New Frontiers in the Detection & Management of Diabetic Retinopathy

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Objectives

• Epidemiology & Demographic Trends
• What IS Diabetic Retinopathy
• What’s New for Detecting Diabetic Retinopathy
• Assaulting Diabetic Retinopathy
• Prevention & Optometry’s Role

Worldwide Statistics

1 billion will have diabetes by 2050 (100 million in the US!)
Highest increases in diabetes & prediabetes in Asia and Sub-Saharan Africa

International Diabetes Federation, 2015; www.diabetesatlas.org

2020 CDC Diabetes Statistics

• 34.2 million Americans
• 7.3 million undiagnosed
• 88 million have prediabetes
• 1.4 million legally blind from DR

National Diabetes Statistics Report 2020
US Centers for Disease Control & Prevention
national-diabetes-statistics-report.pdf

Increasing Prevalence of Diabetes Over Time

Percent of Total Population with Diabetes (Diagnosed and Undiagnosed):

Disclosures

• I have spoken for, consulted for, or been paid honorarium by the following:
  • ZeaVision, VSP, Risk Medical Solutions, Konan, EyeNuk, Regeneron, Zeiss, Genentech, AI Optics
• These associations did not unduly influence the content of this presentation or my patient care recommendations
Increasing Annual Cost of Diabetes

<table>
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<tr>
<th>Year</th>
<th>Total Annual Direct Medical and Indirect Societal Costs of Diabetes in Billions of Dollars</th>
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<tr>
<td>2020</td>
<td>$622 B</td>
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<td>2025</td>
<td>$699 B</td>
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<td>$776 B</td>
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Cost of Diabetes to the US Economy

- $327 Billion in 2017
- $92 Billion in lost productivity
- 1 in 4 health care dollars
- Up from $245 Billion in 2012
- 26% increase after adjusting for inflation

Diabetes Care. 2018 May;41(5):917-928

Blue Things

- Worldwide diabetes prevalence is now 483 million
- Half of people who have diabetes are undiagnosed
- Five million deaths attributable to diabetes in 2017 – half of these were in patients < 60 yo
- You or the person next to you almost certainly has or soon will have diabetes or prediabetes


We Need A Whole Lotta

# Type 2 Diabetes is the BIGGEST in the World

US = 30 million
India = 60 million
China = 100 million With Diabetes

483,000,000

Burger King

BREAKFAST 6AM
**Diabetic Retinopathy**

- Almost 5% of US adults with diabetes have sight-threatening diabetic retinopathy
  - Native American ethnic groups
  - Macular edema (DME) is the biggest cause of vision loss
- Improving blood glucose & blood pressure control lowers the risk of diabetic retinopathy and its progression
  - Disease duration most important risk factor
- No level of average blood glucose is totally protective against diabetic retinopathy


**Ocular Affects of Diabetes**

- Diabetes can produce any of the following ophthalmic manifestations
  - Refractive changes
  - Ocular surface disease
  - Glaucoma and cataracts
  - Diabetic vitreopathy
  - Cranial nerve palsies
  - Deficits in visual function
  - Retinal vascular occlusion
  - Diabetic retinopathy

Diabetes and DR affect more than visual acuity

**What IS Diabetic Retinopathy?**

Two distinct but inter-related processes

- Microvascular disease detected by observation of vascular abnormalities
- Retinal neuro-degeneration with loss/derangement of neural elements including ganglion cell bodies, nerve fiber layer, and photoreceptors causing *loss of visual function*


**Diabetic Retinopathy (& diabetes writ large) is a Neurovascular Disease**

- Retinal Neurodegeneration
  - Loss of ganglion cell bodies
  - Glial reactivity
  - Neuronal apoptosis

- Retinal Vasculopathy
  - Microaneurysms
  - Capillary non-perfusion
  - Neovascularization

- Generalized Neurodegeneration
  - Peripheral nerves
  - Autonomic nervous system
  - Brain

- Generalized Vasculopathy
  - Renal
  - Heart
  - Brain

Early Detection of Diabetes-Induced Retinal Vascular & Neural Dysfunction

- Careful dilated fundus exam, including the periphery
- OCT and OCTA
- Multi-spectral Imaging/FAF
- Widefield Retinal Imaging
- Macular pigment optical density
- ERG/VEP and OCT
- Contrast sensitivity
- Threshold Color Contrast Vision
- Threshold perimetry (FDT)

Retinal Vasculopathy
Retinal Neuropathy

Essential Questions
- Does earlier detection result in better real-world outcomes?
- Do early detected changes predict future progression?
- What does intervention look like when we detect subclinical DR?
- Evidence is limited

Metabolic Memory aka “Legacy Effect”
- Predominantly peripheral diabetic retinopathy lesions (PPL) significantly associated with increased non-perfusion, risk of progression and 50% more Hm/m detected with UWF imaging than SSFP
- DRCR.net Protocol AA is attempting to confirm the predictive value of PPL and association with other diabetes comorbidities (CV events, ESRD)

The Vast Majority of T2DM Patients Don’t Achieve Metabolic Targets within 5 YEARS of DX!

- Mean A1c = 8.3% (Europe = 8.1%; US = 8.6%)
- Mean Age at Dx = 51.8 years (EU = 61.9; US = 58.3)
- Only 17.6% with HbA1c < 7% (18.7% EU; US = 17.1%)
- Only 49.2% with HbA1c < 8% (53.9% EU; 47.1% US)
- Microvascular Dz = 18.9%    CAD/Stroke = 12.9%
- Metformin alone = 55.6%   met + SFU = 20.9%
- Metformin + DPP4 inhibitor (Januvia) = 23.5%

Importance of the Retinal Periphery in DR

- Study at Joslin showed that patients with predominantly peripheral DR lesions (PPL) were significantly more likely to progress (3.2X) and develop PDR (4.7X) \( p = 0.005 \)
- Patients with PPL had significantly more ischemia on UWF angiography
- Compared to standardized seven-field stereo photos (ETDRS standard), UWF suggested a more severe level of DR in 10% of cases
- DRCR.net Protocol AA will evaluate the predictive value of UWF imaging on ocular/systemic endpoints (study completion in 2020)

UWF Imaging is available from Eidon, Optos and Zeiss

Automatic For the People?

IDx-DR

- Topcon NW400 retinal camera images are uploaded to a cloud server running the IDx-DR algorithm for comparison to an image database

Is Everything “A-IK”? 

- for AI-detection of DR in PCP offices
- 87% sensitivity for detecting ‘more than mild’ DR
- 100% sensitivity for DR equal to or worse than ETDRS moderate severity (level 43)
- Binary Output: (1) More than mild DR detected – refer to an eye care specialist; (2) Negative for more than mild DR – rescreen in 12 months
EyeArt® by EyeNuk

- FDA cleared for autonomous detection of more-than-mild AND vision-threatening DR
- 91.3% sensitivity/91.1% specificity for referrable DR (more-than-mild)
- 98.5% sensitivity for VTR (n = 101,710)
- Disk + macula centered images analyzed
- VTR defined as severe NPDR, PDR, CSME
- Examiner+AI mode maybe ideal for ECPs

Survey of 200 US physician leaders found 80+% believe AI will improve diagnosis & patient care BUT
- 54% believe AI will result in fatal diagnostic errors and half believe it won’t meet expectations

A Few Words About AI

- It's here and imperfect
- It's going to get better – much better
- It WILL allow optometrists to do a better job of taking care of our patients
  - Earlier detection and risk stratification
  - Individualized therapy
- AI will NOT replace human providers
  - Genuine empathy
  - Human communication
  - Balancing Tx options with patient preferences and values

FAF imaging detects significantly more microaneurysms than does standard color photography (p < 0.016)

Key Point for Optometry

- DME is the leading cause of vision loss from diabetes
  - OCT is THE BEST WAY to identify DME
sdOCT is great for monitoring DME, response to therapy & detection of subclinical DME

Up to 30% of DME is undetected by stereo funduscopy and these patients are 3X more likely to develop CSME. Ophthalmologica. 2013;230(4):201-6.

OCTA
- Optical coherence tomography angiography
- 64,000 sequential B-scans/sec allows visualization of vascular perfusion
- Fast, dye-less, no iatrogenic risk
- Allows visualization of subclinical microaneurysm formation, capillary non-perfusion, neovascularization at the vitreoretinal interface


Patient with T1DM x 10 years

20/15 Vision  Minimal NPDR on clinical exam

OCTA shows DR NOT seen on clinical exam

OCTA Findings Linked to DR Progression
- 57 eyes with mild/moderate/severe NPDR and PDR
- Increased FAZ, and both decreased vessel density and flow area in the DCP were highly associated with worsening DR severity (p < 0.01)

OCTA Identifies Pre-Clinical DR
- Parafoveal vessel density in the choriocapillaris, superficial and deep capillary plexi of diabetes subjects is significantly reduced compared to controls. Acta Diabetol. 2018 May;55(5):469-477
- Density normals > DM sans DR > DM with DR
- OCTA showed ma and nonperfusion in 11%/28% of patients without clinical DR
Retinal Diabetic Neuropathy (RDN): Detecting Neuro-degeneration with OCT

OCT Imaging
- Nerve fiber layer
- Inner plexiform layer
- Inner nuclear layer
- Outer plexiform layer
- Outer nuclear layer
- External limiting layer
- Photoreceptor IS/OS
- Retinal pigment epithelium

Retinal diabetic neuropathy (RDN) manifests on optical coherence tomography as significant thinning of the retinal nerve fiber layer and ganglion cell and inner plexiform layers.


Diabetes & RDN Affect Visual Function
- Snellen visual acuity is a 150+ yr old test that does not always reflect real world visual function
- DM/DR also impair: color perception, contrast sensitivity, visual field sensitivity & dark adaptation


Color Vision Deficits
- 40% of DM patients with no ophthalmoscopically detectable retinopathy have acquired color vision deficits
- Selective loss of S-cone function predominates
  - S-cone paucity & heightened phototoxicity

Chromatic Contrast Threshold is a Marker of RDN

- Chromatic visual disturbance in association with retinal diabetic neuropathy precedes clinical diabetic retinopathy in 55% of patients
- 55%-65% of patients with diabetic retinopathy have color vision defects
- Blue-yellow deficiency is found in almost 90% of patients with diabetic retinopathy

Computer-assisted extended color vision testing determines the type of color vision defect and the severity of the diabetes-induced dyschromatopsia

Abnormal ERG in Long-term Diabetes

Abnormal S-cone Function

Abnormal flicker ERG ↑risk of intervention in DR

Other OD-Friendly Tests

- Perimetry and Contrast sensitivity progressively distinguish DM and worsening DR from age-matched subjects without DM

- Macular Pigment is reduced in patients with DM and is inversely associated with DR severity
  - Retina. 2015 Sep;35(9):1895-1902, 1990

- Several RCTs show that carotenoid + antioxidant supplementation improves visual function in DM and DR
  - Br J Ophthalmol. 2015 Feb;199(2):227-34
  - Optom Vis Sci. 2017 Jul;94(7):527-31

Evidence-based Tips for Minimizing Diabetic Retinopathy

- Don’t get diabetes/Don’t get prediabetes
- Get HbA1c as low as safely possible a quickly as possible after Dx; Get TIR > 70%; keep BP < 140/90
- Identify and treat obstructive sleep apnea
- Consume at least 500mg LCu3PUFA/day
- Increase dietary fiber & macular pigment
- Consider science-based nutritional supplements for DR
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Diabetes. 2015 Feb;64(2):631-42
Diabetes Care. 2019 Aug;42(8):1593-1603

Macular Pigment

- and lower still in patients with increasing severity of DR
- Macular pigment is inversely associated with visual function in many studies
- ECPs should measure and optimize MPOD in our patients with and at-risk for diabetes


IMPACT OF INTENSIVE THERAPY OF DIABETES: Summary of Major Clinical Trials

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<thead>
<tr>
<th>Trial</th>
<th>Microvascular</th>
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<td>UKPDS</td>
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<tr>
<td>DCCT/EDIC</td>
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<td>ADVANCE</td>
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<td>VADT</td>
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Metabolic Memory

Good Control Does NOT Eliminate Risk of Severe DR

- 10 year risk of PDR and/or CSME in a newly Dx patient with A1c = 6.5% and BP = 120/80 is nearly 4%
- With mild NPDR the 10 yr risk is 8.4%

Diabetologia. 2011 Oct;54(10):2525-32
Blood Glucose Reality

- Many patients never or rarely check their glucose
- Many patients never get A1c < 7% within the first 5 years - when tight glucose control is most effective at preventing DR

Is HbA1c the Best Predictor of DR Risk?
- Disease duration and HbA1c thought to be most predictive YET....
- Analysis of DCCT/EDIC data shows that mean A1c during the studies accounted for a mere 6-11% of DR risk!
- Moreover, the Joslin “Gold Medlist” study showed little correlation between development of sight-threatening DR and A1c in patients with T1DM > 50 years......

Glacco et al. Diabetes. 2015 Sep;64(9):3273-84

Why HbA1c Isn’t the Whole Story
- Doesn’t reflect glucose variability or the burden of acute hypoglycemia
- US spent $1.25 billion in 2009 on hospitalizations for severe hypoglycemia

Glucose Spikes Increase DR Risk

- T1DM patients > 10 years (n = 23)
- Continuous glucose monitoring (DexCom) showed same A1c but dramatic increase in glucose spikes ≥ 400 mg/dl in subjects with moderate-severe NPDR (no difference if > 350 or 250)

The Perils of Transient Hyperglycemia

- A 6 hour episode of elevated glucose (> 100 mgdl) results in a 6-day massive increase in mitochondrial reactive oxygen species AFTER blood glucose is totally normalized
- High ROS persist for 2 weeks before normalizing
- ROS are the driving force underlying DR
- These glycemic excursions are often too short to be captured by mean glycemia (HbA1c)

Pathophysiology

- Blood vessel damage in diabetes is mediated by four distinct biochemical pathways driven by mitochondrial production of ROS

The Four Pathways

- Polyol
- Hexosamine
- Protein Kinase C (PKC)
- Advanced Glycation Endproducts (AGEs)

Each of these pathways depends on over-production of reactive oxygen species (O2•) by mitochondria exposed to excess glucose and/or free fatty acids

Glucose Metabolism

- Glucose → Polyol Pathway
- Glucose-6-phosphate → Fructose-6-phosphate → Hexosamine Flux
- Glyceraldehyde-3-phosphate → Protein Kinase C
- ATP + 1,3 Diphosphoglycerate (harmless metabolite) → Advanced Glycation Endproducts

Can We Detect It?

- Retinal Flavoprotein Autofluorescence detects in vivo mitochondrial oxidative stress in diabetes
- University of Michigan OcuSciences OcuMet Beacon
- Not yet commercially available

Detection Before Cell Death Occurs
Post-Prandial Hyperglycemia

- Hyperglycemia > 190 that may be too brief to be captured by HbA1c
- Minimize blood glucose spikes > 400
- Increase the glucose time-in-range

Eat fewer carbs
Inject insulin into muscle
Walk after evening meal
Take apple cider vinegar
Use FIASP/Inhaled Insulin
Wear a CGM

A 10-minute walk after the evening meal lowered glucose 22% more than a 30-minute walk before any meal

CGM Updates

- Monitoring systems
  - Constant biofeedback regarding current blood glucose and trend

- CMS requires insulin use and intensive glucose management with 4 home blood glucose measurements/day

Continuous Glucose Monitoring For Patients on Insulin

- FDA approved for both type 1 and type 2 diabetes
- Distinct from an insulin pump, but may interface with a pump (Medtronic, Tandem pumps)
- Shows blood glucose trends (temporal stability)
- Improve glycosylated hemoglobin (HbA1c)
- Alarms for hypoglycemia and hyperglycemia
- Allow calculation of “glucose time-in-range” (TIR)
Continuous glucose monitoring (CGM) systems capture real-time data and allow measurement of glucose time-in-range (TIR) – < 70, 70-180, > 180 mg/l

- DexCom Clarity & Medtronic Sugar IQ apps measures TIR in tandem with their CGMs

- A 10% decrease of TIR results in a 61% increased risk of retinopathy incidence & 2-step ETDRS progression independently of HbA1c – fingerstick data

Beyond HbA1c in diabetes: It is time to look at other outcomes; ADA Scientific Sessions - June 24, 2018, Orlando, FL

Practical Implications of TIR

• Moderate NPDR
  • T1DM x 10 years
  • HbA1c = 7%  TIR = 60% (14.4 hours)

• To achieve a 40% reduction in risk of progressing to STDR, he could:
  —Reduce HbA1c to 4.1%  Source: www.RetinaRisk.com
  —Increase TIR to 73.6% (17.6 hours)

Biggest Benefit When HbA1c Is Already Lower and TIR is also LOW

Medtronic Sugar IQ Predictive Response App

+36 minutes TIR

FDA-approved Pseudo-Closed Loop

Medtronic 670 G, Tandem Control IQ, Omnipod Horizon Systems & more

Dexcom CLARITY® Weekly Summary
Sun Nov 26, 2017 - Sat Dec 2, 2017

Time in Range

87%

-9%
Increase since last week
110 mg/dL
Average glucose
25 mg/dL
Standard deviation

Target Range Settings:
Daytime (7-15 AM – 11:00 PM): 70 – 140 mg/dL
Nighttime (11:00 PM – 7:15 AM): 70 – 140 mg/dL.
**Vinegar Battles Glucose Spikes**

- 2 Tbsp vinegar consumed before a 75g CHO meal prevented post-prandial glucose spikes in pts with T1DM and reduced AUC BG by 20%
  - glycogen repletion

  *Diabetes Care. 2010 Feb;33(2):e27*

**Super-fast-Acting Insulins**

- **Fiasp** aspart (Novolog with niacinamide adjuvant forms insulin monomer to penetrate SC fat more rapidly)
- 29 point 1-hour reduction in post-prandial glucose; 12 point reduction at 2 hours
- 0.15% drop in HbA1c *Diabetes Technol Ther. 2017 Jan 1; 19(1): 25–33*
- UK study estimates 1% drop in diabetes-related blindness and 1715 pound savings per patient *Diabetes Obes Metab. 2017 Jun 1*
- Lyumjev is new SFA Humalog insulin

**Fenofibrate – oral therapy to prevent progression of DR**

- Approved first-line therapy for mild-moderate NPDR in Australian adults with T2DM
- NNT = 14 for prevention of CSNE or PDR
- Fenofibrate significantly decreases multiple inflammatory cytokines in patients with DR (VEGF, IL1B, LpPLA2)
  - Medicine (Baltimore). 2017 Aug;96(31):e7671

**Brimonodine and Somatostatin Retard Neurodegeneration**

- BID combination eyedrop in 700+ with T2DM followed fo 2 years v. placebo (EuroCondor Trial)
- Those with multifocal electroretinogram abnormalities at baseline had less evidence of neurodegeneration by mfERG (p < 0.01)

  *Br J Ophthalmol. 2016 Feb;100(2):227-34*
Test Formula
- Zeaxanthin & Lutein
- Benfotiamine
- Alpha Lipoic Acid
- Vitamin D
- Vitamins C & E
- Mixed Tocopherols/Tocotrienols
- Resveratrol
- Green Tea
- Curcuminoids
- N-Acetyl Cysteine
- Grape Seed Extract
- CoQ10
- Zinc Oxide
- EPA/DHA
- Pycnogenol
- Vitamin B12

Mean Change/SD in visual function measures, serum lipids, hsCRP, TNF-α, glycohemoglobin, foveal thickness and symptoms of diabetic peripheral neuropathy with 95% p-Values

<table>
<thead>
<tr>
<th>Measured Parameter</th>
<th>Δ from baseline</th>
<th>Suppl v. Plac</th>
<th>p-Value</th>
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<td>Color Error Score</td>
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<td>+7.5±22.01</td>
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<td>HDL-C (mg/dl)</td>
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<td>HbA1c (%)</td>
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<td>Foveal Thickness</td>
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<td>0.34±3.48 µm</td>
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<tr>
<td>DPNSS</td>
<td>-30.7%</td>
<td>+10.7%</td>
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Animal model of DR
- DiVFuSS formula prevents mtDNA damage, normalizes ROS and VEGF, and prevents retinal capillary apoptosis

Long-Chain Omega-3 PUFA
- PrediMed Trial comparing Mediterranean-type diet supplemented with extra virgin olive oil or tree nuts versus AHA diet against CV events in patients with T2DM (n=3482)
- Primary trial halted early because both Med diets were significantly superior, especially for stroke prevention
- Subjects consuming > 500 mg daily long-chain-ω3PUFA were 48% less likely to develop STR over 6 yrs compared to those consuming < 500 mg (p=0.001)

Prevalence of DR in the US
- Approximately 8 million (26%) of people with diabetes have DR
- 5.8 million are diagnosed
- 2.3 million have DME
- 2.2 Million w DR UNDIAGNOSED
  - 800,000 w DME UNDIAGNOSED

How Far Out of the Barn Must the Horse Be to Start Treatment?

Approximately 8 million (26%) of people with diabetes have DR
- 5.8 million are diagnosed
- 2.3 million have DME

8.0MM
5.0MM
2.3MM
1.5MM
0.8MM
1.1MM
400K
240K
2.2 Million w DR UNDIAGNOSED
800,000 w DME UNDIAGNOSED

Prevalence of DR in the US

When to Refer?
• It depends on your comfort level
• My Answer:
  – When the patient needs treatment of DR/DME
  – With unexplained VA loss
  – When I am unsure of the diagnosis
  – When the patient has chronic, sub-optimal metabolic control or is receiving decidedly sub-optimal care; frequent hypoglycemia; kids

Sight-threatening DR – Must Refer

When to Worry About NPDR
• When there is associated DME
• When it qualifies as Severe NPDR
  – Hmg/MA
  – Venous Beading
  – IRMA
  
  Per ETDRS

How Do We Prevent This?

Anti-VEGF Therapy for NPDR
• Both Lucentis (ranibizumab) and Eylea (aflibercept) are now approved to treat any level of DR with or without DME
• Significant improvements in DR severity, especially in those with moderately severe or worse NPDR (DRSS Level 47+)

*ETDRS severity level 47: multiple intra-retinal hemorrhages in two or more quadrants, any vein beading, any prominent IRMA

ETDRS: Early Treatment Diabetic Retinopathy Study
Risk for Progressing to PDR in 1 yr
• Mild NPDR: 5%
• Moderate NPDR: 12%
• Severe NPDR: 52%
• Very Severe NPDR 72%

It is key to identify patients with severe NPDR for referral
Didabetic Retinopathy Severity Score (DRSS) Example of 2-Step Improvement

<table>
<thead>
<tr>
<th>Severe NPDR</th>
<th>Moderate NPDR</th>
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<tbody>
<tr>
<td>DRSS Level 53 (Level 6)</td>
<td>DRSS Level 43 (Level 4)</td>
</tr>
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</table>

- Severe retinal hemorrhages in 4 quadrants,
or
- Venous beading in ≥2 quadrants,
or
- Moderately severe intraretinal microvascular abnormalities (IRMAs) in ≥1 quadrant
- Memaneuromas, plus
- Mild IRMAs, or
- Moderate retinal hemorrhages

ALL HAD DME

RISE/RIDE and VIVID/VISTA showed significant reductions in DR severity in DME patients receiving ranibizumab or aflibercept for the treatment of macular edema

DRCR.net Protocol S and CLARITY trials showed that ranibizumab or aflibercept are non-inferior to PRP for the treatment of PDR

PANORAMA Phase 3 100 Week Data
- Aflibercept (Eylea) Q8 or Q16 weeks for moderately severe to severe NPDR sans DME
- 80%/65% achieved 2-step DRSS improvement – p < 0.0001
- VTC (PDR/ASneo) reduced 82-85%
- CI-DME reduced 68-74%

Regeneron Press Statement, October 25, 2018

Benefits of AVT Against DR

Does AVT Benefit NPDR Sans DME?

PANORAMA Phase 3 100 Week Data

Intravitreal Aflibercept for Moderately Severe to Severe Non-Proliferative Diabetic Retinopathy (NPDR) The Phase 3 PANORAMA Study

Charles C. Wykoff MD PhD
On Behalf of the PANORAMA Investigators

Regeneron Press Statement, October 25, 2018
Only 3 patients with moderately severe or worse NPDR need to be treated to prevent 1 vision-threatening complication

**Take Home Messages**

- There has been a paradigm shift toward treating DR at an earlier stage with anti-VEGF Therapy
- Patients with moderate+ NPDR should be referred to a retina specialist to consider AVT
  - Widefield FA often demonstrates worse DR severity than does clinical exam (4X more non-perfusion and 2X more NVE compared to ETDRS imaging)
- DR represents one of the very few diabetes complications that we can actually make BETTER rather than merely stabilizing it

Wessel et al 2012, Retina

**Potential Benefits of anti-VEGF Therapy in NPDR**

- Significantly reduces VTC in moderately severe to severe NPDR and may result in long-term VA benefits, including prevention of blindness
  - DRCR.net Protocol W found significant regression of DR severity/63% reduced risk of VTC in moderate to severe NPDR, but no VA benefit at 2 years with aflibercept versus close monitoring for Tx of VTC as needed (4-year data pending) (consistent with PANORAMA trial)
  - In real-world settings, patients may be lost-to-follow-up (LTFU) and fare worse for visual outcomes
  - the US diabetes population shows a 57.7% relative decrease/2.6% absolute decrease in blindness (BCVA < 20/200) over ten years in severe NPDR with anti-VEGF Tx versus monitoring

Data from thennt.com, accessed September 14, 2019
Lancet 2007;370(9600):1687-97

**Why some people with DR are Lost to Follow-up (LTFU)**

- A study from San Francisco looked at risk for non-compliance
- 209 patients mean age 58yo w A1c 8.5
- 46% of patients attended <80% of f/u
- Risk factors for missing f/u:
  - Foot involvement OR 2.4
  - Foot/kidney OR 3.7
  - Major depressive disorder OR 2.1
  - MediCal or SF Health insurance. OR 5.01/6.79


**Projected Reduced Risk of Legal Blindness in Severe NPDR Patients Receiving anti-VEGF Therapy vs Monitoring based on data from PANORAMA/RISE/RIDE Trials**

57.7% risk reduction in severe vision loss if every severe NPDR patient in the US received anti-VEGF therapy

**Is this a favorable NNT?**

- NNT to prevent one CV death with 5 years of statin therapy in a patient with known heart disease = 83
  - NNT to prevent one non-fatal MI is 39 (NNT = 104 if no Hx of CVD)
- NNT = 333 to prevent a first, non-fatal MI with aspirin therapy
- NNT = 17 to prevent one case of PDR and/or CSME with oral fenofibrate therapy in T2DM with mild NPDR

Data from thennt.com, accessed September 14, 2019
Lancet 2007;370(9600):1687-97
Emerging Treatments for DR/DME

- Combined Anti-VEGF & Angiopoietin-2 Blockade → Farcimab™
- Anti-Integrin Therapy (injected & Topical)
- Adenoviral-Associated Vector Gene Therapy (intravitreal & sub-RPE)

VEGF + ANG-2 Blockade - RESULTS

Farcimab compared to Lucentis:
- 3.6 more letters gained
- More gain 1+ to 3+ lines
- More have a >2 step DRSS improvement
AT 24 WEEKS

Anti-Integrin Therapy

- Integrins are transmembrane receptors that facilitate cell-to-cell and extracellular matrix adhesion
  - Analogous to a thermostat (VEGF turns AC on/off)
  - Integrins tell RPE cells A/C needs to be turned on/off
- Integrins have been implicated in BRB breakdown and ocular neovascularization independently of and in concert with VEGF
- At least one company is developing a topical anti-integrin drug for treating DR (OcuTerra

Key Points

- Diabetes causes both vascular and neuronal damage within the retina
- Multiple technologies can help us detect both
- WE CAN DO MORE than simply monitor patients for the development of sight-threatening retinopathy
- Therapies for advanced DR save vision
- Preventing diabetes is the best way to prevent ocular complications
Evidence-Based Tips To Avoid Diabetes

- Exercise 30 minutes each day (soon after waking) & minimize added sugars
- Eat a predominantly plant based diet including a variety of fruits and vegetables and more vegetables
- Minimize processed meats
- Drink coffee or tea
- Sleep > 6 hours per night and < 9 hours
- Get your serum vitamin D > 40 ng/ml
- Don’t smoke
- Live away from smog
- Breast Feed
- Turn down the thermostat
- Reduce Light at Night
- Fast if you’re obese

References:

- Environ Health Perspect. 2015 May; 123(5): 581-289
- 2014 US Surgeon General’s Report