VISION ACADEMY

people | research | education

Diabetic eye disease: A treatable complication of diabetes

Mr. Ian Pearce

Royal Liverpool University Hospital, UK

Vision Academy

Date of preparation: September 2017 | G.MKT.SM.STH.09.2017.1464 | UKMED08170246a | L.PT.MKT.09.2017.1622

The Vision Academy is an educational initiative that is fully funded by Bayer.

BAYER

Financial disclosures

- Honoraria / advisory boards / consultant for:
  - Alcon
  - Bayer
  - Novartis
  - Roche

Vision Academy

What do diabetologists need to know about diabetic eye disease?

- The terminology and methods used by ophthalmologists when assessing patients with diabetic eye disease
- The key stages in the progression of diabetic eye disease
- The patients most at risk of significant disease worsening and visual impairment
- The importance of gains in vision on the quality of life of patients with diabetic eye disease
- The factors for determining treatment choice in patients with diabetic eye disease
- That intravitreal anti-VEGF therapy facilitates visual improvement and regression of retinopathy[1]

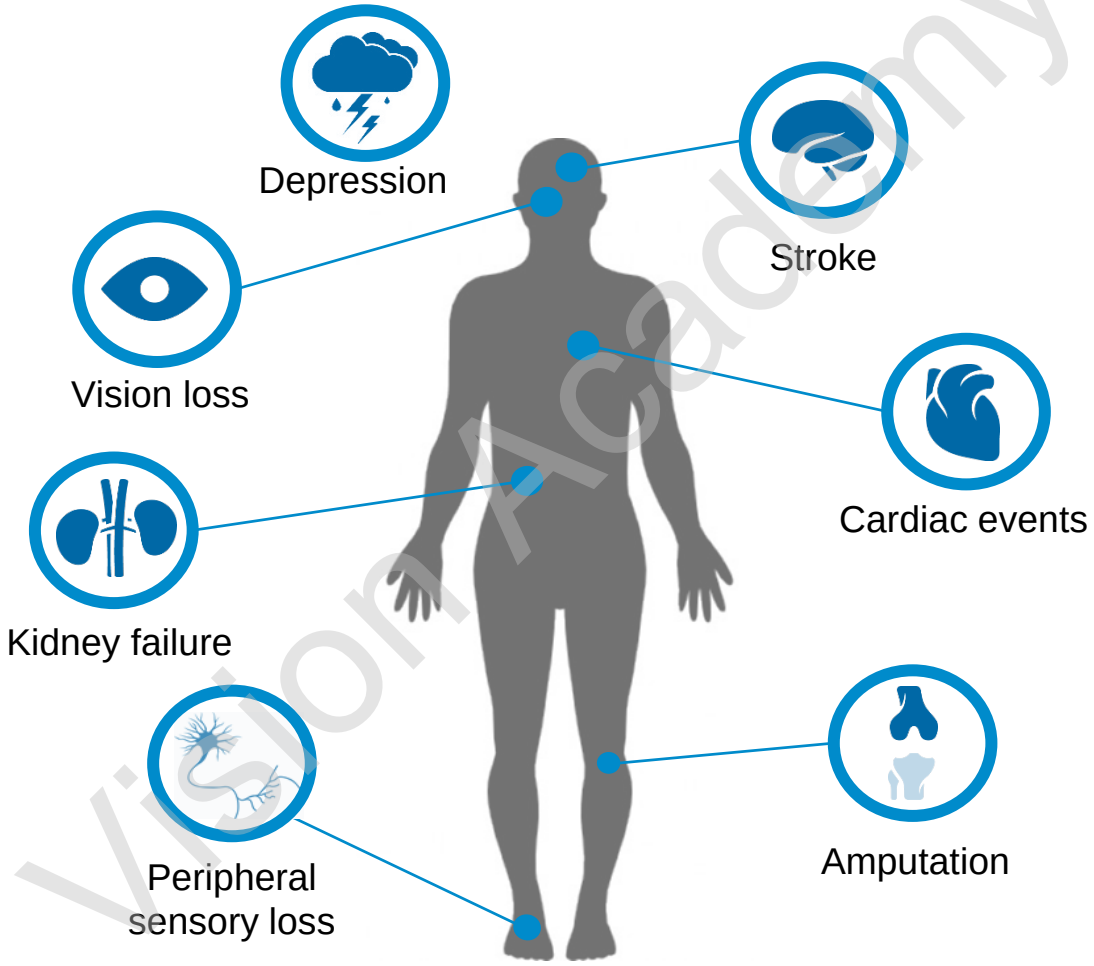
Vision Academy

VEGF, vascular endothelial growth factor.

1. Heier JS *et al. Ophthalmology* 2016; 123 (11): 2376–2385.

VISION ACADEMY

Diabetes can result in a range of serious health consequences



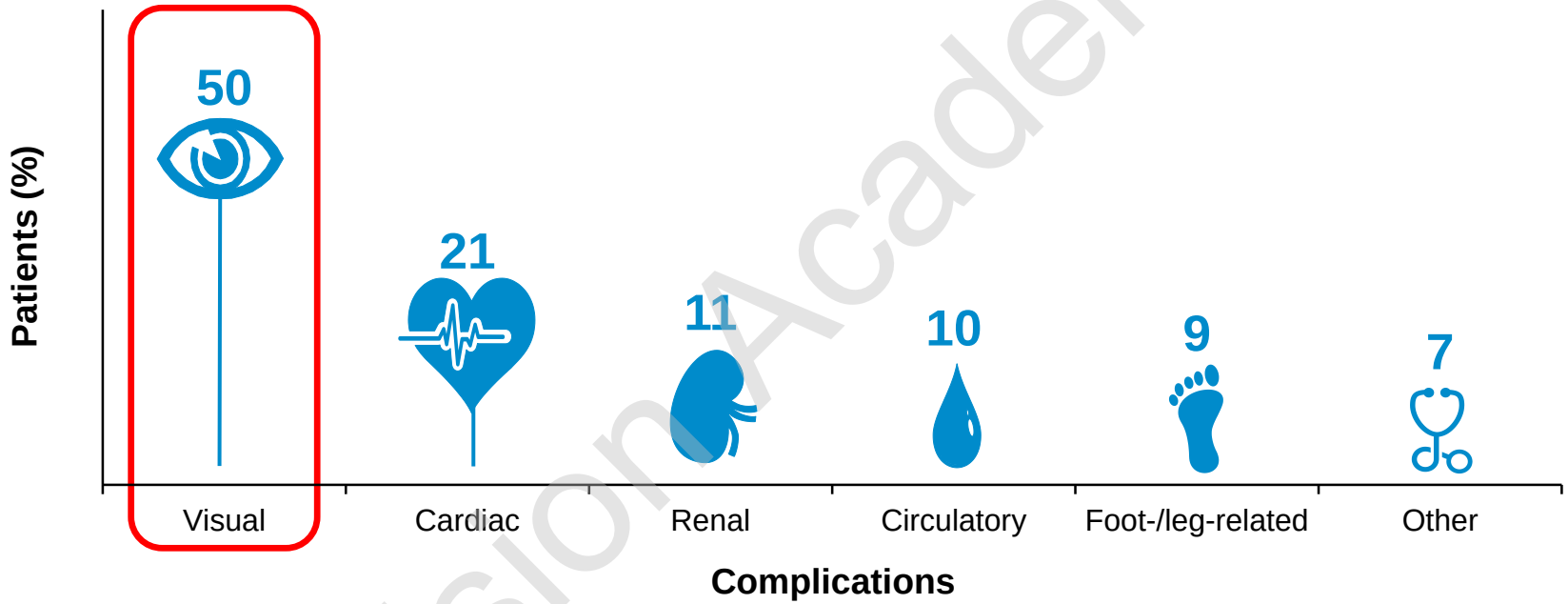
Vision Academy

Facts and stats (Oct 2016). Available at: www.diabetes.org.uk/Professionals/Position-statements-reports/Statistics/. Accessed September 2017.
Stino A *et al. J Diabetes Investig* 2017; 8 (5): 646–655.
Diabetes. Available at: www.who.int/mediacentre/infographic/diabetes/en. Accessed September 2017.

VISION ACADEMY

Vision loss is the most-feared complication of diabetes among patients

- Complications that patients (n=206) were most concerned with at the time of diabetes diagnosis:[1]



- **Diabetic retinopathy** is the most common cause of vision loss in patients with diabetes, and is a leading cause of blindness among working-age adults[2–4]

Vision Academy

1. Strain WD *et al*. *Diabetes Res Clin Pract* 2014; 105 (3): 302–312. 2. The Silver Book: Diabetic Retinopathy; 2016. Available at: http://www.silverbook.org/publication/diabetic-retinopathy. Accessed September 2017. 3. Facts about diabetic eye disease. Available at: https://nei.nih.gov/health/diabetic/retinopathy. Accessed September 2017.
4. Zheng Y *et al. Indian J Ophthalmol* 2012; 60 (5): 428–431.

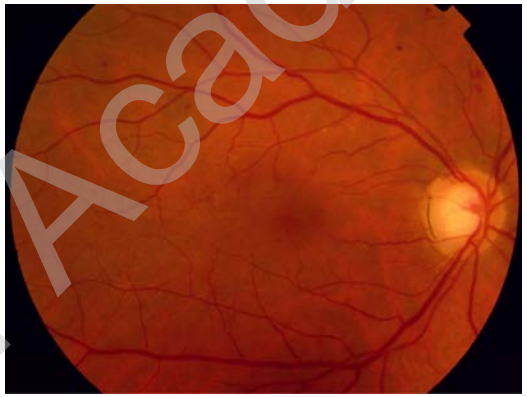
VISION ACADEMY

Assessment of diabetic eye disease

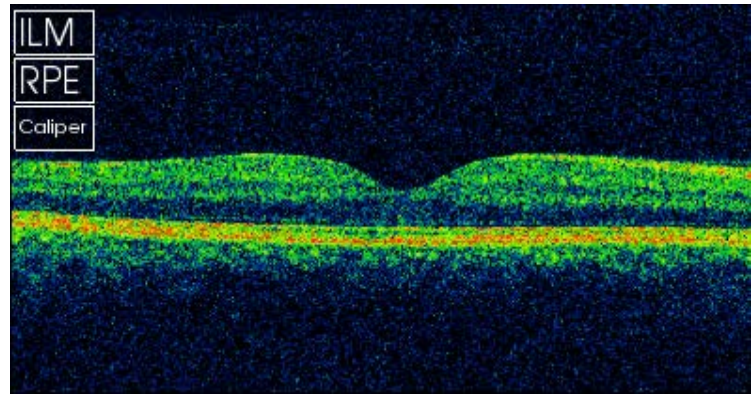
- **Visual acuity** is measured according to the size of letters that can be viewed on a standardized chart at various distances[1]

Standard ETDRS chart

- A range of **imaging techniques** are routinely employed by ophthalmologists when screening for diabetic eye disease, including:



Fundus photography



Optical coherence tomography (OCT)

Diagnosis

Vision Academy

ETDRS, Early Treatment Diabetic Retinopathy Study; OCT, optical coherence tomography.

1. Facts about diabetic eye disease. Available at: https://nei.nih.gov/health/diabetic/retinopathy. Accessed September 2017.

VISION ACADEMY

Assessment of diabetic eye disease

Diagnosis

- **Diabetic retinopathy (DR)** is a term describing **microvascular abnormalities** in the retina of patients with diabetes[1]
- **Diabetic macular edema (DME)** is a manifestation of DR, characterized by **accumulation of fluid** from leaking blood vessels in the central portion of the retina[1,2]

Stages of DR
(Increasing level of severity)

Background

Vision Academy

DME, diabetic macular edema; DR, diabetic retinopathy.

1. Schmidt-Erfurth U *et al. Ophthalmologica* 2017; 237 (4): 185–222.
2. Facts about diabetic eye disease. Available at: https://nei.nih.gov/health/diabetic/retinopathy. Accessed September 2017

VISION ACADEMY

Assessment of diabetic eye disease

- **Diabetic retinopathy (DR)** is a term describing **microvascular abnormalities** in the retina of patients with diabetes[1]
- **Diabetic macular edema (DME)** is a manifestation of DR, characterized by **accumulation of fluid** from leaking blood vessels in the central portion of the retina[1,2]

Stages of DR
(Increasing level of severity)

Vision Academy

DME, diabetic macular edema; DR, diabetic retinopathy.

1. Schmidt-Erfurth U *et al. Ophthalmologica* 2017; 237 (4): 185–222.
2. Facts about diabetic eye disease. Available at: https://nei.nih.gov/health/diabetic/retinopathy. Accessed September 2017

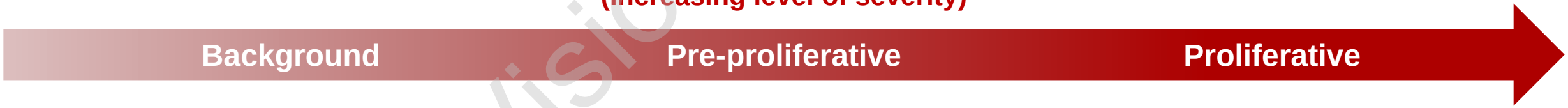
VISION ACADEMY

Assessment of diabetic eye disease

Diagnosis

- **Diabetic retinopathy (DR)** is a term describing **microvascular abnormalities** in the retina of patients with diabetes[1]
- **Diabetic macular edema (DME)** is a manifestation of DR, characterized by **accumulation of fluid** from leaking blood vessels in the central portion of the retina[1,2]

Stages of DR
(Increasing level of severity)



Vision Academy

DME, diabetic macular edema; DR, diabetic retinopathy.

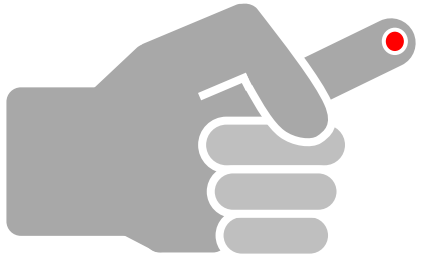
1. Schmidt-Erfurth U *et al. Ophthalmologica* 2017; 237 (4): 185–222.
2. Facts about diabetic eye disease. Available at: https://nei.nih.gov/health/diabetic/retinopathy. Accessed September 2017

VISION ACADEMY

Loss of vision can greatly affect the ability of patients to perform everyday activities

- The **DR Barometer Study** was conducted across 41 countries worldwide
  - 4,340 adults with diabetes and 2,329 healthcare professionals provided information about experiences of living with, managing and treating diabetes, DR and DME
  - Of respondents with vision loss due to DR or DME:

79% said that their condition made everyday activities (such as driving, working, and completing household tasks) difficult to perform



20% said that their condition made it difficult to manage their diabetes

Vision Academy

DME, diabetic macular edema; DR, diabetic retinopathy.
DR Barometer Report: Global findings. Available at: http://drbarometer.com/. Accessed September 2017.

VISION ACADEMY

5-letter gains in vision provide clinically meaningful results for the patient

- It is important to determine when an improvement in vision becomes clinically meaningful
- 5-letter gains in vision have been shown to significantly increase the ability of patients to:[1]

Read print in newspapers

Drive at night

Drive under difficult conditions

- Visual acuity in the better-seeing eye is a major contributor to health-related quality of life[2]
  - Visual acuity in the worse-seeing eye is also important, though to a lesser extent

Vision Academy

1. Barzey V *et al*. Abstract and poster presented at the 15th European School for Advanced Studies in Ophthalmology (ESASO) Retina Academy 2015; Barcelona, Spain, October 22–24, 2015.
2. Brazier J *et al. Invest Ophthalmol Vis Sci* 2017; Accepted.

VISION ACADEMY

5-letter gains in vision provide clinically meaningful results for the patient

Standard ETDRS chart

- 5 letters = one line of vision
- **5 letters** could be the **difference between a patient being able to drive or not**
- **Gaining 3 lines of vision** = doubling your visual angle

Vision Academy

ETDRS, Early Treatment Diabetic Retinopathy Study; OCT, optical coherence tomography.

1. Facts about diabetic eye disease. Available at: https://nei.nih.gov/health/diabetic/retinopathy. Accessed September 2017.

VISION ACADEMY

VISION ACADEMY

people | research | education

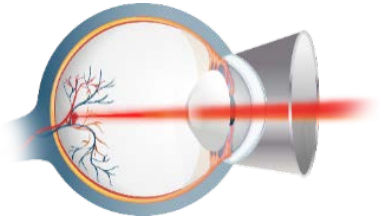
Vision Academy

Evolution of treatment options for DME

DME, diabetic macular edema.

BAYER

Evolution of treatment options for DME



Laser therapy

1980 → 2017

- Laser therapy achieves **vision stability** compared with the natural disease progression[1,2]

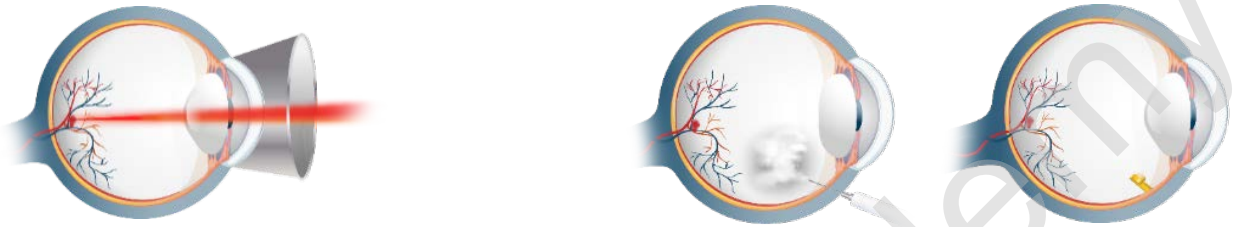
Vision Academy

DME, diabetic macular edema; ETDRS, Early Treatment Diabetic Retinopathy Study.

1. ETDRS Research Group. *Arch Ophthalmol* 1985; 103 (12): 1796–1806.
2. Deschler EK *et al. Semin Ophthalmol* 2014; 29 (5–6): 290–300.

VISION ACADEMY

Evolution of treatment options for DME



Laser therapy

Corticosteroid injections

Corticosteroid implants

1980 — 2017

- **Intravitreal corticosteroids** achieve improvements in vision at the expense of an increased risk of cataract, elevated intraocular pressure and steroid-induced glaucoma[1–3]

Fluocinolone acetonide
European first approval for DME in 2012[*,4]*

Dexamethasone
European approval for DME in 2014[5]

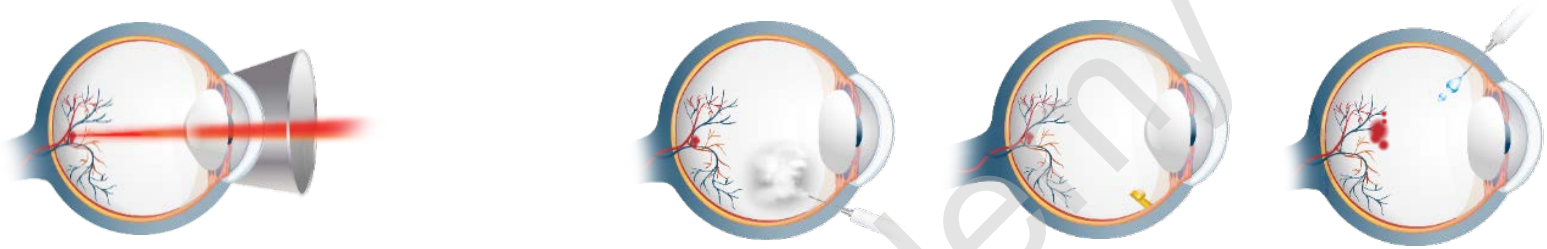
Vision Academy

*Approval for the treatment of vision impairment due to DME granted in 17 European countries between 2012 and 2015. DME, diabetic macular edema.

1. Steroid induced glaucoma. Available at: http://eyewiki.aao.org/Steroid_induced_Glaucoma. 2. Goñi FJ *et al. Ophthalmol Ther* 2016; 5 (1): 47–61.
3. Boyer DS *et al. Ophthalmology* 2014; 121: 1904–1914. 4. Alimera's Iluvien gets its first EU green light in Austria. Available at: http://www.pharmatimes.com/news/alimeras_iluvien_gets_its_first_eu_green_light_in_austria_977432. 5. Allergan's Ozurdex approved for DME in Europe. Available at: https://www.thepharmaletter.com/article/allergan-s-ozurdex-approved-for-dme-in-europe. All websites accessed September 2017.

VISION ACADEMY

Evolution of treatment options for DME



- **Intravitreal corticosteroids** achieve improvements in vision at the expense of an increased risk of cataract, elevated intraocular pressure and steroid-induced glaucoma[1–3]

- **Anti-VEGF therapy** is the current standard of care for the treatment of DME and other retinal diseases[6]

Fluocinolone acetonide
European first approval for DME in 2012[*,4]*

Dexamethasone
European approval for DME in 2014[5]

Ranibizumab
European approval for DME in 2011[7]

Aflibercept
European approval for DME in 2014[8]

Vision Academy

*Approval for the treatment of vision impairment due to DME granted in 17 European countries between 2012 and 2015. DME, diabetic macular edema; VEGF, vascular endothelial growth factor.

1. Steroid induced glaucoma. Available at: http://eyewiki.aao.org/Steroid_induced_Glaucoma. 2. Goñi FJ *et al. Ophthalmol Ther* 2016; 5 (1): 47–61. 3. Boyer DS *et al. Ophthalmology* 2014; 121 (10): 1904–1914. 4. Alimera's Iluvien gets its first EU green light in Austria. Available at: http://www.pharmatimes.com/news/alimeras_iluvien_gets_its_first_eu_green_light_in_austria_977432. 5. Allergan's Ozurdex approved for DME in Europe. Available at: https://www.thepharmaletter.com/article/allergan-s-ozurdex-approved-for-dme-in-europe. 6. Lanzetta P *et al. Graefes Arch Clin Exp Ophthalmol* 2017; 255 (7): 1259–1273. 7. Novartis' Lucentis wins new approval in Europe. Available at: http://www.pharmatimes.com/news/novartis_lucentis_wins_new_approval_in_europe_979809. 8. EYLEA® (aflibercept) injection receives EU approval for the treatment of diabetic macular edema (DME). Available at: http://investor.regeneron.com/releasedetail.cfm?releaseid=865393. All websites accessed September 2017.

VISION ACADEMY

VISION ACADEMY

people | research | education

Vision Academy

Role of anti-VEGF agents in DME

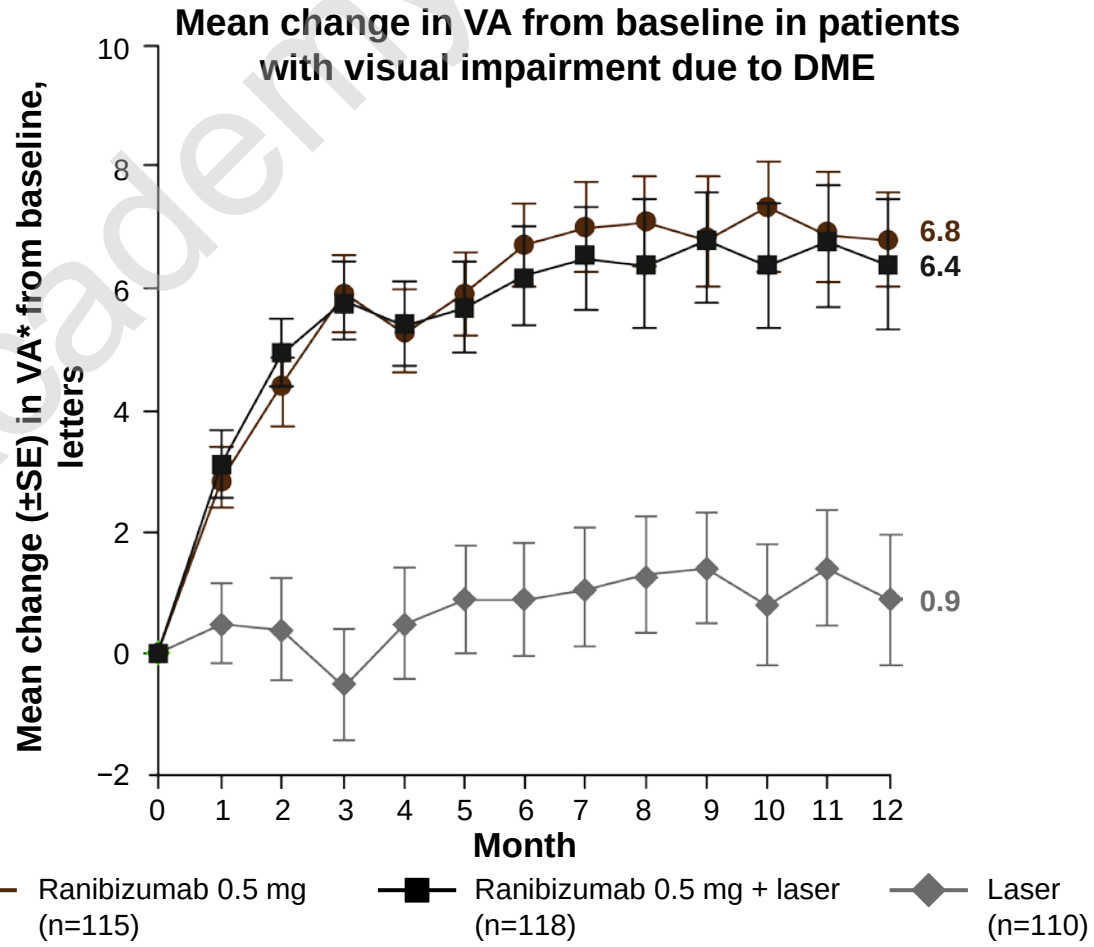
DME, diabetic macular edema; VEGF, vascular endothelial growth factor.

BAYER

2011: The RESTORE study demonstrated superior visual outcomes with ranibizumab monotherapy than with laser

- Phase III, multicenter, laser-controlled trial in patients treated with **ranibizumab** for visual impairment due to DME
  - Visual gains were highest in the **ranibizumab monotherapy** arm at the primary endpoint of 12 months

The RESTORE study was the first study to demonstrate **that anti-VEGF monotherapy provides significantly superior benefit over laser** in patients with vision loss due to DME



Vision Academy

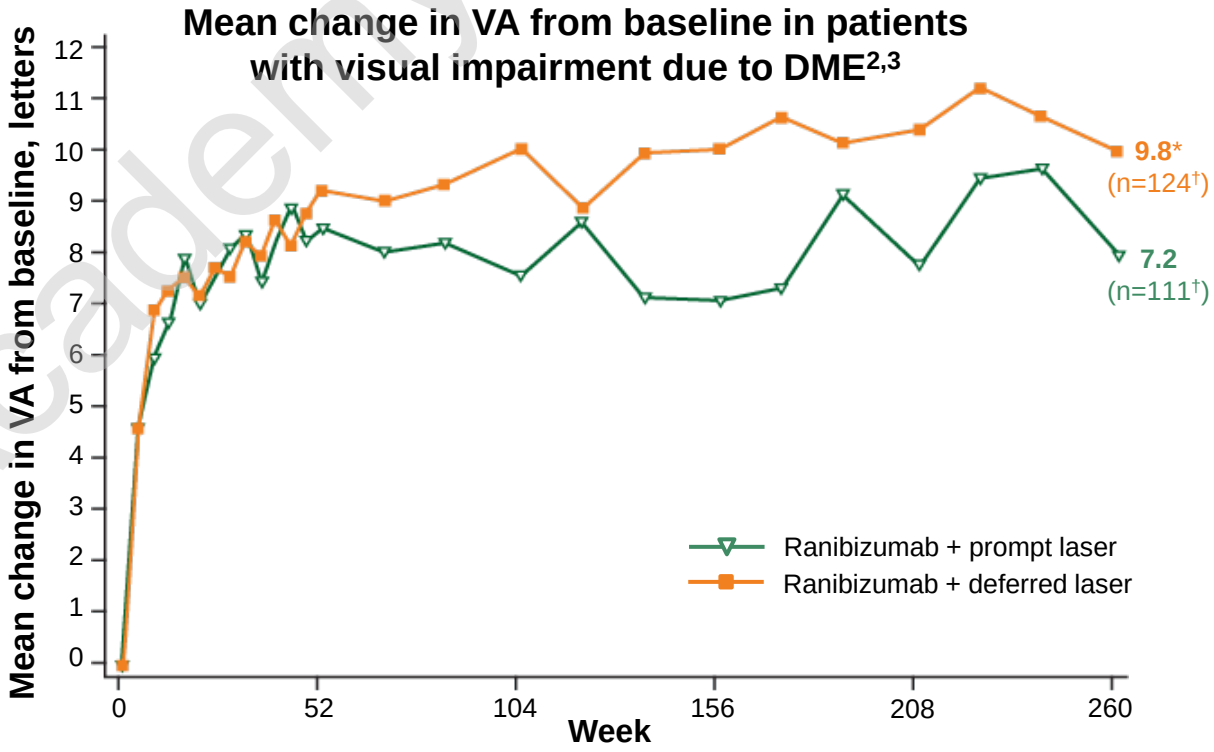
*VA measured as BCVA.
BCVA, best corrected visual acuity; DME, diabetic macular edema; SE, standard error; VA, visual acuity; VEGF, vascular endothelial growth factor.
Mitchell P *et al. Ophthalmology* 2011; 118 (4): 615–625.

VISION ACADEMY

2015: In Protocol I, visual gains with ranibizumab were maintained for 5 years with the need for progressively fewer injections

- Phase III, multicenter trial in patients with DME treated with intravitreal **ranibizumab** and either prompt or deferred laser therapy[1]

Disease activity appears to plateau in DME despite decreasing dosing over time; this may be explained by the **disease-modifying mechanism of VEGF inhibition**[3]



		Year 1	Year 2	Year 3	Year 4	Year 5
Injections	Ranibizumab + prompt laser arm	8	2	1	0	0
	Ranibizumab + deferred laser arm	9	3	2	1	0

*Ranibizumab + prompt laser vs. ranibizumab + deferred laser: *P*=0.09 (adjusted for baseline VA). †Study participants completing the 5-year follow-up.
DME, diabetic macular edema; SE, standard error; VA, visual acuity; VEGF, vascular endothelial growth factor.
1. Diabetic Retinopathy Clinical Research Network *et al. Ophthalmology* 2010; 117 (6): 1064–1077. 2. Elman MJ *et al. Ophthalmology* 2015; 122 (2): 375–381.
3. Schmidt-Erfurth U *et al. Ophthalmologica* 2017; 237 (4): 185–222.

Vision Academy

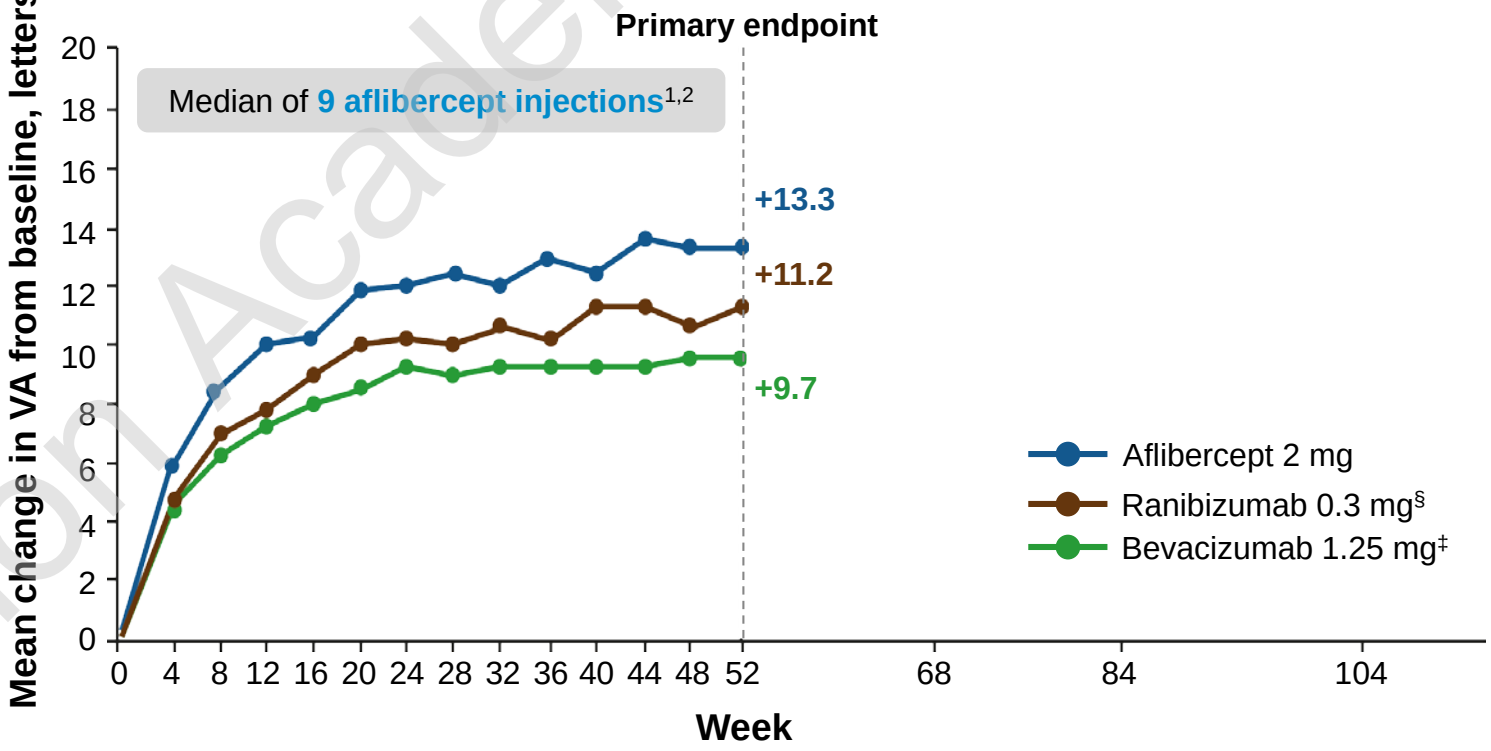
VISION ACADEMY

2015: In Protocol T, superior visual outcomes were achieved with aflibercept than with either comparator at the primary endpoint*,†

- Phase III, NIH-funded trial comparing the efficacy of **aflibercept**, **bevacizumab**‡, and **ranibizumab**§ for the treatment of visual impairment due to DME[1]

Rapid and robust gains in vision were achieved across all anti-VEGF study arms with intensive treatment in Year 1, but they were **highest with aflibercept**[1]

Changes in VA in patients with DME treated with aflibercept, bevacizumab, or ranibizumab[1]



Vision Academy

Patient numbers at Year 1: aflibercept, n=208; bevacizumab, n=206; ranibizumab, n=206.
*Anti-VEGF treatment posology not in accordance with EMA labeling. †Aflibercept vs. bevacizumab, *P*<0.001; aflibercept vs. ranibizumab, *P*=0.034; ranibizumab vs. bevacizumab, *P*=0.12 (all *P*-values adjusted for baseline VA and multiple comparisons). ‡Bevacizumab is not licensed for the treatment of visual impairment due to DME. §The licensed dose for ranibizumab outside the USA is 0.5 mg; please consult your local prescribing information.
DME, diabetic macular edema; EMA, European Medicines Agency; NIH, National Institutes of Health; VA, visual acuity; VEGF, vascular endothelial growth factor.
1. Diabetic Retinopathy Clinical Research Network. *N Engl J Med* 2015; 372 (13): 1193–1203. 2. Diabetic Retinopathy Clinical Research Network. *N Engl J Med* 2015; 372 (13): 1193–1203 – Supplementary appendix.
3. Wells JA *et al*. *Ophthalmology* 2016; 123 (6): 1351–1359.

VISION ACADEMY

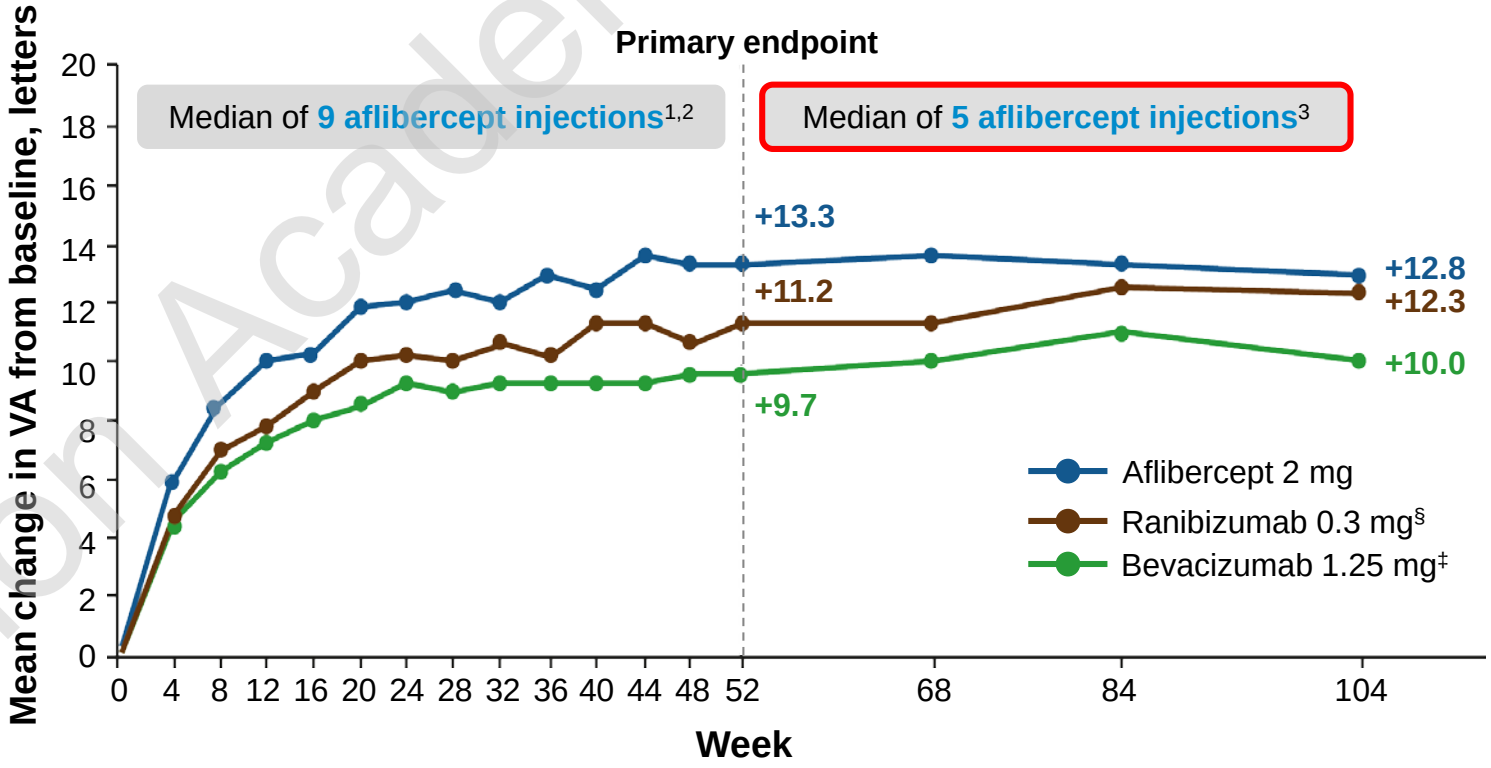
2016: In Protocol T, visual outcomes were maintained in Year 2, with fewer injections required compared with Year 1*,†

- Phase III, NIH-funded trial comparing the efficacy of **aflibercept**, **bevacizumab**‡, and **ranibizumab**§ for the treatment of visual impairment due to DME[1]

Rapid and robust gains in vision were achieved across all anti-VEGF study arms with intensive treatment in Year 1, but they were **highest with aflibercept**[1]

Visual gains were maintained in Year 2, with the need for **fewer injections** than in Year 1[1–3]

Changes in VA in patients with DME treated with aflibercept, bevacizumab, or ranibizumab[1,3]



Vision Academy

Patient numbers at Year 2: aflibercept, n=201; bevacizumab, n=185; ranibizumab, n=191.
*Anti-VEGF treatment posology not in accordance with EMA labeling. †Aflibercept vs. bevacizumab, *P*=0.02; aflibercept vs. ranibizumab, *P*=0.47; ranibizumab vs. bevacizumab, *P*=0.11 (all *P*-values adjusted for baseline VA and multiple comparisons). ‡Bevacizumab is not licensed for the treatment of visual impairment due to DME. §The licensed dose for ranibizumab outside the USA is 0.5 mg; please consult your local prescribing information.
DME, diabetic macular edema; EMA, European Medicines Agency; NIH, National Institutes of Health; VA, visual acuity; VEGF, vascular endothelial growth factor.
1. Diabetic Retinopathy Clinical Research Network. *N Engl J Med* 2015; 372 (13): 1193–1203. 2. Diabetic Retinopathy Clinical Research Network. *N Engl J Med* 2015; 372 (13): 1193–1203 – Supplementary appendix.
3. Wells JA *et al*. *Ophthalmology* 2016; 123 (6): 1351–1359.

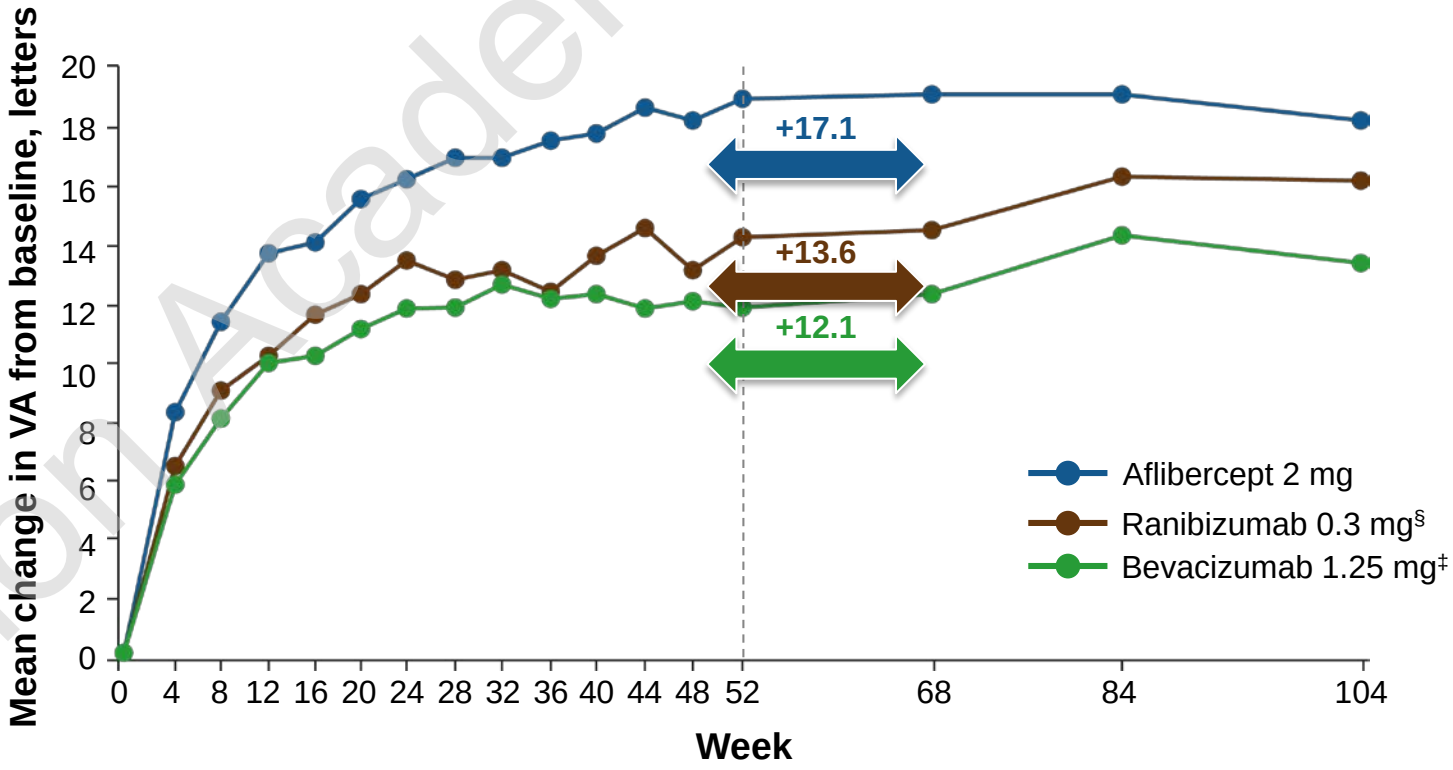
VISION ACADEMY

2016: In Protocol T, the average change in VA over 2 years was superior with aflibercept than with either comparator in patients with worse baseline vision*,†

The **average change in visual acuity over time** with each anti-VEGF agent is represented by the corresponding **area under the curve**

The AUC was **greater with aflibercept** than with either comparator, demonstrating the superiority of aflibercept in patients with baseline vision worse than 69 letters[1]

Mean change in VA from baseline over 2 years in patients with DME and baseline vision worse than 69 letters[1,2]



Vision Academy

Patient numbers at Year 2: aflibercept, n=98; bevacizumab, n=92; ranibizumab, n=94.
*Anti-VEGF treatment posology not in accordance with EMA labeling. †Aflibercept vs. bevacizumab, *P*<0.001; aflibercept vs. ranibizumab, *P*=0.009; ranibizumab vs. bevacizumab, *P*=0.35 (all *P*-values adjusted for baseline VA and multiple comparisons). ‡Bevacizumab is not licensed for the treatment of visual impairment due to DME. §The licensed dose for ranibizumab outside the USA is 0.5 mg; please consult your local prescribing information.
AUC, area under the curve; DME, diabetic macular edema; VA, visual acuity; VEGF, vascular endothelial growth factor.
1. Jampol LM *et al*. *JAMA Ophthalmol* 2016; 134 (12): 1429–1434. 2. Wells JA *et al*. *Ophthalmology* 2016; 123 (6): 1351–1359.

VISION ACADEMY

VISION ACADEMY

people | research | education

Vision Academy

Disease modifying effects of anti-VEGF therapy

VEGF, vascular endothelial growth factor.

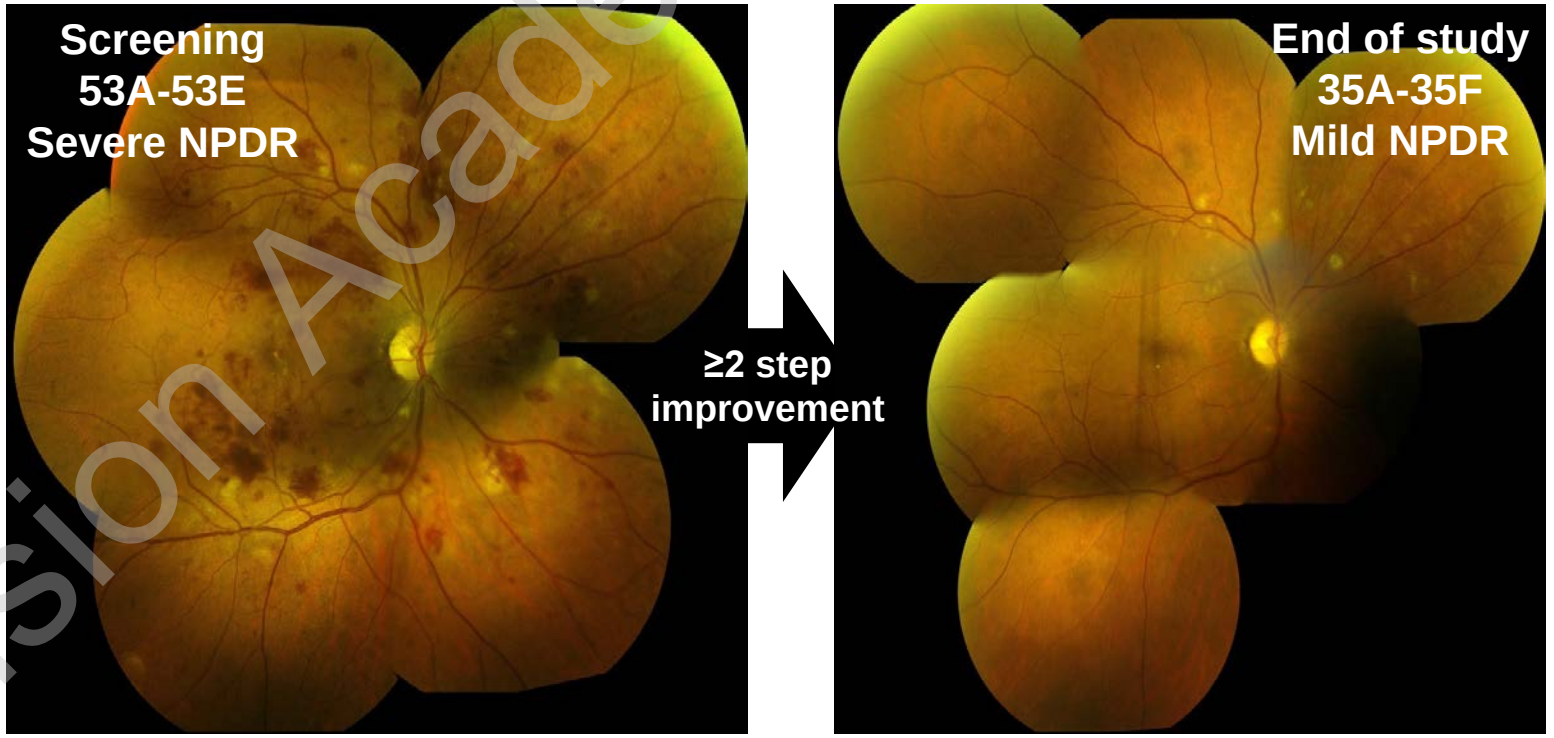
BAYER

Disease modifying effects of anti-VEGF therapy

Level	Severity
10	No retinopathy
20	Very mild non-proliferative DR
35	Mild non-proliferative DR
43	Moderate non-proliferative DR
47	Moderately severe non-proliferative DR
53A–D	Severe non-proliferative DR
53E	Very severe non-proliferative DR
61	Mild proliferative DR
65	Moderate proliferative DR
71, 75	High-risk proliferative DR
81, 85	Advanced proliferative DR

Abbreviated summary of the DRSS[1]

- The **Diabetic Retinopathy Severity Scale (DRSS)** is a staging system for grading the severity of DR[1]



Case images courtesy of Dr. Peter Kaiser.

Vision Academy

DR, diabetic retinopathy; DRSS, Diabetic Retinopathy Severity Scale; NPDR, non-proliferative diabetic retinopathy; VEGF, vascular endothelial growth factor.

1. Davis MD *et al. Invest Ophthalmol Vis Sci* 1998; 39 (2): 233–252.

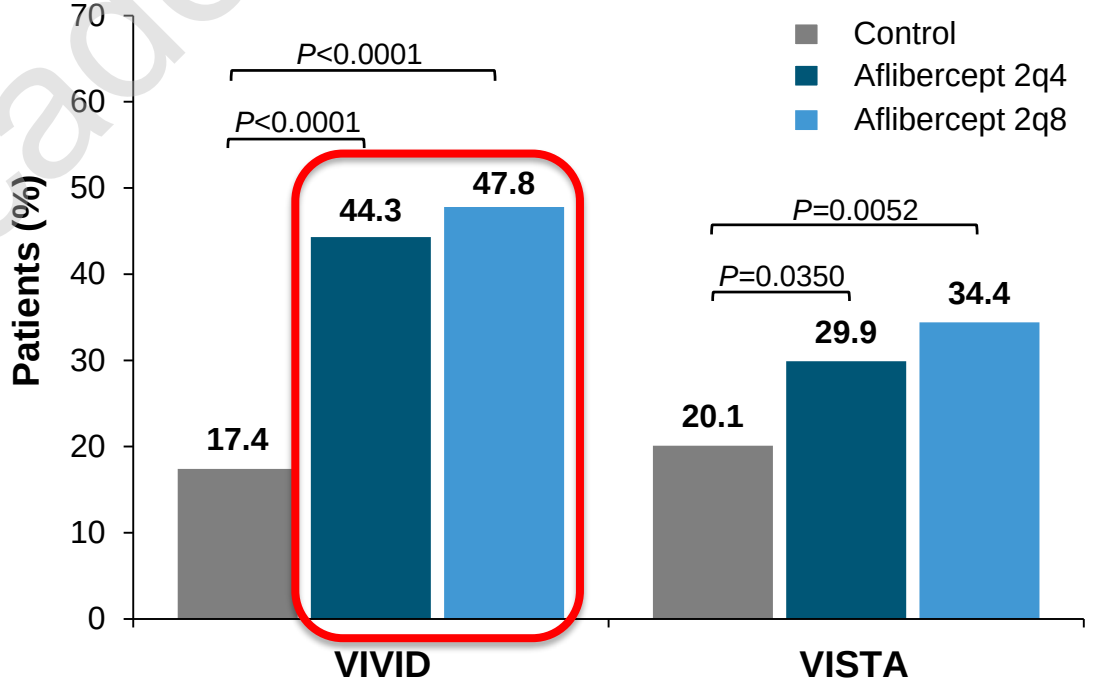
VISION ACADEMY

2016: In VIVID and VISTA, aflibercept demonstrated superior visual outcomes to laser for the treatment of DME

- In the Phase III **VIVID** and **VISTA** trials, aflibercept demonstrated significant superiority over laser in the mean change in BCVA from baseline to Week 52[1]
- In VIVID, nearly half of the patients treated with intravitreal aflibercept had a ≥2-step improvement in DRSS at Week 148[2]

These data support previous observations that anti-VEGF agents may **alter the underlying pathogenesis of DR** beyond just the macula, which is the likely reason that **anti-VEGF dosing needs decrease over time** in diabetic eye disease[2]

Percentage of patients with a ≥2-step improvement in DRSS from baseline to Week 148[2]



Vision Academy

Primary analysis (LOCF): Excludes patients who received rescue treatment. VIVID: Only includes evaluable patients, defined as those with baseline DRSS score and at least one post-baseline assessment. In VIVID, LOCF: laser control, n=86; aflibercept 2q4, n=88; aflibercept 2q8, n=92.
2q4, 2 mg every 4 weeks; 2q8, 2 mg every 8 weeks, after 5 initial monthly doses; BCVA, best corrected visual acuity; DME, diabetic macular edema; DR, diabetic retinopathy; DRSS, Diabetic Retinopathy Severity Scale; LOCF, last observation carried forward; VEGF, vascular endothelial growth factor.
1. Korobelnik J-F *et al. Ophthalmology* 2014; 121 (11): 2247–2254. 2. Heier JS *et al. Ophthalmology* 2016; 123 (11): 2376–2385.

VISION ACADEMY

Session summary

- Small gains in vision can have a significant impact on the ability of patients to perform everyday activities[1]

- **Anti-VEGF agents** are the current standard of care in DME therapy and facilitate improvement of vision and disease regression in DME[2–5]

- Plateauing of DME disease activity over time, despite decreasing anti-VEGF dosing, may be explained by the **disease-modifying mechanism** of VEGF inhibition[3]

Vision Academy

DME, diabetic macular edema; VEGF, vascular endothelial growth factor.

1. Barzey V *et al*. Abstract and poster presented at the 15th European School for Advanced Studies in Ophthalmology (ESASO) Retina Academy 2015; Barcelona, Spain, October 22–24, 2015.
2. Elman MJ *et al. Ophthalmology* 2015; 122 (2): 375–381. 3. Heier JS *et al. Ophthalmology* 2016; 123 (11): 2376–2385.
4. Diabetic Retinopathy Clinical Research Network. *N Engl J Med* 2015; 372 (13): 1193–1203. 5. Wells JA *et al*. *Ophthalmology* 2016; 123 (6): 1351–1359.

VISION ACADEMY