Overview of the Pathogenesis of Diabetic Retinopathy

• Leading cause of new cases of blindness in US adults ages 20 to 74 years¹
• Duration of diabetes is a strong predictor for DR development and progression²
• DR prevalence¹-⁴:
  - All people ≥40 years of age with diabetes: 28.5%
  - Type 1 diabetes mellitus 20 to 35 years' duration: 95%
  - Type 2 diabetes mellitus ≥16 years' duration: 60%

Diabetic Macular Edema (DME)

- DME is the leading cause of moderate-to-severe vision loss in patients with diabetes.
- The pathogenesis of DME is complex:
  - Involves several inter-related pathway processes that are initiated by sustained hyperglycemia.
  - These processes culminate in increased vascular permeability and the breakdown of the blood-retina barrier.
  - Fluid and proteins leak into the macula, causing the macula to swell, which in turn affects visual function.

Image courtesy of Dr. Alfredo Garcia Layana.

Diabetic Macular Edema (DME) in Diabetic Patients with Diabetic Retinopathy:

- Patients with DME have a 2-fold higher risk of cerebrovascular accidents.
- Patients with DME have a 2.5-fold higher risk of myocardial infarction.

Retinopathy and DME Can Be Predictors of Other Diabetic Complications:

- Diabetic retinopathy/PDR:
  - Independent predictor of nephropathy.
  - Associated with increased risk for all-cause mortality/cardiovascular events.
  - Correlation with diabetic peripheral neuropathy and impaired peripheral arterial circulation.

- Patients with DME have:
  - A 2-fold higher risk of cerebrovascular accidents.
  - A 2.5-fold higher risk of myocardial infarction.

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Patients with Diabetic Macular Edema May Not Have Symptoms

- Patients should be referred for a retina (dilated) eye exam before any vision loss
- Symptoms and pain are often both absent in the early stages
- Vision loss can occur suddenly, and regular examinations are crucial to ensure treatment is obtained

Symptoms of DME include:
- Blurred Vision
- Double Vision
- Patchy vision loss

Prevalence of DME in the US

- Approximately 8 million (21%) of people with diabetes have DR
  - 5.8 million are diagnosed
  - 2.3 million have DME

- Prevalence of DME in the US
  - 8.0MM
  - 2.3MM
  - 1.5MM
  - 5.8MM

- Diagnosis Rate
  - 1.5 mm
  - 2.3 mm

- Treatment Rate
  - 800K
  - ~400K

DME in the United States

- Nearly 800,000 Americans suffer from DME but remain undiagnosed
- Another 1.1 million are diagnosed with DME but are not receiving treatment

- Prevalence
  - 2.3 mm
  - 1.5 mm

- Diagnosis Rate
  - 800K

- Treatment Rate
  - ~400K

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Guidelines: Annual Dilated Eye Exams

<table>
<thead>
<tr>
<th>Diabetes type</th>
<th>Recommended time for first examination</th>
<th>Recommended follow-up*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>3-5 years after diagnosis</td>
<td>Yearly</td>
</tr>
<tr>
<td>Type 2</td>
<td>At time of diagnosis</td>
<td>Yearly</td>
</tr>
<tr>
<td>Prior to pregnancy (Type 1 or Type 2)</td>
<td>Prior to conception and early in the first trimester</td>
<td>No DR to mild or moderate NPDR: every 3-12 months. Severe NPDR or worse: every 1-3 months.</td>
</tr>
</tbody>
</table>

It is important for patients to understand there are different types of eye exams they need (eg, dilated eye exam, retina eye exam, diabetes eye exam).

*Abnormal findings may dictate more frequent follow-up exams.

Diagnosing DR and DME

- Patients should undergo a comprehensive dilated eye exam soon after their diabetes diagnosis and receive annual follow-up examinations.
- An examination for DR and DME includes:
  - Visual acuity
  - Slit-lamp biomicroscopy
  - Intraocular pressure
  - Gonioscopy, when indicated
  - Dilated funduscopy, including stereoscopic examination of the posterior pole
  - Examination of the peripheral retina and vitreous
  - Fundus photography, fluorescein angiography, or OCT as indicated.


Gaps in Ophthalmic Care for Patients With Diabetes

- Many patients are not getting sufficient care to prevent visual impairment.
- In a recent cross-sectional analysis of NHANES data:
  - 49.7% of patients ≥40 with DME reported no visits with a dietitian/diabetes nurse educator in the previous 12 months.
  - 44.7% reported being informed that their eyes had been affected by DME.
  - 59.7% reported receiving a dilated eye examination in the previous 12 months.
  - 28.7% had some degree of visual impairment (based on visual acuity at initial examination).

Improving Management of Patients with Diabetic Eye Disease

### Percentage of US Adults With Diabetes (Ages 18-75) With Retinal Examination Performed

<table>
<thead>
<tr>
<th>YEAR</th>
<th>COMMERCIAL</th>
<th>MEDICAID</th>
<th>MEDICARE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HMO</td>
<td>PPO</td>
<td>HMO</td>
</tr>
<tr>
<td>2012</td>
<td>56.8</td>
<td>48.8</td>
<td>53.2</td>
</tr>
<tr>
<td>2011</td>
<td>56.9</td>
<td>48.4</td>
<td>53.3</td>
</tr>
<tr>
<td>2010</td>
<td>57.7</td>
<td>45.5</td>
<td>53.1</td>
</tr>
<tr>
<td>2009</td>
<td>56.5</td>
<td>42.6</td>
<td>52.7</td>
</tr>
<tr>
<td>2008</td>
<td>56.5</td>
<td>35.8</td>
<td>52.8</td>
</tr>
</tbody>
</table>

Some improvement, but there is still work to do!


### Awareness of Eye Disease Among Study Participants

Among patients with DME, percentage that reported having had a dilated eye exam within past year

- Yes: 40%
- No: 60%


### Why Patients Do Not Receive Annual Eye Exams

As reported by patients diagnosed with diabetes who are not receiving annual eye exams

- Patients with visual impairments are more likely to cite "no need" as a reason for not receiving an eye exam and less likely to report "cost" or "lack of insurance"

Common Reasons Patients Reported

- No need: 39.7%
- Cost/lack of insurance: 32.3%
- "Consisted of "have not thought of it" and "no reason to go": 6.4%
- Other: 21.5%
- No eye doctor, no transportation, or could not get appointment: 0.6%

Clinically Significant Macular Edema (CSME)

- The ETDRS first described CSME to define morphological severity when DME threatens the center of the macula (fovea)\(^1\).
- Current recommendations for the treatment of CSME are based on the involvement of the center of the macula (foveal involvement) and associated vision loss\(^2\).
- CSME is diagnosed if any of the following parameters are met:\(^1\)
  - Retinal thickening within 500 µm of the center of the macula
  - Hard exudates within 500 µm of the center of the macula, if associated with thickening of the adjacent retina
  - Retinal thickening of >1 disk area in size, any part of which is located within 1 disk diameter of the center of the macula

Charting DME Progression

The following tests may help to chart disease progression:

- Optical coherence tomography (OCT)
  - Detect and assess thickening of the retina due to edema\(^1,2\)
- Color fundus photography
  - Reproducible documentation of progression and treatment response\(^1\)
- Fluorescein angiography
  - Evaluate unexplained decrease in visual acuity\(^3\)
  - Determine leakage sites\(^2,3\)

Risk Factors for Diabetic Retinopathy

**Non-modifiable factors:**
- Duration of diabetes
- Patient age (type 2)
- Level of retinopathy
- Albuminuria*
- Pregnancy

**Modifiable factors:**
- HbA1C level\(^1\)
- Hypertension\(^1\)
- Dyslipidemia\(^2\)
- Cigarette smoking\(^3\)

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**Diabetes Control & Complications Trial (DCCT)**

- Intensive blood glucose control:
  - 76% risk reduction in the development of any retinopathy
  - 54% risk reduction of retinopathy progression for those who had retinopathy at baseline


**Diabetes Control & Complications Trial (DCCT)**

- Results by duration of diabetes
  - Duration of DM <2.5 years:
    - 89% risk reduction of retinopathy
  - Duration of DM >2.5 years:
    - 70% risk reduction of retinopathy


**ACCORD Study**

- 2856 patients evaluated over 4 years for retinopathy progression
  - Subjects randomized to:
    - Intensive or standard treatment for glycemia (target glycated hemoglobin level, <6.0% or 7.0% to 7.9%, respectively)
    - Dyslipidemia (160 mg daily of fenofibrate plus simvastatin) versus placebo plus simvastatin)
    - Systolic blood-pressure control (target, <120 or <140 mm Hg)

ACCORD Study

- Progression Rates:

<table>
<thead>
<tr>
<th></th>
<th>Intensive</th>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycemic Therapy</td>
<td>7.3%</td>
<td>10.4%</td>
</tr>
<tr>
<td>Dyslipemia</td>
<td>6.5%</td>
<td>10.2%</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>10.4%</td>
<td>8.8%</td>
</tr>
</tbody>
</table>

- Conclusion:
  - Intensive glycemic control and dyslipidemia control did slow progression but not blood pressure


Effect of Fenofibrate on the Need for Laser Treatment for Diabetic Retinopathy (FIELD Study): A Randomized Controlled Trial


New Methods in the Treatment of Diabetic Macular Edema
RISE/RIDE Study Design

- **Diabetic Macular Edema**
  - Screening: BCVA 20/30 to 20/300, OCT CRT ≥275 μm
  - 1:1 Randomization One Eye per Subject

- **Sham Injection**
  - 150 subjects (n=257)

- **Ranibizumab 0.3 mg**
  - 150 subjects (n=250)

- **Ranibizumab 0.5 mg**
  - 150 subjects (n=252)

**Primary Endpoint**
- Long-term Open-label Extension with 0.5 mg ranibizumab
- Ranibizumab is approved for a 0.3 mg dose in DME

**RISE/RIDE: Subjects Gaining ≥15 ETDRS Letters**
- A significant number of patients did not gain 3 lines of vision
- **Percent of subjects**
  - Sham: 15.2%
  - 0.3 mg: 39.2%

**RISE/RIDE: Mean Change in BCVA from Baseline Through 36 Months**
- Significant numbers of injections were given.
- **Sham subjects who crossed over to ranibizumab 0.5 mg at or after month 25: n=190**

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**Study Design**

- Randomized, multicenter, double-masked trials in patients with clinically significant DME with central involvement and ETDRS BCVA 20/40 to 20/120
- Patients randomized 1:1:1
- Primary endpoint: Week 52
- Key secondary endpoint: Change from baseline in Retinopathy Severity Scale (DRSS)
- Continued treatment through Year 3

**Primary Endpoint: Mean Change in BCVA Through Week 52**

- VIVID
- VISTA

**Mean Change in Central Retinal Thickness Through Week 100**

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Protocol I Study Design

Eyes Randomized:
N = 854 (691 Participants)

- Sham + Prompt Laser N = 293
- Ranibizumab + Prompt Laser N = 187
- Ranibizumab + Deferred Laser N = 188
- Triamcinolone + Prompt Laser N = 186

1 Year Visit Completion: 94%*
2 Year Visit Completion: 87%**

* Includes deaths
** Includes deaths and excludes pending and dropped who are not yet in window


Protocol I: 5-year Mean Change in Visual Acuity*

Visits:
N = 854 (691 Participants)

1 Year Visit Completion:
94%
2 Year Visit Completion:
87%

* Includes deaths
** Includes deaths and excludes pending and dropped who are not yet in window


DRCR Protocol I Subanalysis
Anti-VEGF Responders Have Better Outcomes with Fewer Injections

Change in Visual Acuity from Baseline to 1 Year

Number of Injections in Year 1

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### Diabetic Retinopathy Clinical Research Network

**Comparative Effectiveness Study of Aflibercept, Bevacizumab, or Ranibizumab for DME**

Supported through a cooperative agreement from the National Eye Institute, National Institute of Diabetes and Digestive and Kidney Diseases; National Institutes of Health, Department of Health and Human Services EY14231, EY14229, EY018817

#### Mean Change in Visual Acuity Letter Score, Full Cohort

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Weeks</th>
<th>Change in Visual Acuity Letter Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aflibercept</td>
<td>52</td>
<td>~+13</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>52</td>
<td>~+11</td>
</tr>
<tr>
<td>Ranibizumab</td>
<td>52</td>
<td>~+10</td>
</tr>
</tbody>
</table>

*P*-values adjusted for baseline visual acuity and multiple comparisons


#### Mean Change in Visual Acuity Letter Score Baseline Visual Acuity 20/32 to 20/40

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Weeks</th>
<th>Change in Visual Acuity Letter Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aflibercept</td>
<td>52</td>
<td>~50% of Cohort</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>Ranibizumab</td>
<td>52</td>
<td></td>
</tr>
</tbody>
</table>

Improving Management of Patients with Diabetic Eye Disease

Mean Change in Visual Acuity Letter Score
Baseline Visual Acuity 20/50 or Worse

Mean Change in Visual Acuity Letter Score
Baseline Visual Acuity 20/50 or Worse

Potential AEs of Anti-VEGF Treatment in Diabetic Patients

- Ocular AEs
  - Vitreous hemorrhage
  - Vitreomacular traction
  - RPE tears
  - Retinal detachment
  - Elevated intraocular pressure
  - Intraocular inflammation
  - Endophthalmitis

- Systemic AEs
  - Hypertension
  - Proteinuria
  - Impairment of wound healing
  - Arterial thromboembolic events
    - Myocardial infarctions
    - Stroke
    - Dyspnea

RIDE and RISE Arterial Thromboembolic Events Through Months 24 and 36

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What Are the Effects of Intraocular Anti-VEGF Drugs on Serum VEGF?

Serum VEGF concentrations have been measured in patients receiving intravitreal anti-VEGF injections:

\[ [\text{serum VEGF}] \sim \frac{1}{\text{serum half-life (drug)}} \]

<table>
<thead>
<tr>
<th>Serum VEGF</th>
<th>Ranibizumab</th>
<th>Aflibercept</th>
<th>Bevacizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17</td>
<td>21</td>
<td></td>
</tr>
</tbody>
</table>

Author: Presented at ARVO 2012

Meta-analyses of Anti-VEGF Safety

<table>
<thead>
<tr>
<th>Authors</th>
<th>Journal (year)</th>
<th>Drug(s)</th>
<th>Findings (Dx)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abouammoh</td>
<td>Can J Oph (2013)</td>
<td>Ranibizumab</td>
<td>No risk for TIEE (DME)</td>
</tr>
<tr>
<td>Wang</td>
<td>Retina (2013)</td>
<td>Ranibizumab Bevacizumab</td>
<td>No risk for AE (Myopic CNVM)</td>
</tr>
<tr>
<td>Virgili</td>
<td>Cochrane (2012)</td>
<td>Ranibizumab Bevacizumab</td>
<td>No risk for AE (DME)</td>
</tr>
<tr>
<td>Jyothi</td>
<td>Eye (2011)</td>
<td>Bevacizumab</td>
<td>Similar to other anti-VEGF (AMD)</td>
</tr>
<tr>
<td>Zhou</td>
<td>Clin Exp Oph (2013)</td>
<td>Ranibizumab Aflibercept</td>
<td>No increase in AE (DME)</td>
</tr>
</tbody>
</table>

Conclusion: No systemic safety problems identified.

Summary of Our Current Anti-VEGF Treatments

- More than 50% of people do not achieve 15-letter improvement in vision, based on clinical trials
- Requires multiple injections over extended periods
- Not all people gain vision
- Some people lose vision
- Adverse effects are low but not zero
Improving Management of Patients with Diabetic Eye Disease

DRCR.net Protocol B
Study Design

Major Eligibility Criteria Assessed:
• ≥18 years old
• Type 1 or type 2 diabetes
• Center-involved DME (with OCT CSF ≥250 µm)
• VA letter score 73 to 24 (20/40 to 20/320)

Eligible eyes randomized
Subjects with 2 study eyes assigned alternative treatment in 2nd eye

Focal/Grid Laser • 1 mg IVT • 4 mg IVT

Steroids Not as Good as Laser?

• Protocol B conclusion: “focal/grid photocoagulation is more effective and has fewer adverse effects than intravitreal triamcinolone”

Mean change in vision

Steroids Caused Cataract

• Protocol B: Dramatic increase in cataract extraction rates in steroid group

Rate of Cataract Extraction
Improving Management of Patients with Diabetic Eye Disease

**MEAD Study Design**

- DME, one eye per patient (eye with shortest duration of DME selected)
- Randomization (1:1:1)
- DEX 700 µg N=347
- DEX 350 µg N=343
- Sham N=350
- Evaluated for retreatment every 3 months after Month 6 visit
- Retreatment was allowed every 6 months (if central retinal thickness > 175 µm or any evidence of residual retinal edema)
- Primary Endpoint at 3 years

**MEAD Study: Mean Improvement in Vision Based on Pseudophakic and Phakic Status**

- Mean IOP in the study eye increased following each injection of DEX
- The incidence or magnitude of IOP elevation did not increase over time with repeated injection of DEX and resolved after each injection

**Effect of DEX Treatment on IOP**

- Mean IOP in the study eye increased following each injection of DEX
- The incidence or magnitude of IOP elevation did not increase over time with repeated injection of DEX and resolved after each injection

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FAME Study Design

2 randomized, multicenter, double-masked, parallel-group, 36-month clinical trials (FAME A and FAME B) in patients with DME previously treated with laser.

- Fluocinolone: 0.2 µg/d FAc (n=376)
- Fluocinolone: 0.5 µg/d FAc (n=395)
- Control: sham injection (n=185)

<table>
<thead>
<tr>
<th>Month</th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2 µg/d FAc (n=376)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5 µg/d FAc (n=395)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control: sham injection (n=185)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- 6 months: Additional laser allowed
- 12 months: Retreatment if needed
- 12 months: Study ends

FAME Study Countries: Canada, France, Germany, India, Italy, Poland, Portugal, Spain, United Kingdom, United States

FAME Study Design


FAME Study Efficacy at 24 Months: Percentage of Patients with ≥15-Letter Improvement

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcomes</th>
<th>Fluocinolone</th>
<th>Sham</th>
<th>Estimated Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAME A*</td>
<td>Gain of ≥15 letters in BCVA, n (%)</td>
<td>31 (27)</td>
<td>14 (15)</td>
<td>12.1 (2.6 to 21.6)</td>
</tr>
<tr>
<td>FAME B*</td>
<td>Gain of ≥15 letters in BCVA, n (%)</td>
<td>37 (26)</td>
<td>16 (18)</td>
<td>13.0 (2.7 to 23.4)</td>
</tr>
</tbody>
</table>


Mean Change From Baseline in BCVA Letter Score


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FAME: Summary of Elevated IOP-Related Adverse Reactions

<table>
<thead>
<tr>
<th>EVENT</th>
<th>Fluocinolone (N = 375) n (%)</th>
<th>Sham (N = 185) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IOP elevation ≥ 10 mm Hg from baseline</td>
<td>127 (34%)</td>
<td>18 (10%)</td>
</tr>
<tr>
<td>IOP elevation ≥ 30 mm Hg</td>
<td>75 (20%)</td>
<td>8 (4%)</td>
</tr>
<tr>
<td>Any IOP-lowering medication</td>
<td>144 (38%)</td>
<td>26 (14%)</td>
</tr>
<tr>
<td>Any surgical intervention for elevated intraocular pressure</td>
<td>18 (5%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>


Management of Proliferative Diabetic Retinopathy

- Panretinal photocoagulation reduces risk of SVL by 50%*


Current Algorithm for PDR: Wait Until High-Risk (or Close to High-Risk) PDR Develops

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Available Systemic Treatments and Interventions

- Available systemic treatments and interventions for reducing the risk of progression of retinopathy:
  - Glycemic control (DCCT, UKPDS, ACCORD)\(^1,2,3\)
  - Hypertensive control (UKPDS)\(^2\)
  - Renin-Angiotensin system blockade with enalapril or losartan (RASS)\(^4\)
  - Fenofibrate (ACCORD and FIELD)\(^4,5\)

2. UKPDS. BMJ. 1998;317:703-713.

Impact of Treating Risk Factors on DR

- Hyperglycemia > 1% decrease in A1C = decreased risk of:
  - Retinopathy by 40%
  - Vision-threatening retinopathy by 25%
  - Need for laser therapy by 25%
  - Blindness by 15%

- Hypertension > 10 mm Hg decrease in systolic BP = decreased risk of:
  - Retinopathy progression by 35%
  - Need for laser therapy by 35%
  - Visual loss by 50%


36-month data

Fluocinolone Acetonide Implant: Change in Diabetic Retinopathy Severity Scores

- > 1 step improvement
- 1 step improvement
- No change
- 1 step worsened
- > 1 step worsened

(\(P<.001\), CMH Chi squared)

Improving Management of Patients with Diabetic Eye Disease

**DRCR Protocol B (Triamcinolone vs Laser): Cumulative Probability of Progression of Retinopathy**

<table>
<thead>
<tr>
<th>Months</th>
<th>Laser</th>
<th>1mg</th>
<th>4mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>4</td>
<td>21%</td>
<td>10%</td>
<td>14%</td>
</tr>
<tr>
<td>8</td>
<td>31%</td>
<td>20%</td>
<td>30%</td>
</tr>
<tr>
<td>12</td>
<td>37%</td>
<td>30%</td>
<td>21%</td>
</tr>
<tr>
<td>16</td>
<td>42%</td>
<td>29%</td>
<td>19%</td>
</tr>
<tr>
<td>20</td>
<td>47%</td>
<td>24%</td>
<td>14%</td>
</tr>
<tr>
<td>24</td>
<td>53%</td>
<td>21%</td>
<td>13%</td>
</tr>
<tr>
<td>28</td>
<td>57%</td>
<td>19%</td>
<td>11%</td>
</tr>
<tr>
<td>32</td>
<td>61%</td>
<td>14%</td>
<td>10%</td>
</tr>
<tr>
<td>36</td>
<td>65%</td>
<td>11%</td>
<td>9%</td>
</tr>
</tbody>
</table>

Cumulative probabilities calculated using the Kaplan-Meier method. Progression was defined by (1) progression from NDR (DR severity level < 60) at baseline to PDR (DR severity level ≥ 60) at a later time point, (2) need for PRP laser, (3) vitreous hemorrhage (AE or slit lamp grade 0 at baseline to > 0 at a later time point), (4) cases identified by ophthalmoscopy, (5) vitrectomy, (6) iris neovascularization AE, or (7) retinal neovascularization AE. 1 month = 30 days. AE, adverse event; PRP, panretinal photocoagulation.


**RISE/RIDE: Risk of Composite PDR Outcomes in Sham vs Ranibizumab Groups**

**DRCR Protocol I: Ranibizumab Has a Beneficial Effect on DR Level**

- Defined worsening of diabetic retinopathy on a composite scale
- Cumulative probabilities were:
  - 23% (sham/laser)
  - 18% ranibizumab with prompt laser
  - 7% ranibizumab with deferred laser ($P=0.001$)

- Data from DRCR Protocol I are consistent with the retinopathy level findings from the RIDE/RISE studies

Improving Management of Patients with Diabetic Eye Disease

Proportion of Patients With ≥ 2 Step Improvement in DRSS at Week 100

VIVID

- VIVID vs laser
- 2q4 vs laser
- 2q8 vs laser

VISTA

- VISTA vs laser
- 2q4 vs laser
- 2q8 vs laser

VIVID: Only includes evaluable patients defined as those with baseline ETDRS-DRSS score and at least 1 post-baseline assessment
VISTA: FAS
Compared with baseline; last observation carried forward
DRSS: Diabetic Retinopathy Severity Score

Proportion of Patients With ≥ 2 Step Worsening in DRSS at Week 100

VIVID

- VIVID vs laser
- 2q4 vs laser
- 2q8 vs laser

VISTA

- VISTA vs laser
- 2q4 vs laser
- 2q8 vs laser

VIVID: Only includes evaluable patients defined as those with baseline ETDRS-DRSS score and at least 1 post-baseline assessment
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