VISION ACADEMY

people | research | education

Discussion and debate:

Optimal treatment regimen with anti-VEGF

Reactive: Mr James Talks

Proactive: Professor Francesco Bandello

Presentation of viewpoint: Professor Paolo Lanzetta

The Vision Academy is sponsored by Bayer. This presentation has been developed independently by Vision Academy members and does not necessarily reflect the views of Bayer. This presentation reflects the views of a majority of Vision Academy members; individual views may vary. The Vision Academy Steering Committee comprises Bora Eldem, Alex Hunyor, Antonia M. Joussen, Adrian Koh, Jean-François Korobelnik, Paolo Lanzetta, Anat Loewenstein, Monica Lövestam-Adrian, Rafael Navarro, Lihteh Wu, Annabelle A. Okada, Ian Pearce, Francisco J. Rodríguez, Sebastian Wolf, and David Wong.

Session aims

- To debate and discuss evidence for a ‘reactive’ versus a ‘proactive’ anti-VEGF therapeutic regimen
- To provide a summary of the Vision Academy’s Viewpoint on the optimal treatment regimen with anti-VEGF
  - The Viewpoint can be found in your symposium pack

VISION ACADEMY
people | research | education

VEGF, vascular endothelial growth factor.

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

Mr James Talks

Royal Victoria Infirmary,
Newcastle Upon Tyne, UK

Financial and other disclosures

I have the following financial interests or relationships to disclose	Disclosure code
Allergan	S
Bayer	C, L, S
Boehringer Mannheim	S
Optos	C
Heidelberg Engineering	C, S
Novartis Pharmaceuticals Corporation	S

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

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. Pedersen KB *et al. Retina* 2010; 30: 1025–1033.

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 *et al. 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.

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

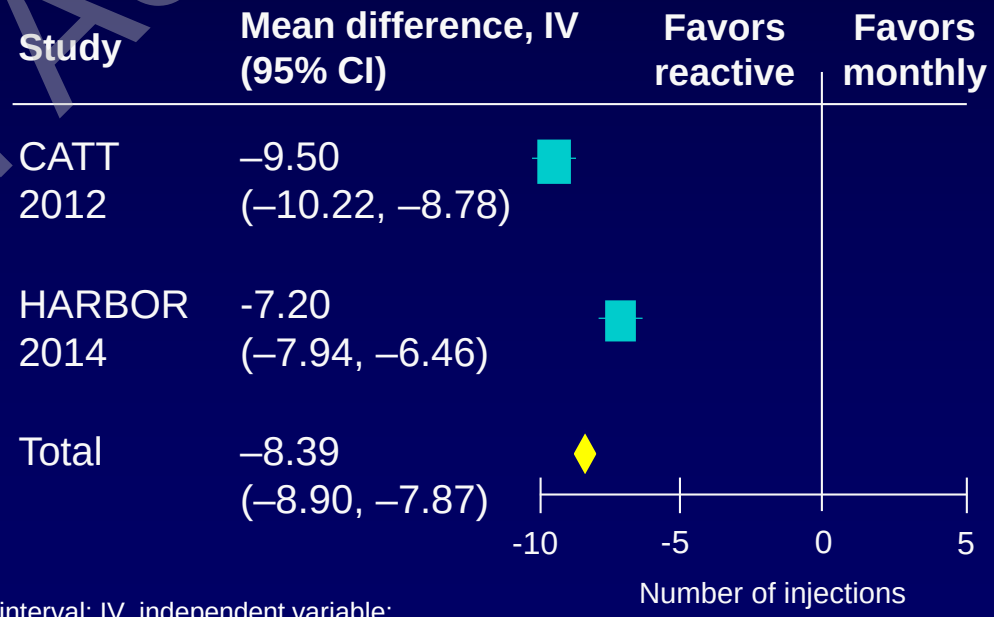
IVT, intravitreal.

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

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]



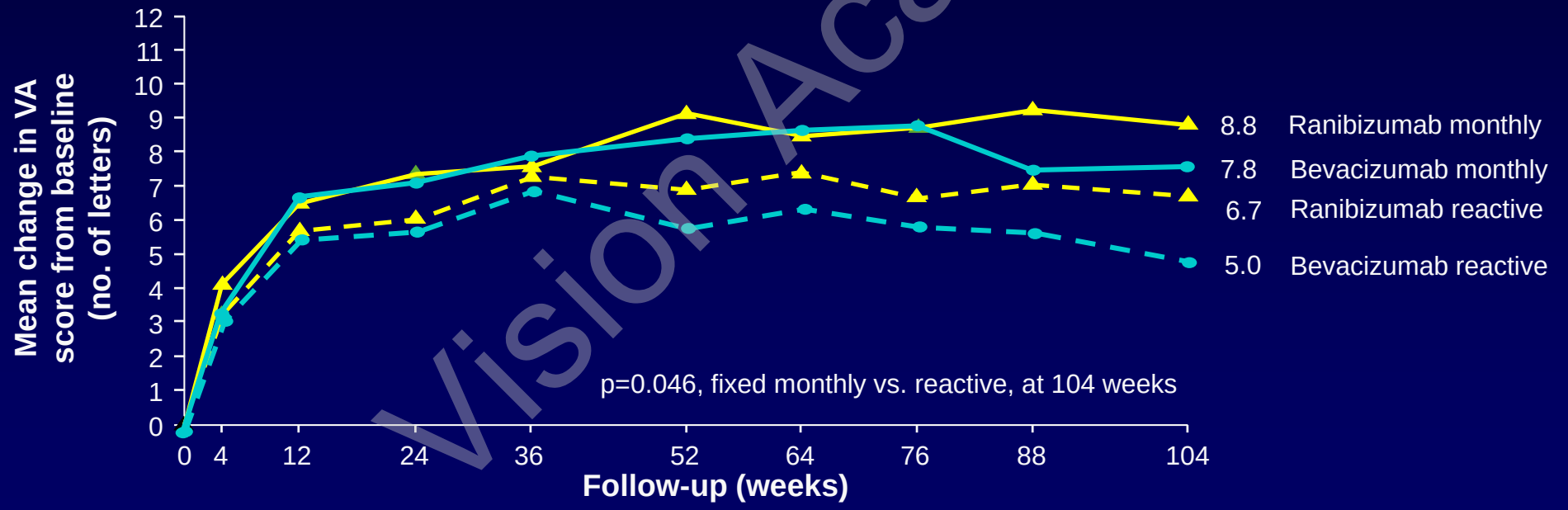
CATT, Comparison of Age-Related Macular Degeneration Treatments Trials; CI, confidence interval; IV, independent variable; nAMD, neovascular age-related macular degeneration.

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.

VISION ACADEMY
people | research | education

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.

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

VISION ACADEMY
people | research | education

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

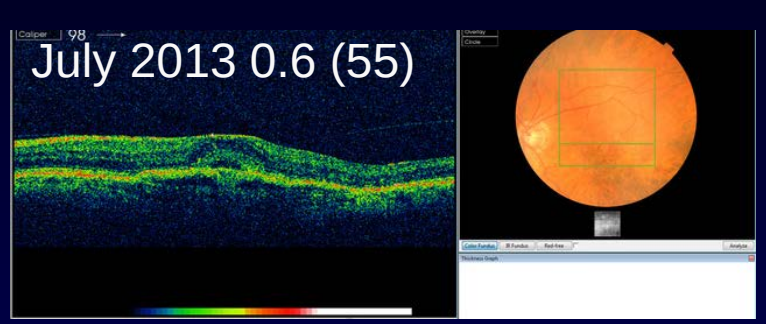
- **Retrospective comparisons of reactive and T&E regimens are inconclusive:**
  - **In nAMD, no strong differences in anatomical and functional improvements were observed[1]**
  - **Poor performance of reactive regimens in real-world studies has been attributed to a low mean number of injections and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

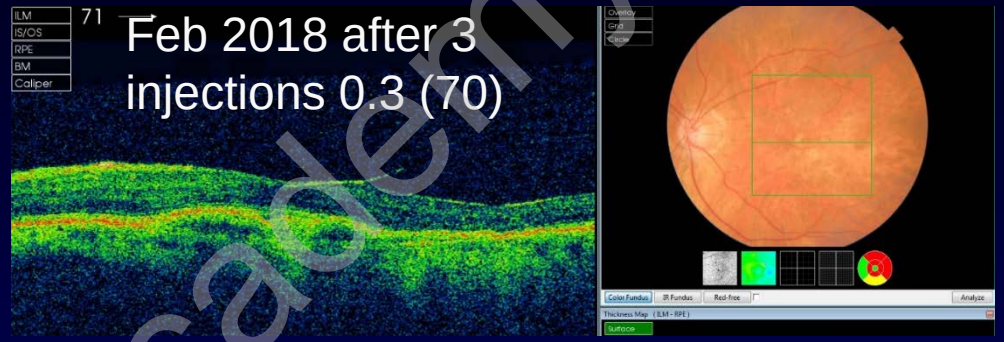
nAMD, neovascular age-related macular degeneration; T&E, treat-and-extend; VA, visual acuity.

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

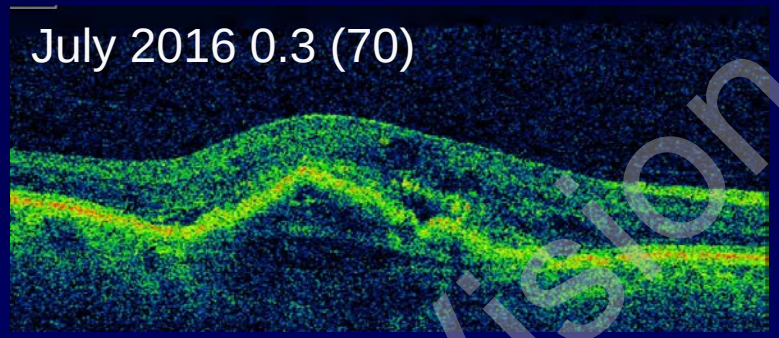
2013: 89-year-old female

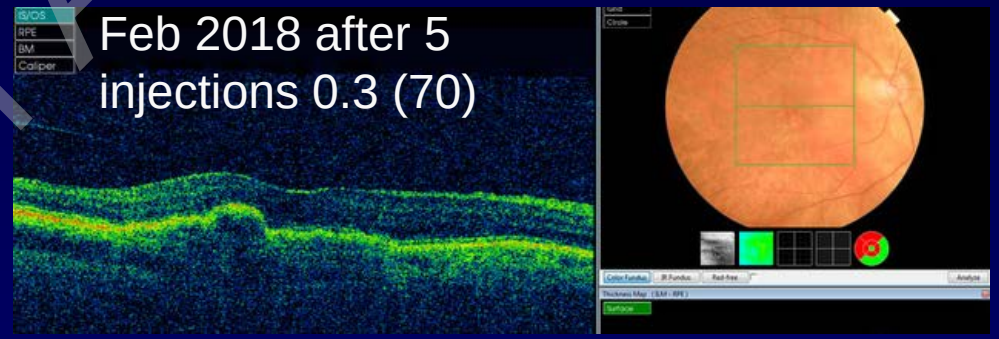
Left eye





Right eye





Now aged 93 years: 4.5 years since first treatment,
vision maintained with 3 injections in left eye and 5 in right eye

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

Clinically meaningful improvements in VA

Increased injection frequency

Patient burden

Financial burden

IVT, intravitreal; VA, visual acuity.

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

VISION ACADEMY
people | research | education

Optimal treatment regimen with anti-VEGF in AMD: Proactive

Francesco Bandello, MD, FEBO

Professor and Chair, Department of Ophthalmology,
University Vita-Salute, Scientific Institute San Raffaele, Milan, Italy

VISION ACADEMY
people | research | education

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

Financial and other disclosures

I have the following financial interests or relationships to disclose	
Alcon	
Allergan	
Bayer	
Boehringer Mannheim	
Hoffmann-La Roche	Advisory board member
Carl Zeiss Meditec	
Novartis Pharmaceuticals Corporation	
NTC Pharma	
Sifi	
Sooft	
ThromboGenics	

Anti-VEGF treatment regimens in AMD

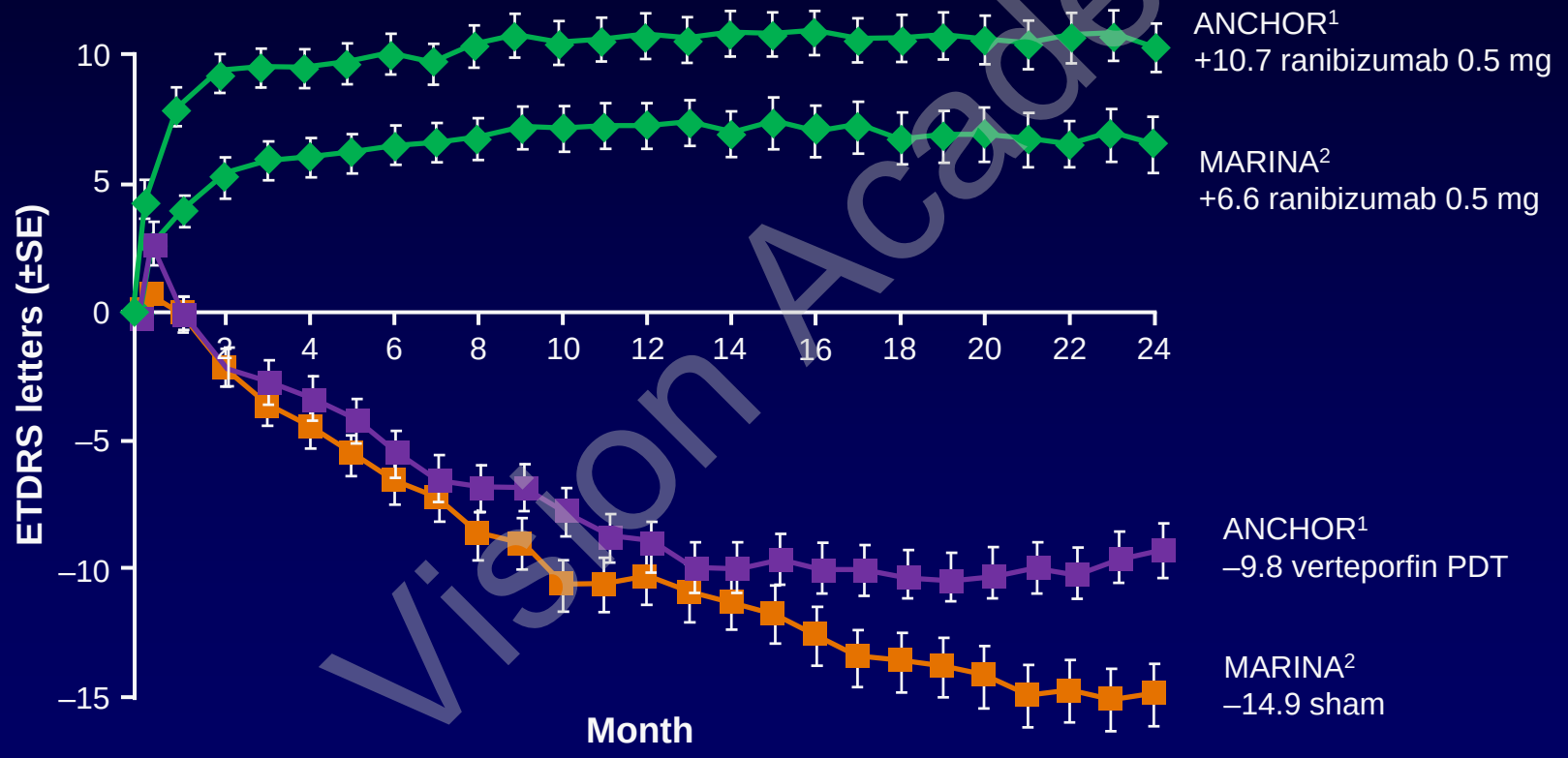
PROACTIVE	REACTIVE
➢ **Fixed dosing** – **Monthly[1-3] or quarterly[4]** ➢ **Treat-and-extend**	➢ ***Pro re nata* (PRN): as needed** – **Monthly visits[3,5-6]** – **Extended visits[7-8]** – **Treat-to-target**

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. Regillo CD *et al*. *Am J Ophthalmol* 2008; 145: 239–248. 5. Lalwani GA *et al*. *Am J Ophthalmol* 2009; 148: 43–58.e1. 6. Holz FG *et al*. *Ophthalmology* 2011; 118: 663–671; 7. Schmidt-Erfurth U *et al*. *Ophthalmology* 2011; 118: 831–839. 8. Boyer DS *et al*. *Ophthalmology* 2009; 116: 1731–1739.

Optimal ≠ perfect

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



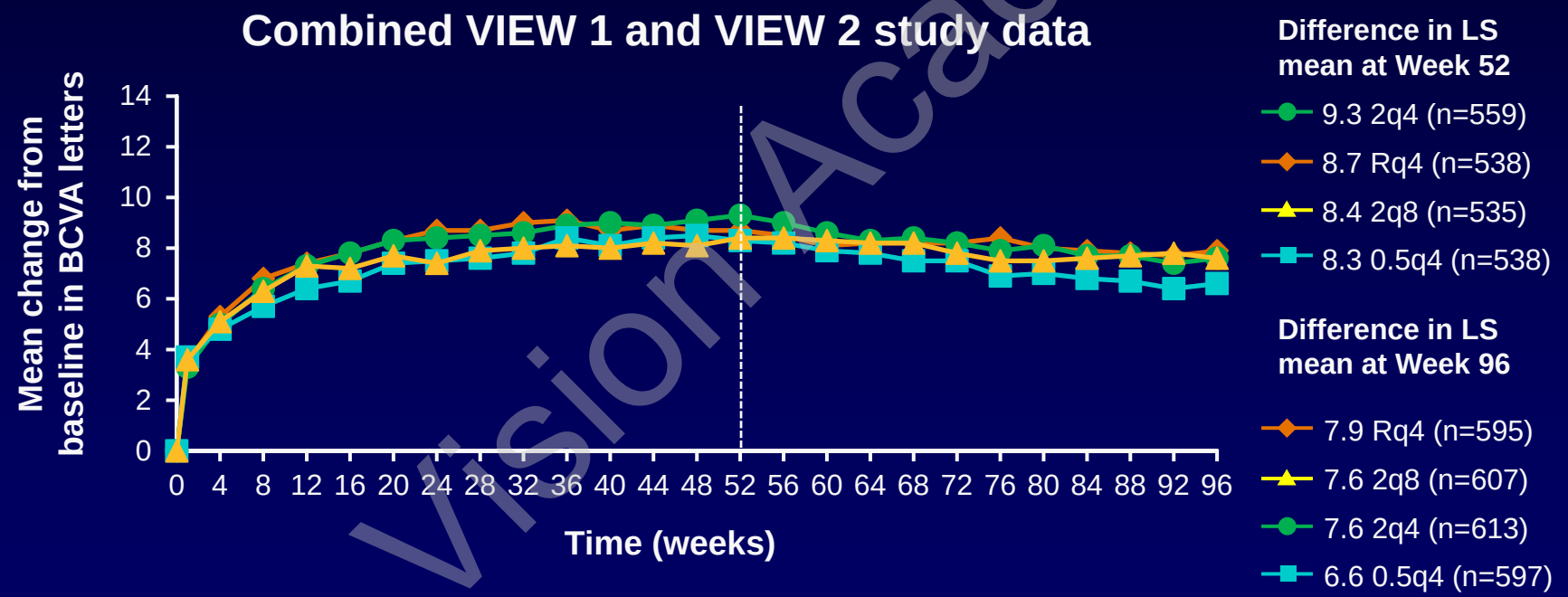
ETDRS, Early Treatment Diabetic Retinopathy Study; nAMD, neovascular age-related macular degeneration; PDT, photodynamic therapy; SE, standard error.

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

VISION ACADEMY
people | research | education

VIEW: fixed dosing with aflibercept q8 achieved optimal results

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



0.5q4, aflibercept 0.5 mg every 4 weeks; 2q4, aflibercept 2 mg every 4 weeks; 2q8, aflibercept 2 mg every 8 weeks; 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.

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

PRN re-treatment criteria: ALL REQUIRED MONTHLY MONITORING!

PRONTO (n=40)

- **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
- Re-treatment 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**

SUSTAIN (n=513)

- 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**

SAILOR cohort I (n=2378)

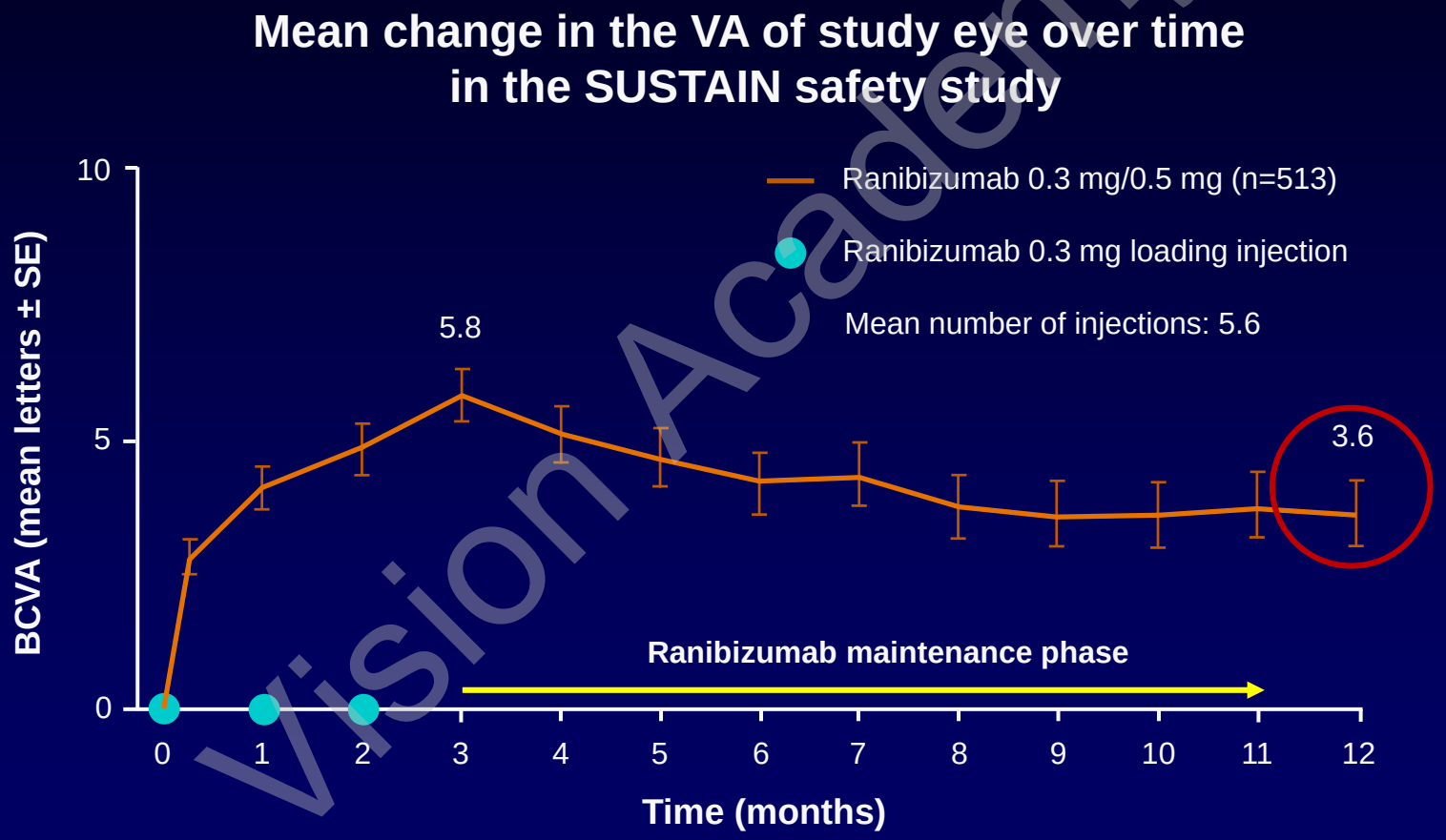
- A 100 µm increase in CRT from the thinnest measurement recorded at any prior scheduled study visit
- Decreased VA >5 letters compared with any prior scheduled study visit
- **Mean change from baseline in BCVA at 12 months: +2.3 letters**

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* (as needed); VA, visual acuity.

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

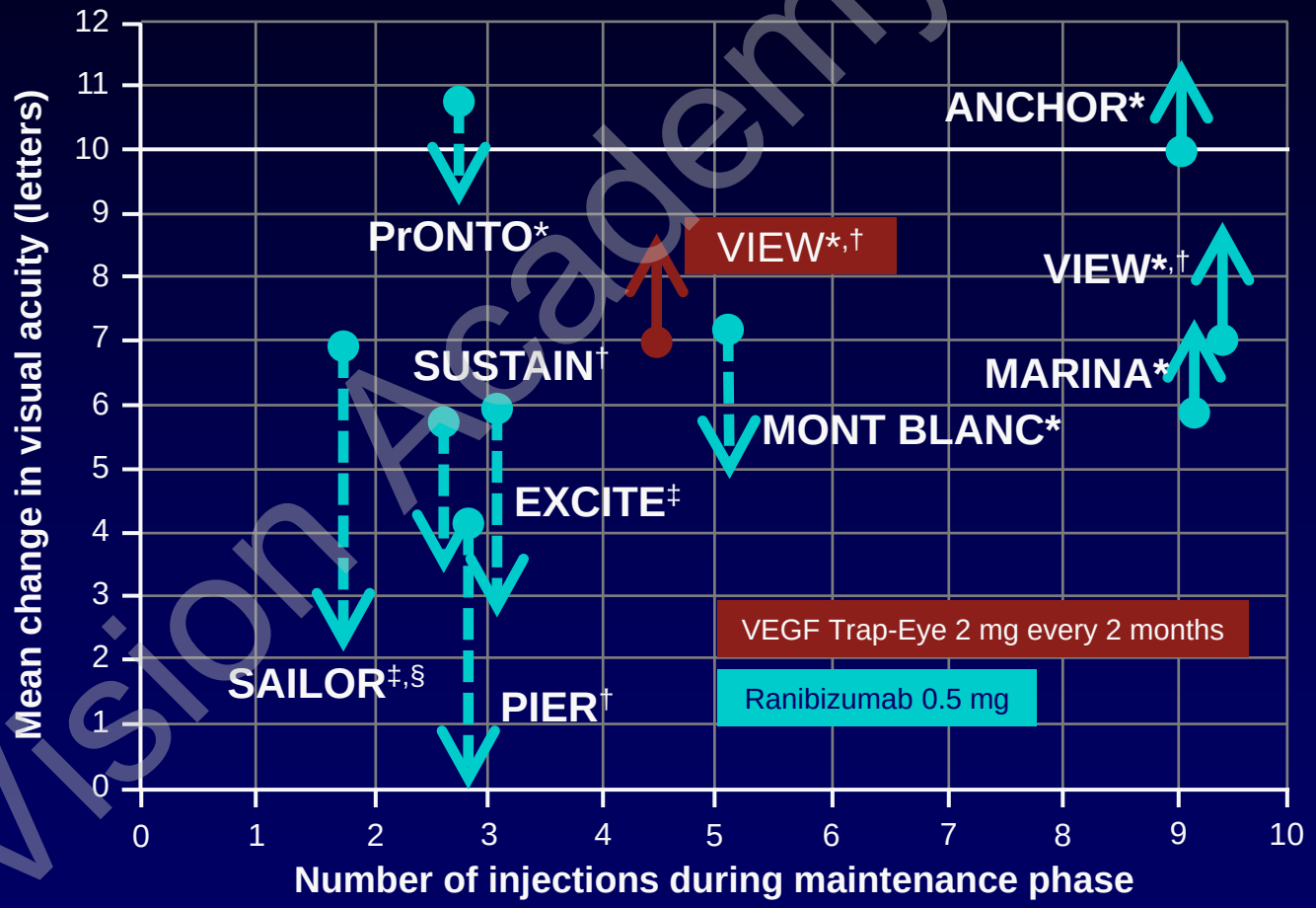


BCVA, best corrected visual acuity; SE, standard error; VA, visual acuity.

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

The simple fact is: visual outcomes correlate with number of injections

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

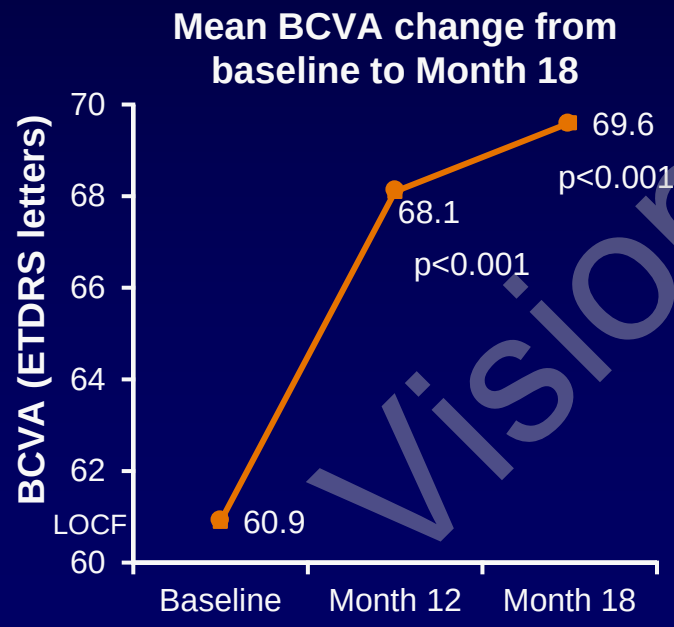


*Monthly visits; †Integrated data; ‡Quarterly visits; §Cohort 1 ranibizumab-naïve.
VEGF, vascular endothelial growth factor.
Lanzetta P *et al*. *Br J Ophthalmol* 2013; 97: 1497–1507.

VISION ACADEMY
people | research | education

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 when patients were treated as per the bimonthly licensed posology, and the improvement 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 two 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; LOCF, last observation carried forward; T&E, treat-and-extend; VA, visual acuity.

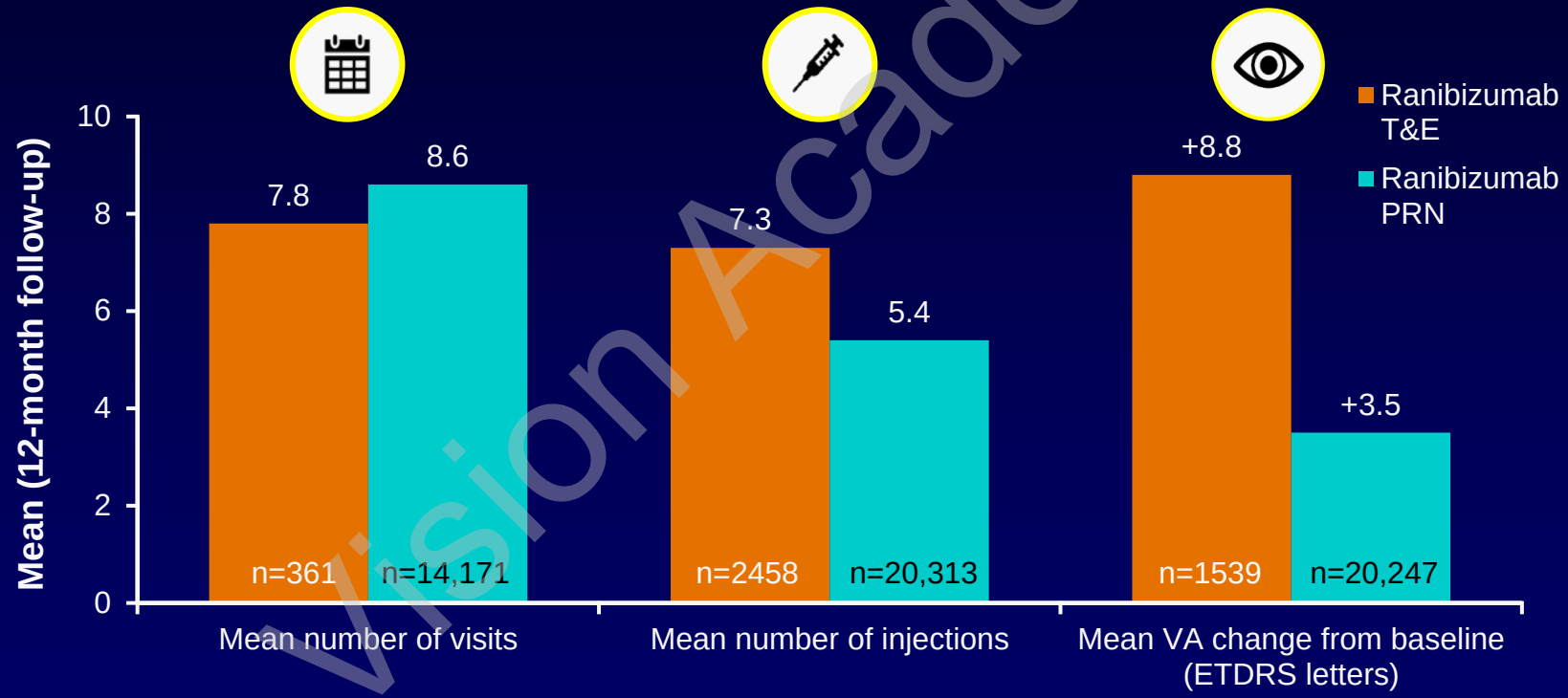
Epstein D, Amrén U. *Retina* 2016; 36: 1773–1777.

VISION ACADEMY
people | research | education

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* (as needed); T&E, treat-and-extend; VA, visual acuity.

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

VISION ACADEMY
people | research | education

However, 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 neovascularization; PED, pigment epithelial detachment; RAP, retinal angiomatous proliferation; T&E, treat-and-extend.

Optimal treatment regimen with anti-VEGF in AMD: <u>proactive</u>

VISION ACADEMY
people | research | education

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

VISION ACADEMY

people | research | education

What is the Vision Academy's position?

Professor Paolo Lanzetta

University of Udine, Italy

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

VISION ACADEMY
people | research | education

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

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.

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).

VISION ACADEMY
people | research | education

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[1-3]
- 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).

VISION ACADEMY
people | research | education

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

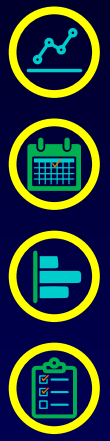
Help alleviate patients' fear of disease recurrence through the adoption of a proactive approach and the knowledge that treatment will not be delayed[1]

VISION ACADEMY
people | research | education

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

Summary

- The fundamental principles identified were:



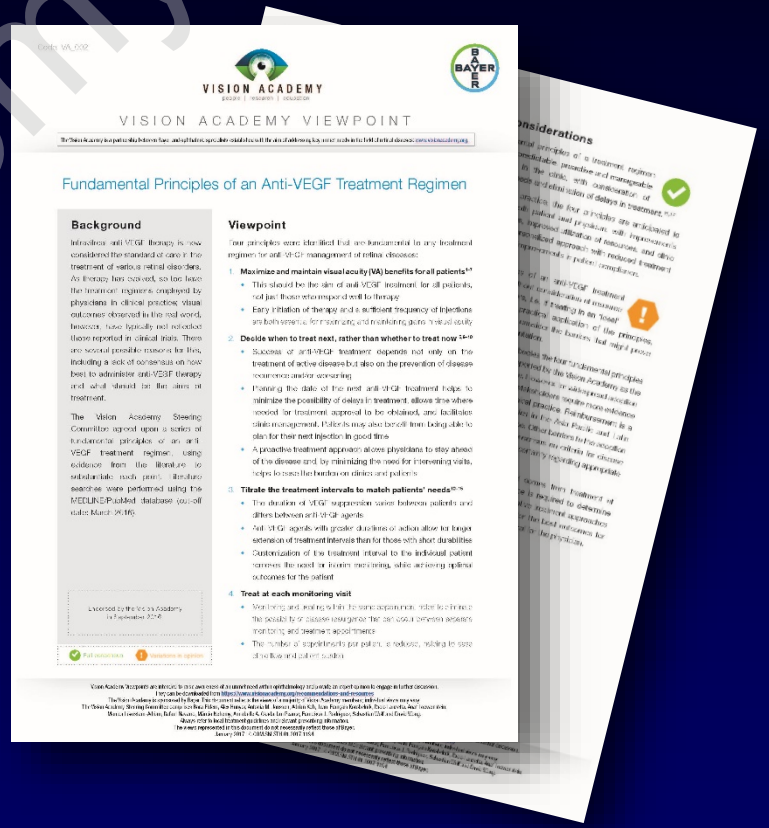
1. Maximize and maintain visual acuity benefits for all patients
2. Decide when to treat next, rather than whether to treat now
3. Titrate the treatment intervals to match patients' needs
4. Treat at each monitoring visit

- 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

Further reading

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

www.visionacademy.org



VISION ACADEMY
people | research | education