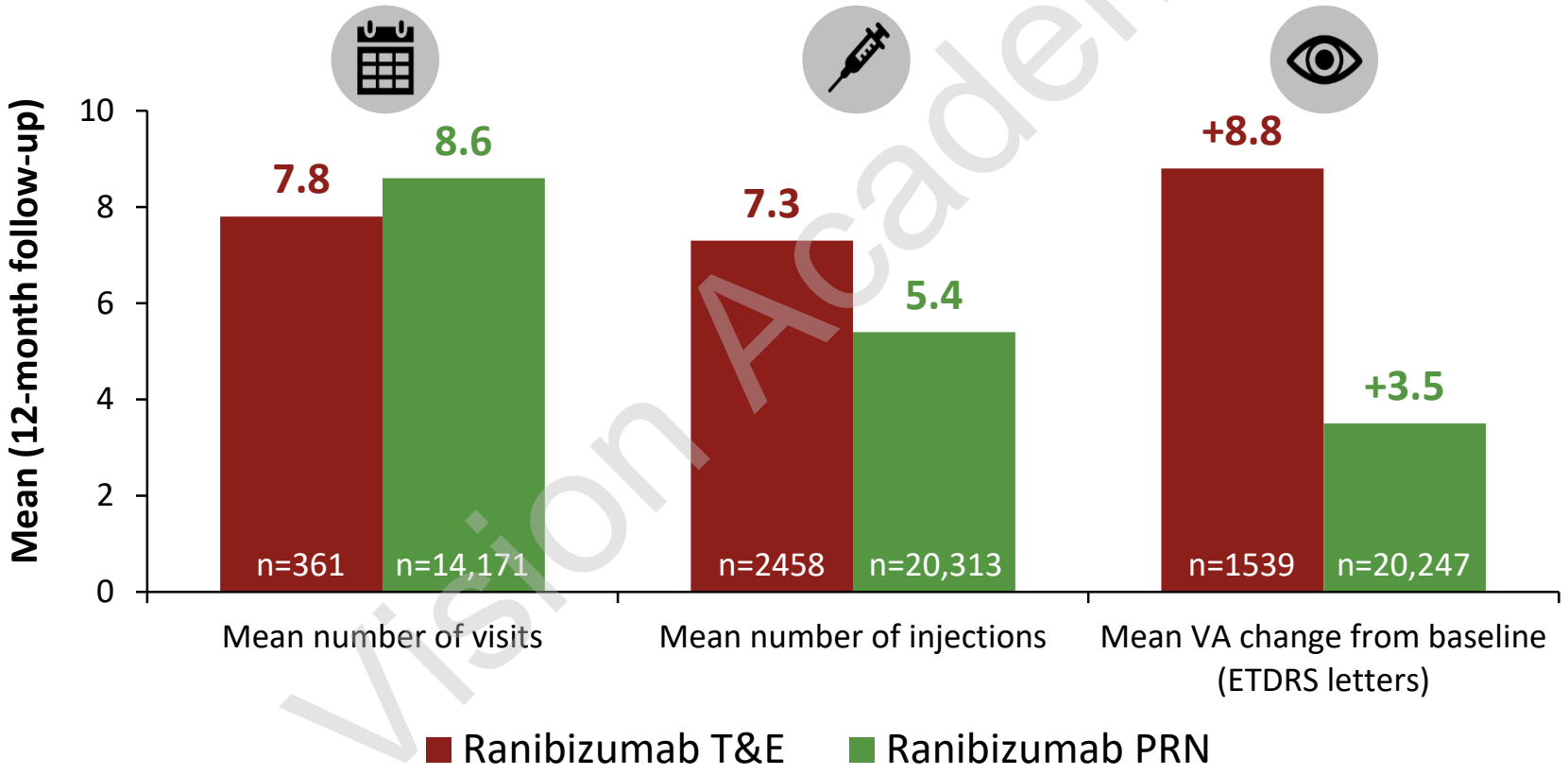


*Three monthly injections at the 1st three visits; †Mean length of treatment during the PRN maintenance phase was 17 months (range 3–55 months)
CRT, central retinal thickness; OCT, optical coherence tomography; PRN, *pro re nata*; SD, standard deviation
Hatz K and Prünte C. *Br J Ophthalmol* 2016; 100: 1341-5

Real-world evidence: PRN limitation due to insufficient visits and injections compared to T&E

Meta-analysis

PRN tends to lead to UNDER-TREATMENT



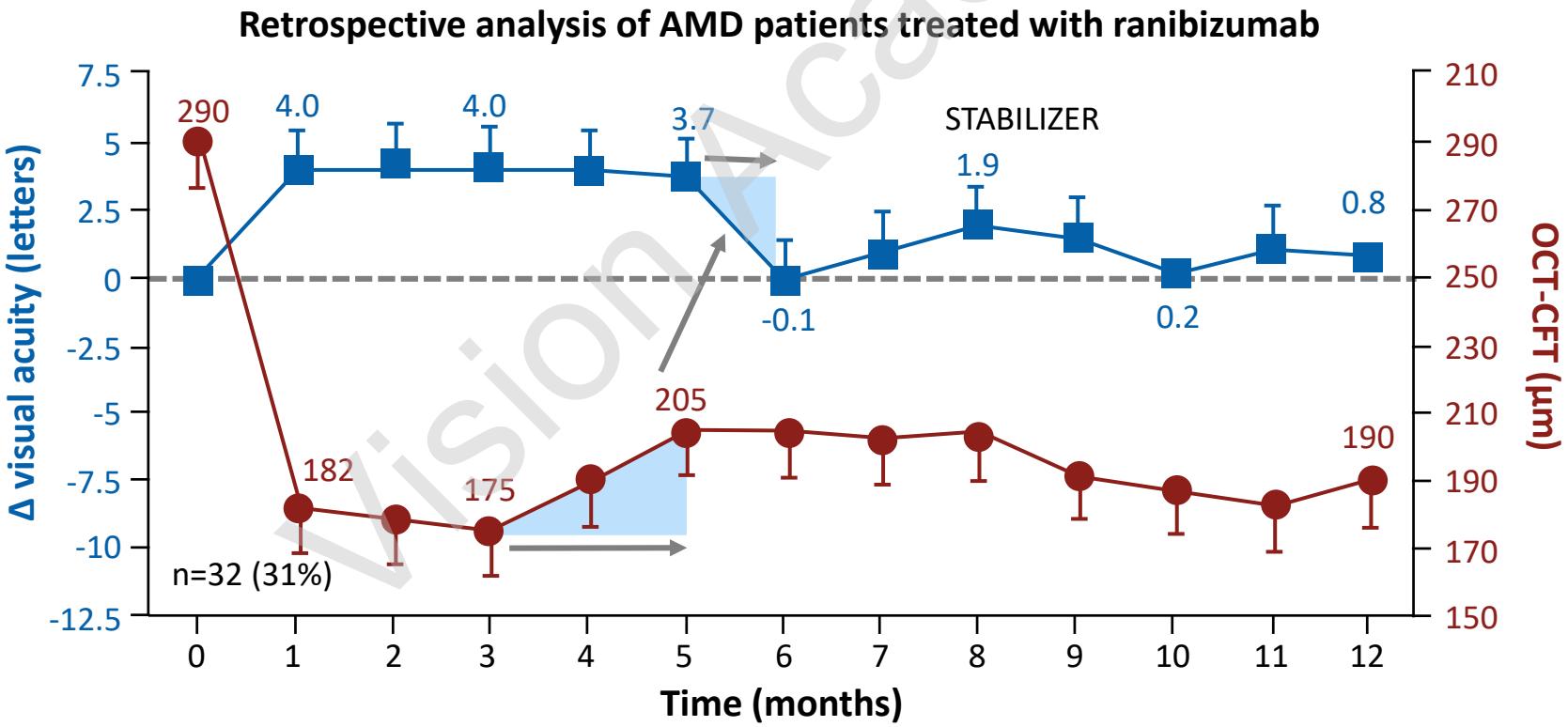
Meta-analysis of ~26,360 patients from 42 real-world observational studies, published between 2007 and 2015, reporting outcomes of intravitreal ranibizumab for nAMD. Random-effects estimate given.

ETDRS, Early Treatment Diabetic Retinopathy Study; nAMD, neovascular age-related macular degeneration; PRN, *pro re nata*; T&E, treat-and-extend; VA, visual acuity.

Kim LN *et al. Retina* 2016; 36: 1418–31

Why do patients on PRN tend to be UNDER-TREATED?

- Less-than-monthly monitoring visits – if patients miss their appointments, visual loss may occur and long-term results are poor
- Patients may feel that they do not need treatment if their vision is still maintained



AMD, age-related macular degeneration; PRN, *pro re nata*; OCT-CFT; optical coherence tomography-central foveal thickness

There is no evidence that proactive treatments result in more GA than reactive treatments

Multivariate analysis of risk factors for GA growth by 5 years among all trial participants

	N	Mean growth rate (mm/yr) (95% CI)	Mean difference (mm/yr) (95% CI)	P value
Drug in first 2 years				
Ranibizumab	108	0.38 (0.32, 0.43)	0.09 (0.02, 0.17)	0.009
Bevacizumab	87	0.28 (0.22, 0.34)	0	
Regimen in first 2 years				
Monthly	55	0.32 (0.25, 0.40)	0.00 (-0.09, 0.10)	0.94
Switch	48	0.32 (0.25, 0.40)	0	
PRN	92	0.34 (0.28, 0.39)	0.01 (-0.07, 0.10)	
Baseline GA in fellow eye				
No	139	0.28 (0.24, 0.33)	0	0.03
Yes	56	0.37 (0.30, 0.44)	0.09 (0.01, 0.17)	
Hemorrhage associated with CNV				
No	56	0.29 (0.22, 0.36)	0	0.049
Yes	139	0.37 (0.32, 0.41)	0.08 (0.00, 0.16)	
Sub-RPE fluid				
None	90	0.40 (0.35, 0.46)	0.14 (0.06, 0.23)	0.003
Not subfoveal	46	0.32 (0.25, 0.39)	0.06 (-0.04, 0.16)	
Subfoveal	59	0.26 (0.19, 0.33)	0	

CI, confidence interval; CNV, choroidal neovascularization; GA, geographic atrophy; PRN, *pro re nata*; RPE, retinal pigment epithelium

Grunwald JE *et al. Ophthalmology* 2017; 124: 97-104

That does not mean that ALL patients require proactive treatment

I prefer T&E in the following situations:

- Aggressive disease needing proactive rather than reactive treatment (e.g., RAP, CNV due to angioid streaks, vascularized PED, large classic CNV)
- Only-eye patients
- Inability to monitor disease frequently (4–6 weekly intervals) and indefinitely (e.g., co-morbidities, foreigners)
- Early recurrent disease: return of disease activity during months 3–5 is critical

CNV, choroidal neovascularisation; PED, pigment epithelial detachment; RAP, retinal angiomatous proliferation; T&E, treat-and-extend

Optimal treatment regimen with anti-VEGF in AMD: proactive

Breakfast Session: Vision Academy Perspectives

AMD, age-related macular degeneration; VEGF, vascular endothelial growth factor

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What is the Vision Academy's position?

The fundamental principles of an anti-VEGF treatment regimen

The Vision Academy has identified four principles that are fundamental to any treatment regimen for anti-VEGF management of retinal diseases

1. Maximize and maintain VA benefits for all patients

2. Decide when to treat next, rather than whether to treat now

3. Titrate the treatment intervals to match patients' needs

4. Treat at each monitoring visit

VA, visual acuity; VEGF, vascular endothelial growth factor.

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The fundamental principles of an anti-VEGF treatment regimen

1. Maximize and maintain VA benefits for all patients

- This principle should be the aim for all patients undergoing anti-VEGF treatment
- The impact on a patient's quality of life of improving and maintaining VA gains should not be underestimated
  - A five-letter gain in VA has been shown to nearly double a patient's ability to read a newspaper, and it increases their ability to drive at night or in difficult conditions[1]
- Early initiation of therapy and a sufficient frequency of injections are both essential for maximizing and maintaining gains in VA[2-5]

VA, visual acuity.

1. Barzey C *et al.* Presentation at the 15th European School for Advanced Studies in Ophthalmology (ESASO) Retina Academy 2015; Barcelona, Spain, October 22–24, 2015. 2. Holz FG *et al. Br J Ophthalmol* 2015; 99 (2): 220–226.
3. Holz FG *et al. Eye* 2016; 30 (8): 1063–1071. 4. Richard G *et al. Ophthalmology* 2015; 122: 2497–2503.
5. Lim JH *et al. Am J Ophthalmol* 2012; 153: 678–686.

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The fundamental principles of an anti-VEGF treatment regimen

2. Decide when to treat next, rather than whether to treat now

- **A proactive approach, where therapy is administered to minimize the risk of disease recurrence, may be necessary in order to stay ahead of the disease**
  - **At each clinic visit, the physician administers treatment and decides when to administer the next injection***

Improves patient experience

- Predictable timing of the next injection
- Knowledge that an injection will be administered at every visit

Improves clinic flow

- Advance planning gives physicians more time to submit the necessary paperwork in health systems where approval is required prior to the next injection

- **Current and emerging data suggest that better VA outcomes can be achieved with T&E versus PRN[1,2]**

*Based on current VA and anatomic status.
PRN, *pro re nata* (as needed); T&E, treat-and-extend; VA, visual acuity.
1. Oubraham H *et al. Retina* 2011; 31 (1): 26–30. 2. Hatz K *et al. Br J Ophthalmol* 2016; Epub ahead of print (DOI: 10.1136/bjophthalmol-2015-307299).

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The fundamental principles of an anti-VEGF treatment regimen

3. Titrate the treatment intervals to match patients' needs

- **The duration of VEGF suppression varies between patients and differs between anti-VEGF agents:**

36 **Ranibizumab 0.5 mg** has been shown to suppress VEGF in the eyes of nAMD patients for a mean duration of **36 days**[1]

71 **Aflibercept 2 mg** suppresses intraocular VEGF in nAMD patients for a mean duration of **71 days**[2]

x2 A recent study by Fauser and Muether (2016) revealed that in nAMD patients who switched from ranibizumab to aflibercept treatment, the VEGF suppression time was **two times greater** with aflibercept than with ranibizumab[3]

- **Treatment should be personalized to the patient's individual needs, with consideration of the VEGF suppression time of the agent used**

nAMD, neovascular age-related macular degeneration; VEGF, vascular endothelial growth factor.

1. Muether PS *et al. Am J Ophthalmol* 2013; 156 (5): 989–993.e2. 2. Fauser S *et al. Am J Ophthalmol* 2014; 158 (3): 532–536. 3. Fauser S, Muether PS*. Br J Ophthalmol* 2016; Epub ahead of print (DOI: 10.1136/bjophthalmol-2015-308264).

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The fundamental principles of an anti-VEGF treatment regimen

4. Treat at each monitoring visit

- **Elimination of any delay between patient assessment and treatment minimizes the risk of unidentified disease recurrence**
- **A reduction in the number of appointments per patient will also have a positive impact on clinic flow**
  - **Scheduling one appointment for both monitoring and treatment should:**

Make it easier for patients to manage travel to and from the clinic; this is particularly important for those who have to travel long distances or who require assistance

Help ease some of the burden on the clinic and thus improve clinic flow

Help alleviate patients' fear of disease recurrence through the adoption of a proactive approach and the knowledge that treatment will not be delayed[1]

1. Droege KM *et al. Graefes Arch Clin Exp Ophthalmol* 2013; 251 (5): 1281–1284.

Further considerations: Practical barriers

- **For maximum applicability across different health systems, the Vision Academy's principles were developed without consideration of resource limitations or practical barriers**

Payers and other stakeholders require further evidence

- For widespread adoption of a T&E approach, as outlined by the fundamental principles, payers and other stakeholders require further evidence of the advantages of this regimen
  - Reimbursement is a significant obstacle in many Asia-Pacific and Latin American countries, as well as some European countries

There is a lack of consensus on treatment criteria

- Other barriers to the adoption of the principles might be:
  - The lack of consensus on criteria for disease stability and stopping treatment
  - Uncertainty regarding appropriate monitoring procedures

T&E, treat-and-extend.

Summary

- The fundamental principles identified were:

1. Maximize and maintain visual acuity benefits for all patients

2. Decide when to treat next, rather than whether to treat now

3. Titrate the treatment intervals to match patients' needs

4. Treat at each monitoring visit

- These principles support the adoption of a predictable, proactive, and manageable treatment regimen with consideration of individual patient needs and minimization of delays in treatment
- A treat-and-extend approach, as outlined by these principles, is supported by the Vision Academy as the treatment regimen of choice in retinal disease

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Further reading

The Viewpoint ‘Fundamental principles of an anti-VEGF treatment regimen’ can be downloaded from:

www.visionacademy.org

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