Update on Current Definitions and Treatment of Diabetic Retinopathy

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No financial disclosures.
I will be discussing off label use of bevacizumab.

Plan

- Case discussions
- Background/prevalence/diabetic goals
- Pathophysiology of Diabetic Retinopathy
- Overview of diabetic retinopathy definitions
- Treatment options
- Clinical trials
- Future directions

Case 1

Type 2 NIDDM x 15 years
20/20 Vision OS
Case 2
Type 2 NIDDM x 15 years
20/50 Vision
Case 3
Type 2 IDDM x 20 years
20/200 Vision OD

Diabetic Retinopathy
- Leading cause of new legal blindness among working age individuals in the US (20-64 year olds)
- US Prevalence rate 40+ year olds: 28.5% (4.2 million)
- Worldwide prevalence 34.6% (93 million people)

Vision Threatening Diabetic Retinopathy
- United States 4.4% (0.7 million)
- Worldwide 10.2% (28 million)

- 2020 projection in US:
  - 6 million with retinopathy
  - 1.34 million with vision threatening diabetic retinopathy

Duration of diabetes is most important

**Type 1**
- 5 years: 25% with retinopathy
- 10 years: 60% with retinopathy
- 15 years: 80% with retinopathy
- 20 years: 99% with retinopathy
- PDR present in 50% for those with 20+ years of diabetes (in those patients less than 30 years old)


**Type 2**
- 30+ year olds with DM2 less than 5 years
  - 40% using insulin have diabetic retinopathy
  - 24% not requiring insulin have diabetic retinopathy
- 19 years duration
  - 60% have diabetic retinopathy
  - Approximately 84% using insulin
  - 53% in non-insulin users
- Proliferative Diabetic Retinopathy
  - <5 years: 2% have PDR
  - 25 years: 25% have PDR

**American Diabetes Association Retinopathy Screening 2015**
- Performed by optometrist or ophthalmologist within 5 years of diagnosis for Type 1 DM (>10yo)
- Shortly after diagnosis of Type 2 DM
- Annual examinations, unless retinopathy is progressing
- Women with diabetes who are contemplating pregnancy and also follow-ups during pregnancy
U.S. Age-Adjusted Percentage of Adults with Diagnosed Diabetes Receiving a Dilated Eye Exam in the Last Year

Percent


50 60 70

CDC.Gov Preventative Statistics 1994-2010

U.S. Percentage of Adults with Diagnosed Diabetes Receiving a Dilated Eye Exam in the Last Year

Diabetic Primary care screening

- Glycemic control
- BP evaluation
- Cholesterol evaluation
- Urinary albumin excretion
- Renal function
- Medication adherence
- Foot examination
- Retinal examination
- Dental examination
Primary Diabetic Goals

- Emphasize importance of Diabetes Self Management Education (DSME)
- Education about glycemic control and microvascular risk
- Discussion of asymptomatic nature of diabetic eye disease
- Overcome barriers
  - Cost and insurance coverage of eye care
  - “But I don’t need new glasses”

Glucose Control

- **UKPDS**: United Kingdom Prospective Diabetes Study
  - Type 2 Diabetes
  - 4209 patients from 1977-1999
  - 25-65 year olds
  - Conventional versus intensive therapy
  - 1 point drop in HgbA1c reduced progression by 35%
  - 47% reduction in moderate vision loss

  Holman et al. NEJM 359; 2008: 1577-1589

- **DCCT**: Diabetes Control and Complications Trial
  - Type 1 Diabetes
  - 1441 patients from 1983-1993
  - Conventional versus intensive therapy

  Patients with 3 steps of DR change from baseline

  NEJM 1993; 329: 977-986
HgbA1C and Glycemic Control

- Action to Control Cardiovascular Risk in Diabetes (ACCORD) study and multiple randomized trials has shown increased risk of mortality with HgbA1C <6.5

- Recent studies including an older population with diabetes have shown a U-shaped relationship of increased mortality associated with low HbA1c.

Frailty and HgbA1c

- No direct causal link between low HbA1c and mortality
- Unclear mechanism of A1c and mortality relationship
- Importantly in these studies: functional status, disability, or frailty was not routinely measured
- Perhaps malnutrition, inflammation, and functional decline are characteristics shared by the populations that showed increased mortality and low HbA1c
Pathophysiology of DR

Hyperglycemia

Inflammation

Breakdown of Blood Retinal Barrier

Nonperfusion

Leakage

Neovascularization

Other Aspects to Consider

- Endocrine Control
- HgbA1c
- Blood Pressure
- Hyperlipidemia
- Kidney Problems
- Neuropathy

- Aspirin is NOT shown to change diabetic retinopathy or complications of vitreous hemorrhage


Defining Diabetic Retinopathy

- Macula Evaluation
- Peripheral Evaluation
- Supplementary Testing:
  - OCT
  - Fluorescein Angiography


Diabetic Macular Edema

- Affects 10% of all diabetic patients
- Moderate vision loss
- Causes decreased vision, contrast sensitivity, metamorphopsia
- If patients notice the symptoms - easier to talk about need for therapy
- Exudates, microaneurysms, leakage on fluorescein angiography, OCT thickening
- Can have uninvolved fovea

Clinically Significant Macular Edema (CSME)

Defined by the ETDRS to include any of the following features:

- Thickening of the retina at or within 500 µm of the center of the macula
- Hard exudates at or within 500 µm of the center of the macula, when associated with adjacent retinal thickening.
- A zone or zones of retinal thickening one disc area or larger, where any portion of the thickening is within one disc diameter of the center of the macula.

Newest terminology:

- ci-CSME Center-Involving Clinically Significant Macular Edema
- nci-CSME Non-Center-Involving CSME (diffuse or elsewhere)
Peripheral Examination

Stages of Diabetic Retinopathy

- Mild Nonproliferative ➔ Microaneurysms only
- Moderate
- Severe ★
- Very Severe ★★
- Proliferative ➔ Neovascularization or vitreous hemorrhage present

Severe NPDR is defined by the ETDRS study and 4:2:1 rule
- 4 quadrants with diffuse intraretinal hemorrhages and microaneurysms
- 2 quadrants with venous beading
- 1 quadrant with intraretinal microvascular abnormalities

Severe NPDR progression:

<table>
<thead>
<tr>
<th>Progression to PDR</th>
<th>High-Risk PDR</th>
</tr>
</thead>
<tbody>
<tr>
<td>50%</td>
<td>15%</td>
</tr>
<tr>
<td>75% in 1 year</td>
<td>45% in 1 year</td>
</tr>
</tbody>
</table>

Update on Diabetic Retinopathy

“Diabetes 2000: Elimination of Preventable Blindness from Diabetes by the Year 2000”

Proliferative Diabetic Retinopathy
- Can cause severe vision loss
- Complications
  - Traction Retinal Detachments
  - Vitreous Hemorrhage
  - Neovascular Glaucoma
- “High-Risk PDR” = any 3 of these
  - NVD
  - NVE
  - Vitreous Hemorrhage/preretinal heme
  - Severe NV (¼ - ⅔ NVD or ½ Disc Area NV)
Traction Retinal Detachment

Treatments Available

- Laser
  - Focal Macular Laser
  - PRP
- Injections
  - Anti-VEGF
    - Bevacizumab
    - Ranibizumab
    - Afiberecept
  - Steroid
    - Dexamethasone
    - Fluocinolide
    - Triamcinolone
- Surgery
  - Removal of Hyaloid Face
  - Vitreomacular Traction
  - Traction Retinal Detachments
**Diabetic Retinopathy Study**

- Established value of laser photocoagulation surgery for patients with severe NPDR and PDR.

### Dr. Treatment Landmarks

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Year</th>
<th>Dr.</th>
<th>Notes</th>
</tr>
</thead>
</table>
| Scatter Laser | 1976-81 | 9 | -
| Panretinal Photocoagulation | 1976-81 | 8 | -
| Intravitreal Fluocinolone Implant | 2003 | 6 | -
| Intravitreal Triamcinolone Acetonide | 2005 | 5 | -
| Intravitreal Bevacizumab | 2010 | 4 | -
| Intravitreal Ranibizumab | 2014 | 3 | -
| Intravitreal Aflibercept | 2016 | 2 | -

### Table: Recommendations for Patients With Diabetes and Macular Edema

<table>
<thead>
<tr>
<th>Severe Visual Loss</th>
<th>Baseline Severity of Retinopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr.</td>
<td>Interval</td>
</tr>
<tr>
<td><strong>Dr.</strong></td>
<td><strong>Interval</strong></td>
</tr>
<tr>
<td>MD</td>
<td>Months</td>
</tr>
<tr>
<td><strong>Dr.</strong></td>
<td><strong>Interval</strong></td>
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<td>Months</td>
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<td><strong>Interval</strong></td>
</tr>
<tr>
<td>MD</td>
<td>Months</td>
</tr>
</tbody>
</table>

**Follow Up**

**Recommended**

- Treat patients with clinically significant macular edema (CSME) with intravitreal anti-VEGF agents.
- Consider panretinal photocoagulation for patients with moderate to severe nonproliferative diabetic retinopathy (NPDR).

**Exceptions**

- Panretinal photocoagulation or intravitreal anti-VEGF agents may be used for patients with high-risk PDR.

**FDA Approval**

- Intravitreal anti-VEGF agents are approved for the treatment of CSME.

**Available at:** [www.aao.org/ppp](http://www.aao.org/ppp)
ETDRS- focal laser

- 3 line vision gain *gold standard to be compared to*
- 3711 patients, completed in 1985
- 50% reduction in 3 line vision loss
- 15% of patients improved by 3 lines

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DR Treatment Landmarks

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1985</td>
<td>DRS1</td>
</tr>
<tr>
<td>1985</td>
<td>ETDRS2</td>
</tr>
<tr>
<td>2005</td>
<td>Focal Laser Photocoagulation (DSST)</td>
</tr>
<tr>
<td>2005</td>
<td>VEGF Inhibitors (Bevacizumab, Ranibizumab, Aflibercept)</td>
</tr>
<tr>
<td>2008</td>
<td>Intravitreal Dexamethasone MEAD Study FDA Approval</td>
</tr>
<tr>
<td>2010</td>
<td>Intravitreal Triamcinolone Acetonide DRCRnet Protocol B FDA Approval</td>
</tr>
<tr>
<td>2012</td>
<td>Intravitreal Fluocinolone Acetonide FAME Study FDA Approval</td>
</tr>
</tbody>
</table>

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DRCR.net Protocol D- Vitrectomy

- 87 eyes
- Eyes with DME and vitreomacular traction

**Macular Thickness Decreased**

- 28-49% of eyes with improvement of visual acuity
- 13-31% had worsening of visual acuity

**Visual Outcome Mixed**

- Improvement

3 Month (N=86)

- Worsening

6 Month (N=86)
DR Treatment Landmarks

- Macular Laser Photocoagulation
- VEGF Inhibitors

DRS1 | ETDRS2 | DRS3 | ETDRS4 | ETDRS5 | BOLT Study6 | RISE/RIDE FDA Approval
---|---|---|---|---|---|---

- Intravitreal Aflibercept Injection FDA Approval
- Intravitreal Fluocinolone Acetonide
- Intravitreal Steroids


DRCR.net Protocol B

- 840 eyes with DME
- Focal/grid laser
- 1mg triamcinolone
- 4mg triamcinolone

- At 4 months, 4mg triamcinolone had better VA
- At 1 year, no significant differences
- At 3 years, visual acuity better in laser group
- Problems with steroids
  - Elevation of IOP
  - Need for cataract surgery

Steroids- MEAD study

- Sustained-release Dexamethasone implant study
- DEX implant 0.7mg (n=351) 22% 3-line improvement
- DEX 0.35mg (n=347) 18% improvement
- Sham injection (n=350) 12% improvement
- Average 4 injections (every 6 months), 3 year follow up
- Cataract formation deteriorated vision
Comparison of DEX Implant in Total MEAD Population

Improvement in BCVA provided by DEX implant reduced by month 15; trend to improve by year 3 after cataract surgery.

Mean Change From Baseline (Letters)

- **DEX implant 0.7 mg (n = 351)**
- **DEX implant 0.35 mg (n = 347)**
- **Sham (n = 350)**

Month

- *P* ≤ 0.046 vs sham.

Comparison of DEX Implant in Pseudophakic Eyes

BCVA improvement in pseudophakic eyes treated with DEX implant was consistently significantly better than sham over the 3-year study with no loss of treatment benefit.

Mean Change From Baseline (Letters)

- **DEX implant 0.7 mg (n = 86)**
- **DEX implant 0.35 mg (n = 88)**
- **Sham (n = 101)**

Month

- *P* ≤ 0.046 vs sham.

Injection of Dexamethasone

- 23 Ga needle at bevel
- Teflon coating of insertion device
- Clinical insertion under topical anesthetic

Allergan video of device
0.2 µg/d Fluocinolone Acetonide (FAc) Intravitreal Implant (ILUVIEN®)

- Indicated for the treatment of diabetic macular edema in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.
- Implant is a cylindrical tube, 3.5 mm long × 0.37 mm diameter = 0.38 µL.
- Implant is inserted into the eye through a self-sealing wound via a 25-gauge needle in a specially designed applicator.
- Nonbioerodible polyimide shell.
- Releases a submicrogram daily dose of the steroid FAc.

FAME Study Efficacy: Percentage of Patients With ≥ 15-Letter Improvement

Study Outcomes 0.2 µg/d FAc (ILUVIEN®) Sham Estimated Difference

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)

14. Wells JA et all. Aflibercept, Bevacizumab, or Ranibizumab for DME Two-Year Results from a Comparative Effectiveness Randomized Clinical Trial Ophthalmology 2016;123:1351-1359.
Bevacizumab or Laser Therapy (BOLT)

- Patients with persistent DME and visual impairment
- 2 year outcome
  - Intravitreal 1.25 mg bevacizumab injections (every 6 weeks)
  - Focal laser treatment (every 4 months).
- Bevacizumab patients 5.1 times as likely to gain at least 10 letters
- No patients lost 10 or more letters in the bevacizumab group, compared with 14% of patients treated with laser.

RISE/RIDE
Time to first progression to PDR

VISTA/VIVID

- Center-involving DME
- Aflibercept 2mg every 4 weeks
- Aflibercept 2mg every 8 weeks after 5 monthly doses
- Laser
- Primary endpoint was 52 weeks
- Now results up to 3 years have been published—similar to year 1 and year 2

DRCR Protocol T

- Compared results of different anti-VEGF injections
  - Bevacizumab
  - Ranibizumab
  - Afiblercept
- Overall, there was not a statistically significant difference between 3 different drugs

Protocol T: comparing 3 anti-VEGF agents
Mean Change in Visual Acuity Over 2 Years

Mean Change in Visual Acuity Letter Score

Weeks

DRCR.net Protocol T
Mean Change in Visual Acuity Over 2 Years
By Baseline Visual Acuity Subgroup

Mean Change in Visual Acuity Letter Score

Weeks
DRCR.net Protocol S- anti-VEGF vs. PRP for PDR

- Study question: Is ranimizumab non-inferior to PRP for treatment of PDR?
- 2 year data published

DRCR.net Protocol S
Mean Change in Visual Acuity

- 2-Year Adjusted Mean Difference: +2.2 letters
- 95% Confidence Interval: (-0.5, +5.0)
- (Meets pre-specified non-inferiority criterion: lower bound of the 95% CI of 0.5 letters was greater than the non-inferiority limit of 5.0 letters)

DR Treatment Landmarks

- Macular Laser Photocoagulation
- VEGF Inhibitors

VEGF or inflammation driven?

- Inflammatory cytokines are elevated in the eyes of patients with diabetes\(^1\).
- Inflammatory cytokines are expressed at a higher level in eyes with DME\(^2\).
- Theory that diabetic eye disease changes at some point from primarily anti-VEGF-driven to primarily inflammation-driven.

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DRCR Protocol I

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EARLY analysis of Protocol I data (anti-VEGF only)

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Future directions

- DRCR.net Protocol V explores using anti-VEGF on asymptomatic very good vision patients
- Observe
- Anti-VEGF
- Laser
- DRCR.net Protocol AB compares anti-VEGF to surgical treatment of vitreous hemorrhage from PDR

OCT Angiography

Micropulse - Clinical Effect
Micropulse Regimens are Nonstandardized

<table>
<thead>
<tr>
<th>Study</th>
<th>DuraIon (ms)</th>
<th>Number of Spots</th>
<th>Spot Size μ</th>
<th>Power</th>
<th>FAZ Duty Cycle %</th>
<th>Temperature</th>
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</thead>
<tbody>
<tr>
<td>Lavinsky</td>
<td>200</td>
<td>768, .25</td>
<td>200</td>
<td>125</td>
<td>120% of the power yielding a faint burn in continuous wave mode</td>
<td>Treat 15</td>
</tr>
<tr>
<td>Nicolo</td>
<td>200</td>
<td>250-450</td>
<td>200</td>
<td>200</td>
<td>200 mW</td>
<td>Treat 5</td>
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<tr>
<td>Figueira</td>
<td>200</td>
<td>125</td>
<td>200</td>
<td>125</td>
<td>120% of the power yielding a faint burn in continuous wave mode</td>
<td>Treat 15</td>
</tr>
<tr>
<td>Othman</td>
<td>200</td>
<td>75-20</td>
<td>75-200</td>
<td>1,000</td>
<td>150-1200 mW</td>
<td>Treat 67</td>
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<tr>
<td>Takatsuna</td>
<td>200</td>
<td>Not given</td>
<td>200</td>
<td>200</td>
<td>200% of the power yielding a faint burn in continuous wave mode</td>
<td>Treat 15</td>
</tr>
<tr>
<td>Friberg</td>
<td>200</td>
<td>Not given</td>
<td>200</td>
<td>200</td>
<td>200% of the power yielding a faint burn in continuous wave mode</td>
<td>Treat 15</td>
</tr>
</tbody>
</table>

Outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>N (eyes)</th>
<th>Mean BL BCVA</th>
<th>Mean 12 Mo Change in BCVA</th>
<th>Mean BL CSMT</th>
<th>12 Mo Change in Mean CSMT, μ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Figueira</td>
<td>64</td>
<td>20/28</td>
<td>+49</td>
<td>+62</td>
<td></td>
</tr>
<tr>
<td>Ohman</td>
<td>220</td>
<td>20/32</td>
<td>+1.5</td>
<td>353</td>
<td>-138</td>
</tr>
<tr>
<td>Takatsuna</td>
<td>56</td>
<td>20/59</td>
<td>+3.5</td>
<td>504</td>
<td>-184</td>
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<tr>
<td>Othman</td>
<td>43</td>
<td>20/28</td>
<td>0</td>
<td>342</td>
<td>-47</td>
</tr>
<tr>
<td>Friberg</td>
<td>62</td>
<td>20/32</td>
<td>+1.5</td>
<td>358</td>
<td>-46</td>
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<tr>
<td>Vujosevic</td>
<td>32</td>
<td>20/100</td>
<td>5</td>
<td>379</td>
<td>-68</td>
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<tr>
<td>LuWrull</td>
<td>20</td>
<td>20/158</td>
<td>+29</td>
<td>371</td>
<td>-145</td>
</tr>
</tbody>
</table>

Decreases thickness. True effect on vision?
American College of Physicians updates recommendations for treatment of type 2 diabetes

"Physicians should prescribe metformin to patients with type 2 diabetes when medication is needed to improve high blood sugar, the American College of Physicians (ACP) recommends in an evidence-based clinical practice guideline published today in Annals of Internal Medicine.

If a second oral medication is needed to improve high blood sugar, ACP recommends that physicians consider adding either a sulfonylurea, thiazolidinedione, SGLT-2 inhibitor, or DPP-4 inhibitor to metformin."

DRCR.net Protocol AB

Patient recruitment:
- Type 1 or 2 diabetes
- Vitreous hemorrhage causing visual impairment (any vision level 20/32 to LP)
- Lens status does not matter
- Prior PRP does not matter
- No eye surgery within 4 months or anti-VEGF for 2 months
- Cannot have a retinal detachment or TRD
- Cannot be on dialysis or have kidney transplant
- Randomized to monthly aflibercept injections or immediate vitrectomy with PRP (within 2 weeks)
- Primary outcome: 24 weeks, duration of study 2 years

For 2 hours of transcript-quality CE, look for correspondence from NOVA within the next 2 weeks
Contact: Vanessa McDonald
Program Manager of Continuing Education
954-262-4224 Office oceaa@nova.edu 954-262-1818 Fax

More information on these slides:
http://www.retinasarasota.com
Beth Richter, MD, PhD
Retina Associates of Sarasota
Offices in Bradenton, Sarasota, Venice, and Port Charlotte
bethmd@me.com
Cell 777-0454
Diabetic Retinopathy Clinical Research Network – Protocol AB
Intravitreous Anti-VEGF vs. Prompt Vitrectomy for Vitreous Hemorrhage from Proliferative Diabetic Retinopathy
(Protocol Version 1.0)

Inclusion
1. Age ≥ 18 years
2. Diagnosis of diabetes mellitus (type 1 or type 2)
3. At least one eye meets the study eye criteria listed below
4. Patient is willing and able to undergo vitrectomy within next 2 weeks and the vitrectomy can be scheduled within that time frame.

Exclusion
5. History of chronic renal failure requiring dialysis or kidney transplant.
6. A condition that, in the opinion of the investigator, would preclude participation in the study (e.g., unstable medical status including blood pressure, cardiovascular disease, and glycemic control).
7. Initiation of intensive insulin treatment (a pump or multiple daily injections) within 4 months prior to randomization or plans to do so in the next 4 months.
8. Participation in an investigational trial that involved treatment within 30 days of randomization with any drug that has not received regulatory approval for the indication being studied.
9. Known allergy to any component of the study drug (including povidone iodine prep).
10. Blood pressure > 180/110 (systolic above 180 or diastolic above 110).
11. Systemic anti-VEGF or pro-VEGF treatment within 4 months prior to randomization.
12. For women of child-bearing potential: pregnant or lactating or intending to become pregnant within the next 2 years.
13. Individual is expecting to move out of the area to an area not covered by another DRCR.net certified clinical center during the next 2 years.

Study Eye Criteria
Inclusion
a) Vitreous hemorrhage causing vision impairment, presumed to be from proliferative diabetic retinopathy, for which intervention is deemed necessary.
   • Prior PRP is neither a requirement nor an exclusion
   • Subhyaloid hemorrhage alone does not make an eye eligible
b) Immediate vitrectomy not required (investigator and participant are willing to wait at least 4 months to see if hemorrhage clears sufficiently with anti-VEGF without having to proceed to vitrectomy).
c) VA letter score ≤ 578 (approximate Snellen equivalent 20/32) and at least light perception.
   • Investigators should use particular caution when considering enrollment of an eye with visual acuity ~20/32 to 20/40 to ensure that the need for vitrectomy and its potential benefits outweigh the potential risks.

Exclusion
d) Evidence of traction detachment involving or threatening the macula.
e) Evidence of neovascular retinal detachment.
f) Evidence of neovascular glaucoma
   • Iris or angle neovascularization is not an exclusion
g) Known DME defined as either
   • OCT central subfield thickness (microns):
     1. Zeiss Cirrus: ≥290 in women; ≥305 in men
     2. Heidelberg Spectralis: ≥305 in women; ≥320 in men
   • DME on clinical exam that the investigator believes currently requires treatment.
h) History of intravitreal anti-VEGF treatment within 2 months prior to current vitreous hemorrhage onset or after onset.
i) History of intravitreal corticosteroid treatment within 4 months prior to current vitreous hemorrhage onset or after onset.
j) History of major ocular surgery within prior 4 months or major ocular surgery other than vitrectomy anticipated within the next 6 months following randomization.
k) History of vitrectomy.
l) History of YAG capsulotomy performed within 2 months prior to randomization.
m) Aphakia.
n) Uncontrolled glaucoma (in investigators judgement).
c) Exam evidence of severe external ocular infection, including conjunctivitis, chalazion, or substantial blepharitis.

Major ocular surgery includes:
• Cataract extraction
• Scleral buckle
• Any intraocular surgery

DRCR AB EligibilityPocket Card 8-26-16