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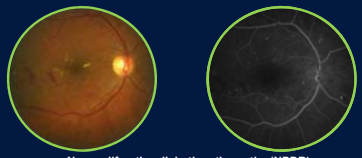
Overview of the Pathogenesis of Diabetic Retinopathy

Diabetic Retinopathy

- Leading cause of new cases of blindness in US adults ages 20 to 74 years[1]
- Duration of diabetes is a strong predictor for DR development and progression[2]
- DR prevalence[2-4]:
  - All people ≥40 years of age with diabetes: 28.5%
  - Type 1 diabetes mellitus 20 to 30 years' duration: 95%
  - Type 2 diabetes mellitus ≥16 years' duration: 60%



Nonproliferative diabetic retinopathy (NPDR)

1.CDC; http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf. Accessed October 21, 2013.
2.Rosenblatt BJ, et al. *Ophthalmology*. 3rd ed. 2009:613-621.
3.Zhang X, et al. *JAMA*. 2010;304(6):649-656.
4.Yanko L, et al. *Br J Ophthalmol*. 1983;67:759-765.

Diabetic Macular Edema (DME)

- DME is the leading cause of moderate-to-severe vision loss in patients with diabetes[1,2]
- The pathogenesis of DME is complex[3,4]
  - 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

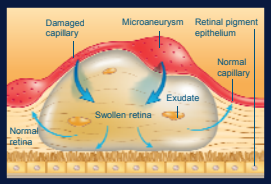


Image courtesy of Dr Alfredo Garcia Layana.

1. Ciulla TA, et al. *Diabetes Care*. 2003;26:2653–2664.
2. International Diabetes Federation; http://www.idf.org/sites/default/files/idf-europe/IDF%20Toolkit_Backgrounder_FINAL.pdf. Accessed June 6, 2014.
3. Lotery AJ. *European Ophthalmic Rev*. 2012;6:236–241.
4. Kleinman ME, et al. *Ophthalmologica*. 2010;224:16–24.

Retinopathy and DME Can Be Predictors of Other Diabetic Complications

Diabetic retinopathy/PDR:

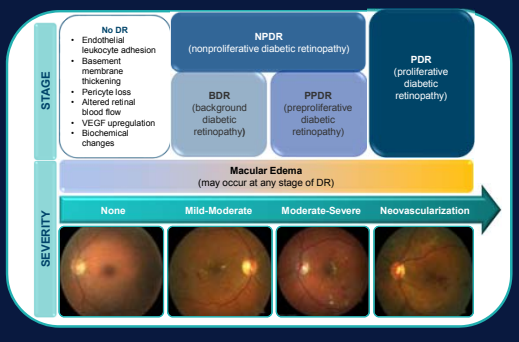
- Independent predictor of nephropathy[1]
- Associated with increased risk for all-cause mortality/cardiovascular events[2]
- Correlation with diabetic peripheral neuropathy[3] and impaired peripheral arterial circulation[4]

Patients with DME have:

- 2-fold higher risk of cerebrovascular accidents[5]
- 2.5-fold higher risk of myocardial infarction[5]

1. El-Asrar AM, et al. *Int Ophthalmol*. 2001;24:1–11.
2. Kramer CK, et al. *Diabetes Care*. 2011;34:1238–1244.
3. Abdollahi A, et al. *Int J Ophthalmol*. 2009;2:57–60.
4. Riccardi G, et al. *Arteriosclerosis*. 1988;8:509–514.
5. Nguyen-Khoa B-A, et al. *BMC Ophthalmology*. 2012;12:11.

Retinal Manifestations of Diabetes



1. American Academy of Ophthalmology; www.aao.org/ppp. Accessed Nov 26, 2013; 2. Brownlee M, et al. *Williams Textbook of Endocrinology*. 12th ed. Elsevier Saunders; 2011;1462-1551; 3. Boyer DS, et al. *Ther Adv Endocrinol Metab*. 2013;4:151-169; 4. Ciulla TA, et al. *Diabetes Care*. 2003;26:2653–2664.

Patients with Diabetic Macular Edema May Not Have Symptoms[1]

- 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[1]
- Vision loss can occur suddenly, and regular examinations are crucial to ensure treatment is obtained[2]

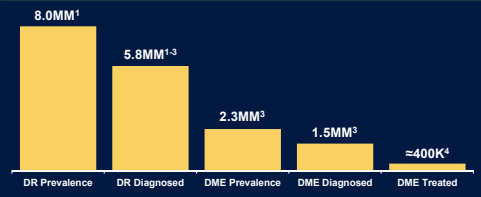
Symptoms of DME include[1]

1. National Eye Institute. Facts about diabetic retinopathy. http://www.nei.nih.gov/health/diabetic/retinopathy.asp. Accessed May 5, 2013. 2. University of Michigan. Diabetic retinopathy. http://www.kellogg.umich.edu/patientcare/conditions/diabetic.retinopathy.html. Accessed May 5, 2013.

Prevalence of DME in the US

Approximately 8 million (21%) of people with diabetes have DR[1]

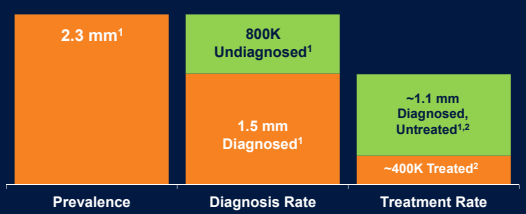
- 5.8 million are diagnosed[1-3]
- 2.3 million have DME[3]



1. NHANES 2005-2008, projected to 2012 US population; 2. Centers for Disease Control and Prevention. www.cdc.gov. Accessed June 9, 2014; 3. Saaddine JB, et al. *Arch Ophthalmol*. 2008;126:1740-1747; 4. BioTrends Research Group. TreatmentTrends®: Diabetic Retinopathy/Diabetic Macular Edema (US) 2013; 5. Proprietary Quantitative Market Research (n=103 retina specialists, n=23,994 DME eyes with central involvement); fielded November 2013.

DME in the United States

- Nearly 800,000 Americans suffer from DME but remain undiagnosed[1]
- Another 1.1 million are diagnosed with DME but are not receiving treatment[1,2]



1.BioTrends Research Group. TreatmentTrends®: Diabetic Retinopathy/Diabetic Macular Edema (US) 2013. 2.Proprietary Quantitative Market Research (n=103 retina specialists, n=23,994 DME eyes with central involvement); fielded November 2013.

Guidelines: Annual Dilated Eye Exams

American Diabetes Association and the American Academy of Ophthalmology: recommended eye examination schedule (including dilated eye exam) for patients with diabetes[1,2]

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

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.

1. Fong DS, et al. *Diabetes Care*. 2003;26:S101.
2. Preferred Practice Pattern® Guidelines, Diabetic Retinopathy. San Francisco, CA: American Academy of Ophthalmology; 2008. http://one.aao.org/CE/PracticeGuidelines/ppp.aspx.

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

American Academy of Ophthalmology Retina/Vitreous Panel. San Francisco, CA: 2014.

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:
  - 46.7% 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)

Bressler NM, et al. *JAMA Ophthalmol*. 2014;132:168-173.

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

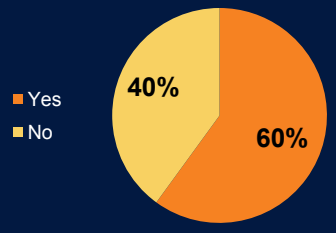
	COMMERCIAL		MEDICAID	MEDICARE	
YEAR	HMO	PPO	HMO	HMO	PPO
2012	56.8	48.8	53.2	66.8	64.6
2011	56.9	48.4	53.3	66.0	63.8
2010	57.7	45.5	53.1	64.6	62.3
2009	56.5	42.6	52.7	63.5	59.4
2008	56.5	35.8	52.8	60.8	52.2

Some improvement, but there is still work to do!

NCQA. State of Health Care Quality 2013.

Awareness of Eye Disease Among Study Participants

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



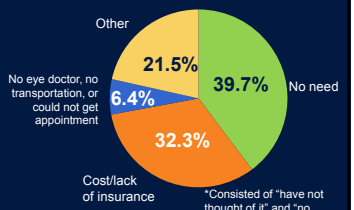
Bressler NM, et al. *JAMA Ophthalmol*. 2014;132:168-173.

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

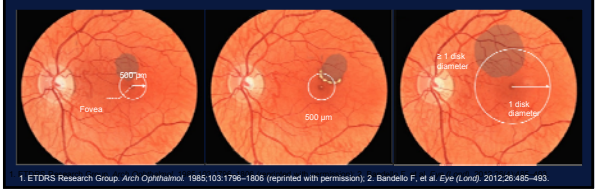


Chou CF, et al. *Diabetes Care*. 2014;37:180-188.

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]

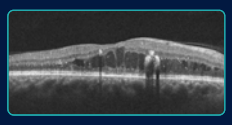
Retinal thickening within 500 µm of the center of the macula	Hard exudates within 500 µm of the center of the macula, if associated with thickening of the adjacent retina	Retinal thickening of >1 disk area in size, any part of which is located within 1 disk diameter of the center of the macula



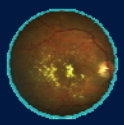
1. ETDRS Research Group. *Arch Ophthalmol.* 1985;103:1796–1808 (reprinted with permission); 2. Bandello F, et al. *Eye (Lond).* 2012;26:485–493.

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]

1. American Academy of Ophthalmology Retina/Vitreous Panel. San Francisco, CA: 2014.
2. Prall FR, et al. *Ophthalmology.* 1991;98:823-833.
3. Rosenblatt BJ, et al. *Ophthalmology.* 3rd ed. China: Mosby Elsevier; 2009:613-621.

Risk Factors for Diabetic Retinopathy

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

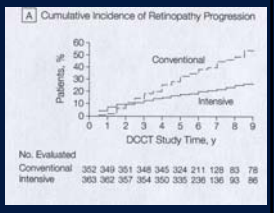
Modifiable factors:
- HbA1C level[1]
- Hypertension[1]
- Dyslipidemia[2]
- Cigarette smoking[3]

*Albuminuria may be modifiable.

1. American Academy of Ophthalmology; http://www.aao.org/education/library/ppp/upload/Diabetic-Retinopathy.pdf. Accessed August, 2006; 2. Chew EY, et al. *Arch Ophthalmol.* 1996;114:1079-1084; 3. Chaturvedi N, et al. *Diabetes Care.*.1995;18:785-792.

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



The DCCT Research Group. *N Engl J Med.* 1993;329:977-986. Figure copyright *NEJM*. Reprinted with permission.

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

Photo courtesy of David M Brown, MD

The DCCT Research Group. *N Engl J Med.* 1993;329:977-986.

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 Group. *N Engl J Med.* 2010;363:233-44.

ACCORD Study

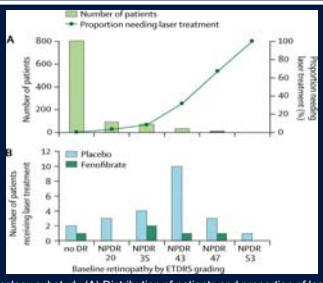
- Progression Rates:

	Intensive	Standard
Glycemic Therapy	7.3%	10.4%
Dyslipidemia	6.5%	10.2%
Blood pressure	10.4%	8.8%

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

Accord Study Group. *N Engl J Med*. 2010;363:233-44. Accord Study Group. *N Engl J Med*. 2010;363:233-44.

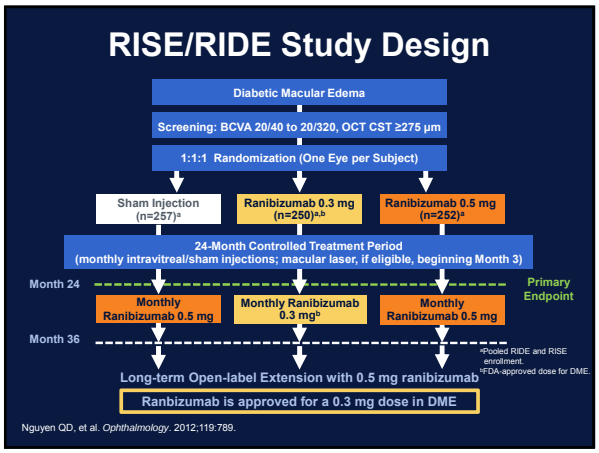
Effect of Fenofibrate on the Need for Laser Treatment for Diabetic Retinopathy (FIELD Study): A Randomized Controlled Trial



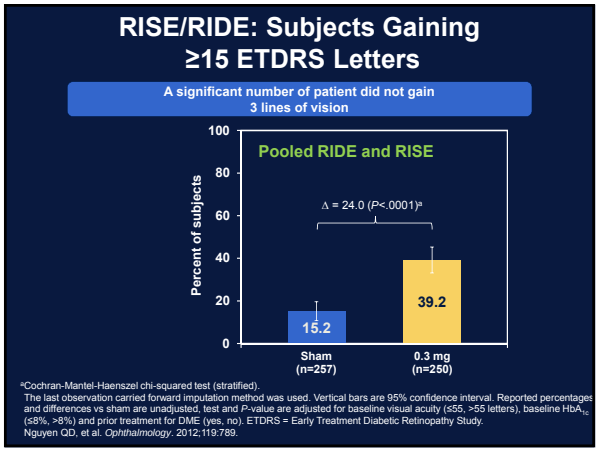
Ophthalmology substudy (A) Distribution of patients and proportion of laser treatment events by ETDRS grading of retinopathy at baseline; (B) number of laser treatment events in each treatment group by ETDRS grading of retinopathy at baseline.

Keech AC, et al. *Lancet*. 2007;370:1687-1697.

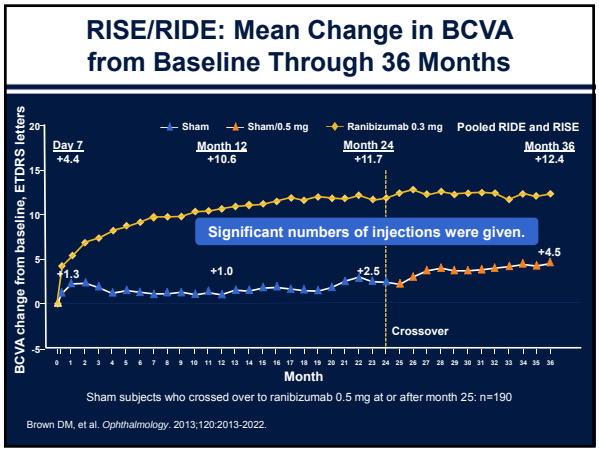
New Methods in the Treatment of Diabetic Macular Edema



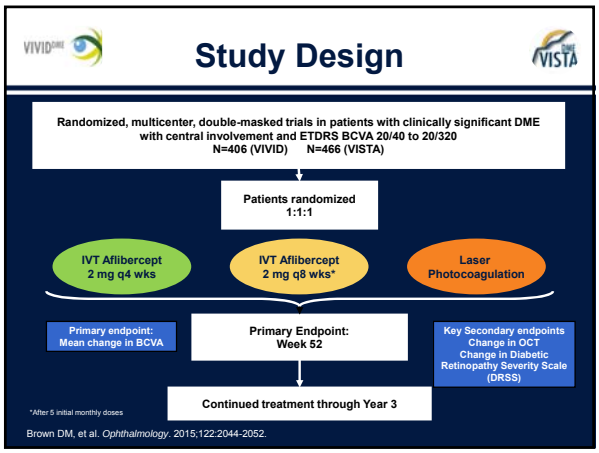
Nguyen QD, et al. *Ophthalmology*. 2012;119:789.

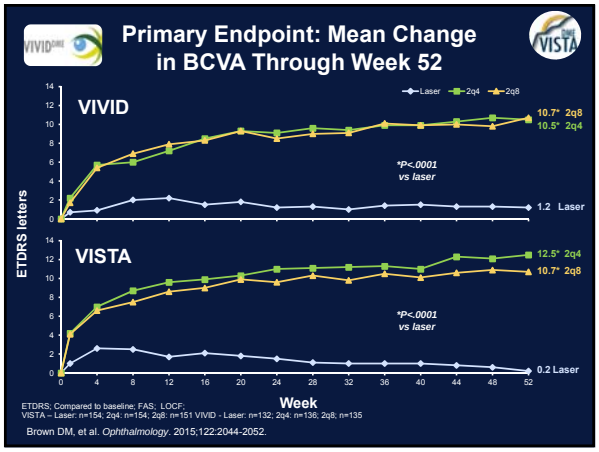


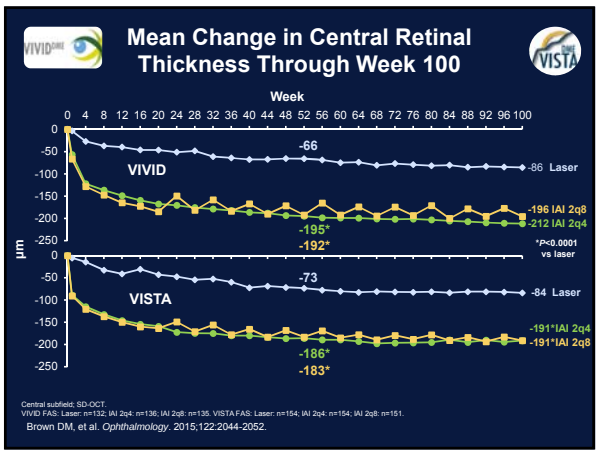
[a]Cochran-Mantel-Haenszel chi-squared test (stratified).
The last observation carried forward imputation method was used. Vertical bars are 95% confidence interval. Reported percentages and differences vs sham are unadjusted, test and *P*-value are adjusted for baseline visual acuity (≤55, >55 letters), baseline HbA_{1c} (≤8%, >8%) and prior treatment for DME (yes, no). ETDRS = Early Treatment Diabetic Retinopathy Study.
Nguyen QD, et al. *Ophthalmology*. 2012;119:789.



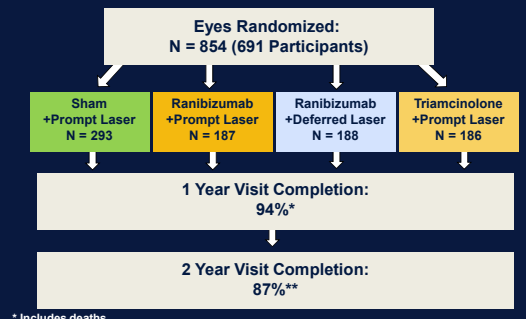
Sham subjects who crossed over to ranibizumab 0.5 mg at or after month 25: n=190
Brown DM, et al. *Ophthalmology*. 2013;120:2013-2022.







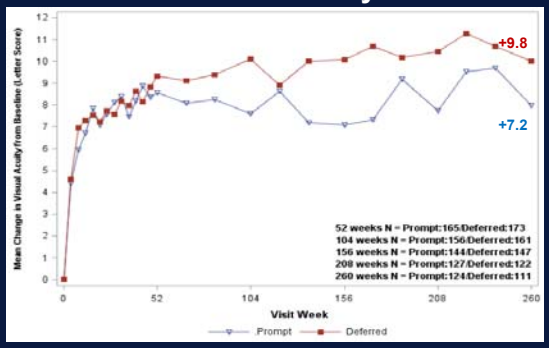
Protocol I Study Design



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

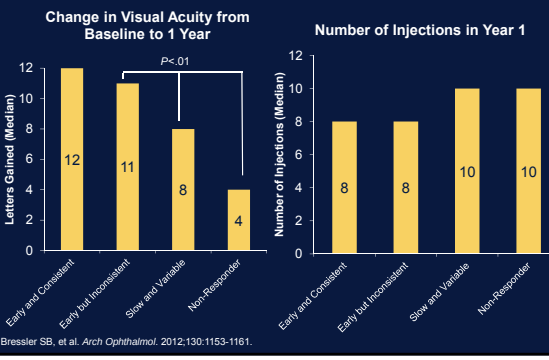
Elman MJ, et al. *Ophthalmology*. 2010;117:1064-1077.

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



Elman MJ, et al. *Ophthalmology*. 2015;122:375-381.

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



Bressler SB, et al. *Arch Ophthalmol*. 2012;130:1153-1161.

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

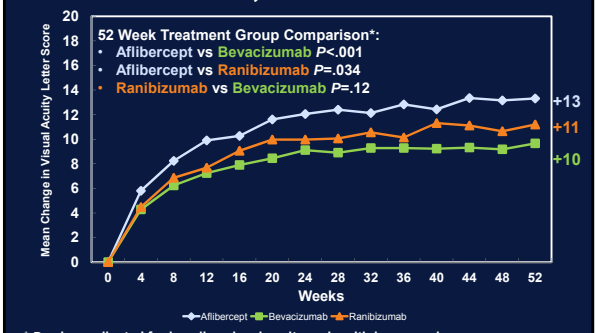
DRCR.net

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Eye Institute

NIDDK

NIH National Eye Institute

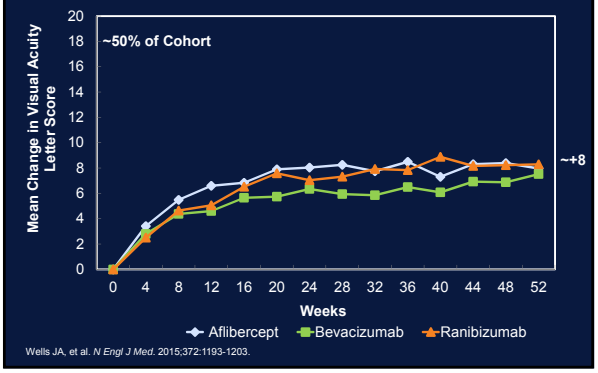
Mean Change in Visual Acuity Letter Score, Full Cohort



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

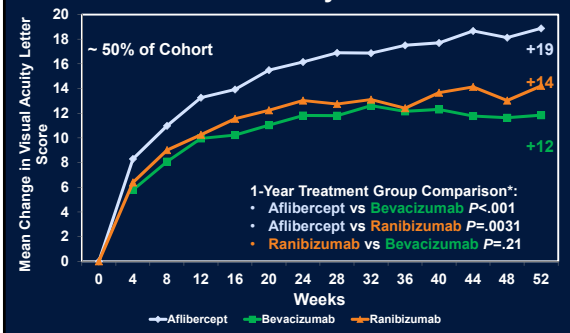
Wells JA, et al. *N Engl J Med*. 2015;372:1193-1203.

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



Wells JA, et al. *N Engl J Med*. 2015;372:1193-1203.

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



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

Wells JA, et al. *N Engl J Med*. 2015;372:1193-1203.

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

	24-Month Pooled RIDE and RISE		36-Month Pooled RIDE and RISE	
SAEs, n (%)	Sham (n=250)	Ranibizumab 0.3 mg (n=250)	Sham/0.5 mg (n=251)[a]	Ranibizumab 0.3 mg (n=250)
Deaths				
Overall	3 (1.2)	7 (2.8)	7 (2.8)	11 (4.4)
Vascular	3 (1.2)	5 (2.0)	5 (2.0)	8 (3.2)
Nonvascular	0	2 (0.8)	2 (0.8)	2 (0.8)
Unknown cause	0	0	0	1 (0.4)
Myocardial infarction				
Overall	9 (3.6)	9 (3.6)	13 (5.2)	18 (7.2)
Fatal	2 (0.8)	2 (0.8)	4 (1.6)	3 (1.2)
Nonfatal	7 (2.8)	7 (2.8)	9 (3.6)	15 (6.0)
CVA				
Overall	4 (1.6)	3 (1.2)	6 (2.4)	5 (2.0)
Fatal	1 (0.4)	1 (0.4)	2 (0.8)	1 (0.4)
Nonfatal	3 (1.2)	2 (0.8)	4 (1.6)	4 (1.6)
APTC events[b]	13 (5.2)	14 (5.6)	18 (7.2)	27 (10.8)

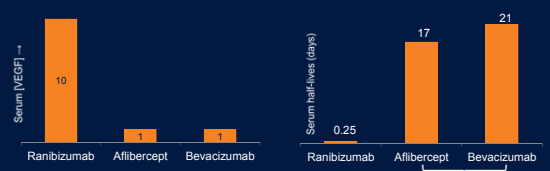
[a]Includes sham and no crossover to 0.5 mg, and sham and crossover to 0.5 mg; [b]Includes vascular deaths, unknown cause deaths, nonfatal MIs, and nonfatal CVAs.

Marcus DM, et al. Presented at the 35th Annual Macula Society Meeting, June 11-15, 2012; Jerusalem, Israel.

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:

[serum VEGF] ~ $^{1}/_{\text{serum half-life (drug)}}$



Avery. Presented at ASRS 2012
Chakravarthy U, et al. *Ophthalmology*. 2013;120:342-8.

Meta-analyses of Anti-VEGF Safety

Authors	Journal (year)	Drug(s)	Findings (Dx)
Abouammoh	*Can J Oph* (2013)	Ranibizumab	No risk for TEE (DME)
Wang	*Retina* (2013)	Ranibizumab Bevacizumab	No risk for AE (Myopic CNVM)
Virgili	*Cochrane* (2012)	Ranibizumab Bevacizumab	No risk for AE (DME)
Wang	*Curr Eye Res* (2012)	Ranibizumab Bevacizumab	No increase AE (DME)
Jyothi	*Eye* (2011)	Bevacizumab	Similar to other anti-VEGF (AMD)
Zhou	*Clin Exp Oph* (2013)	Ranibizumab Aflibercept	No increase in AE (DME)

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

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)

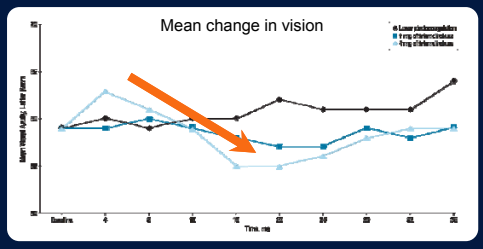
Eligible eyes randomized
Subjects with 2 study eyes
assigned alternative treatment in 2nd eye

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

DRCR. *Ophthalmology*. 2008;115:1447–1459.

Steroids Not as Good as Laser?

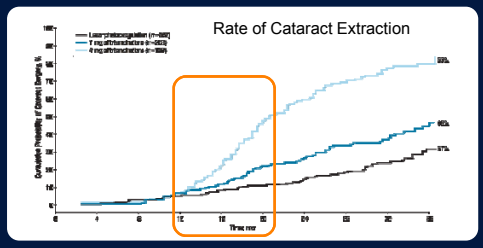
- Protocol B conclusion: "focal/grid photocoagulation is more effective and has fewer adverse effects than... intravitreal triamcinolone"



DRCR. *Ophthalmology*. 2008;115:1447–1459.

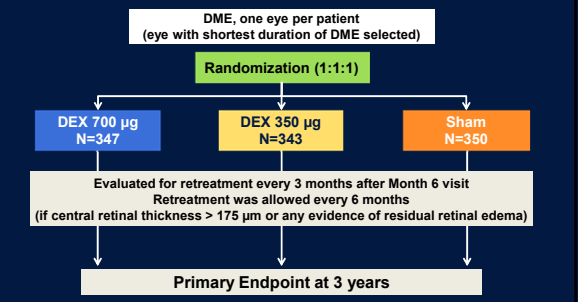
Steroids Caused Cataract

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



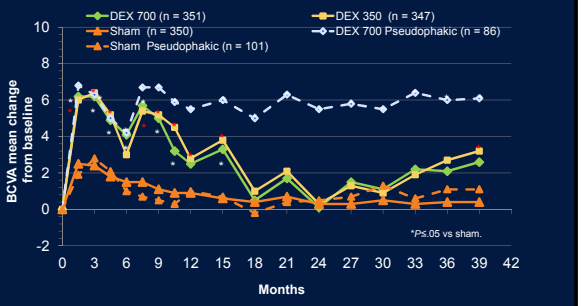
DRCR. *Ophthalmology*. 2008;115:1447–1459.

MEAD Study Design



Boyer DS, et al. *Ophthalmology*. 2014;121:1904-1914.

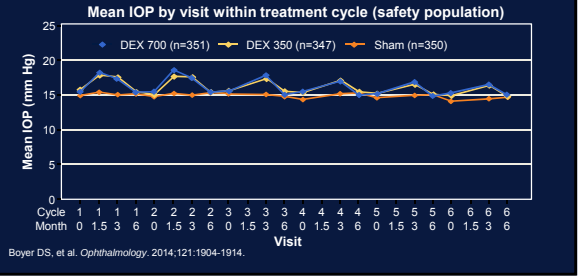
MEAD Study: Mean Improvement in Vision Based on Pseudophakic and Phakic Status



Boyer DS, et al. *Ophthalmology*. 2014;121:1904-14

Effect of DEX Treatment on IOP

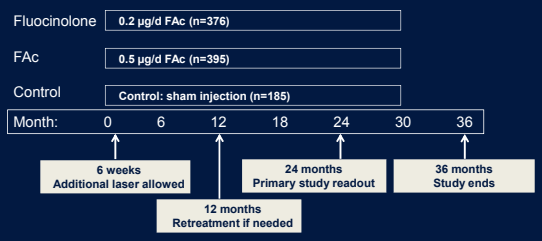
- Mean IOP in the study eye increased following each injection of DEX
- The incidence or magnitude of IOP elevation did not increase over time with repeated injection of DEX and resolved after each injection



Boyer DS, et al. *Ophthalmology*. 2014;121:1904-1914.

FAME Study Design

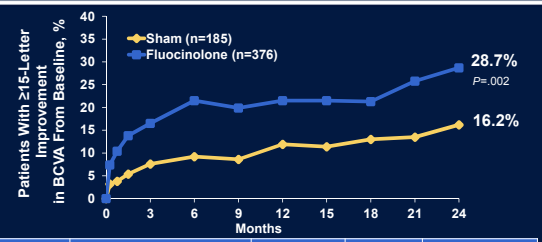
2 randomized, multicenter, double-masked, parallel-group, 36-month clinical trials (FAME A and FAME B) in patients with DME previously treated with laser



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

Campochiaro PA, et al. *Ophthalmology*. 2012;119:2125-2132.

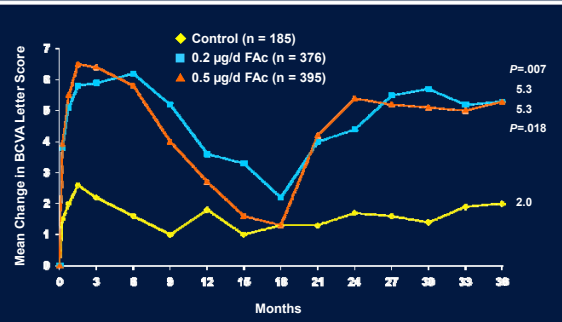
FAME Study Efficacy at 24 Months: Percentage of Patients with ≥15-Letter Improvement[1]



Study	Outcomes	Fluocinolone	Sham	Estimated Difference (95% CI)
FAME A*	Gain of ≥15 letters in BCVA, n (%)	51 (27)	14 (15)	12.1 (2.6 to 21.6)
FAME B*	Gain of ≥15 letters in BCVA, n (%)	57 (31)	16 (18)	13.0 (2.7 to 23.4)

Campochiaro PA, et al. Ophthalmology. 2011;118:626-635..
Prescribing Information; http://www.alimerasciences.com/wp-content/uploads/2014/09/iluvien-prescribing-information.pdf

Mean Change From Baseline in BCVA Letter Score



Campochiaro PA, et al. *Ophthalmology*. 2012;119:2125-2132.

FAME: Summary of Elevated IOP-Related Adverse Reactions

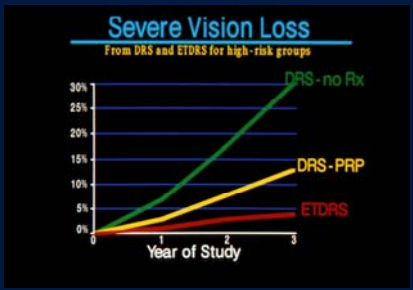
EVENT	Fluocinolone (N = 375) n (%)	Sham (N = 185) n (%)
IOP elevation ≥ 10 mm Hg from baseline	127 (34%)	18 (10%)
IOP elevation ≥ 30 mm Hg	75 (20%)	8 (4%)
Any IOP-lowering medication	144 (38%)	26 (14%)
Any surgical intervention for elevated intraocular pressure	18 (5%)	1 (1%)

Campochiaro PA, et al. *Ophthalmology*. 2012;119:2125-2132.

Management of Proliferative Diabetic Retinopathy

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

- Panretinal photocoagulation reduces risk of SVL by 50%*



* DRS. *Ophthalmology*. 1978;85:82-106.

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]**

1- DCCT. *Arch Ophthalmol*. 1995;113:36-51.
2- UKPDS. *BMJ*. 1998;317:703-713.
3- ACCORD – Chew EY, et al. *N Engl J Med*. 2010;363:233-244.
4- RASS – Harindhanavudhi t, et al. *Diabetes Care*. 2011;34:1838-1842.
5 - FIELD. – Keech AC, et al. *Lancet*. 2007;370:1687-1697.

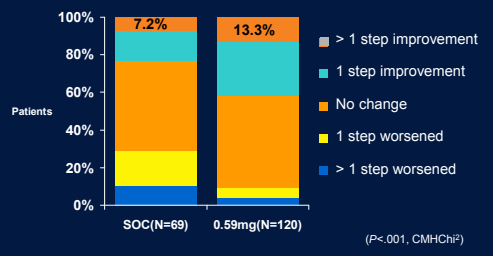
Impact of Treating Risk Factors on DR

- 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%

Cheung N, et al. *Lancet*. 2010;376:124-136.

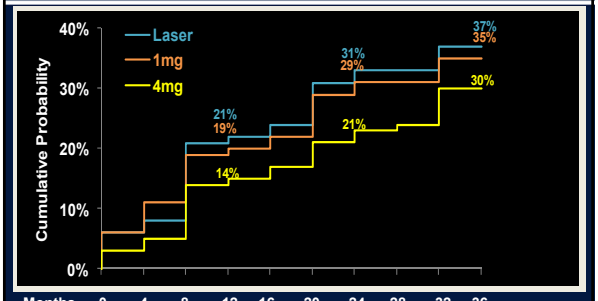
36-month data

Fluocinolone Acetonide Implant: Change in Diabetic Retinopathy Severity Scores



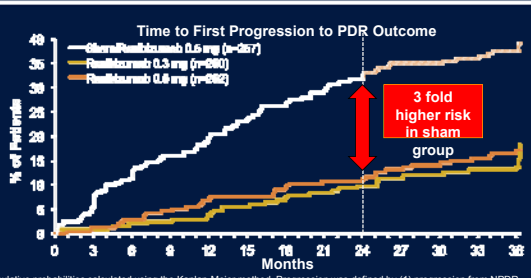
Pearson PA, et al. *Ophthalmology*. 2011;118:1580-1587.

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



Bressler NM, et al. *Arch Ophthalmol.* 2009;127:1566-1571.

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



Cumulative probabilities calculated using the Kaplan-Meier method. Progression was defined by (1) progression from NPDR (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.

Brown DM, et al. *Ophthalmology.* 2013;120:2013-2022.

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*=.001)
- *Data from DRCR Protocol I are consistent with the retinopathy level findings from the RIDE/RISE studies*

Bressler SB, et al. *JAMA Ophthalmol.* 2013;131:1033-1040.