Diabetic eye disease:
A treatable complication of diabetes

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  • Roche
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 retinopathy¹

VEGF, vascular endothelial growth factor.
Diabetes can result in a range of serious health consequences:

- Depression
- Stroke
- Vision loss
- Cardiac events
- Kidney failure
- Amputation
- Peripheral sensory loss


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 adults²⁻⁴

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\(^1\)
- A range of **imaging techniques** are routinely employed by ophthalmologists when screening for diabetic eye disease, including:

  - Fundus photography
  - Optical coherence tomography (OCT)

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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\(^1,2\)

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DME, diabetic macular edema; DR, diabetic retinopathy.

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Stages of DR

(Increasing level of severity)

- Pre-proliferative
- Pre-proliferative

DME, diabetic macular edema; DR, diabetic retinopathy.

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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.

Stages of DR (Increasing level of severity)

- Background
- Pre-proliferative
- Proliferative

DME, diabetic macular edema; DR, diabetic retinopathy.

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

DME, diabetic macular edema; DR, diabetic retinopathy.
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
  • Visual acuity in the better-seeing eye is a major contributor to health-related quality of life²
    • Visual acuity in the worse-seeing eye is also important, though to a lesser extent

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

- 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

ETDRS, Early Treatment Diabetic Retinopathy Study; OCT, optical coherence tomography.
Evolution of treatment options for DME

DME, diabetic macular edema.
Evolution of treatment options for DME

- Laser therapy achieves vision stability compared with the natural disease progression\(^1,2\)

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

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\(^1\)\(^–\)\(^3\)

\(^1\) Approval for the treatment of vision impairment due to DME granted in 17 European countries between 2012 and 2015. DME, diabetic macular edema.

*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.


**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 glaucoma1–3.

- **Anti-VEGF therapy** is the current standard of care for the treatment of DME and other retinal diseases6.
Role of anti-VEGF agents in DME

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

*VA measured as BCVA.
BCVA, best corrected visual acuity; DME, diabetic macular edema; SE, standard error; VA, visual acuity; VEGF, vascular endothelial growth factor.
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

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

Injections

<table>
<thead>
<tr>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranibizumab + prompt laser arm</td>
<td>8</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Ranibizumab + deferred laser arm</td>
<td>9</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

*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.

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 DME¹

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 aflibercept¹
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 DME¹

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 aflibercept¹

Visual gains were maintained in Year 2, with the need for fewer injections than in Year 1¹⁻³

Changes in VA in patients with DME treated with aflibercept, bevacizumab, or ranibizumab¹,³

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.

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*,$\dagger$

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 letters¹.

Mean change in VA from baseline over 2 years in patients with DME and baseline vision worse than 69 letters¹,²

Mean change in VA from baseline, letters

Week

0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64 68 72 76 80 84 88 92 96 100 104

Mean change in VA from baseline over 2 years in patients with DME and baseline vision worse than 69 letters¹,²

Aflibercept 2 mg
Ranibizumab 0.3 mg§
Bevacizumab 1.25 mg‡

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.

Disease modifying effects of anti-VEGF therapy

VEGF, vascular endothelial growth factor.
Disease modifying effects of anti-VEGF therapy

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

<table>
<thead>
<tr>
<th>Level</th>
<th>Severity</th>
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<tbody>
<tr>
<td>10</td>
<td>No retinopathy</td>
</tr>
<tr>
<td>20</td>
<td>Very mild non-proliferative DR</td>
</tr>
<tr>
<td>35</td>
<td>Mild non-proliferative DR</td>
</tr>
<tr>
<td>43</td>
<td>Moderate non-proliferative DR</td>
</tr>
<tr>
<td>47</td>
<td>Moderately severe non-proliferative DR</td>
</tr>
<tr>
<td>53A–D</td>
<td>Severe non-proliferative DR</td>
</tr>
<tr>
<td>53E</td>
<td>Very severe non-proliferative DR</td>
</tr>
<tr>
<td>61</td>
<td>Mild proliferative DR</td>
</tr>
<tr>
<td>65</td>
<td>Moderate proliferative DR</td>
</tr>
<tr>
<td>71, 75</td>
<td>High-risk proliferative DR</td>
</tr>
<tr>
<td>81, 85</td>
<td>Advanced proliferative DR</td>
</tr>
</tbody>
</table>

Abbreviated summary of the DRSS

- **Screening**
  - 53A–53E: Severe NPDR
- **End of study**
  - 35A–35F: Mild NPDR

≥2 step improvement

Case images courtesy of Dr. Peter Kaiser.

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

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\(^2\)

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.

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\(^3\)