Evolving Trends in Retinal Vascular Disease

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Financial Disclosures

- Speaker-Carl Zeiss Meditec
- Advisory Board-Bausch + Lomb, Santen.
- *All relevant relationships have been mitigated*

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Outline

- Pathophysiology review
- The era of anti-VEGF
- Imaging strategies, treatment trends, and developments in the care of patients with:
  - 1) Diabetic retinopathy
  - 2) Neovascular macular degeneration
    - (Geographic atrophy)
  - 3) Retinal vein occlusion

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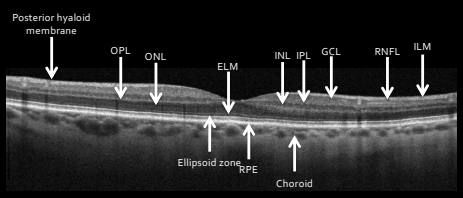

Think "where", then "what"

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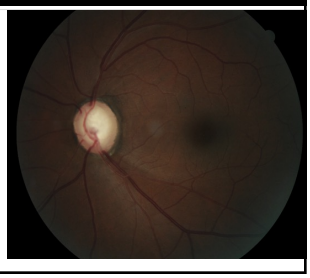
Physiology Review

- Oxygen is delivered by two systems:
  - 1) Retinal vasculature
    - *Non-leaky; inner BRB formed by vascular endothelial cells*
  - 2) Choroidal vasculature
    - Fenestrated-allows exchange of fluid
    - *Outer BRB formed by RPE*



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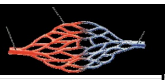
Retinal Vasculature



- Retinal capillaries
  - **1) Superficial capillary plexus (GCL-to a lesser extent RNFL)**
    - Most affected in artery based conditions (HTN)
  - **2) Deep capillary plexus (INL)**
    - Prevenular capillary network
    - Most affected in venous congestive disease (diabetes and RVO)
    - Outer boundary is the outer plexiform layer

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Choroidal Vasculature

- RPE
  - Loose attachment to PRs
  - Strong attachment to Bruch's membrane, choriocapillaris and other RPE cells
    - **RPE-Bruch's membrane complex**
      - **RPE cell bodies + basal lamina of the RPE + remaining layers of Bruch's membrane**
      - **3 layer model**
- Choriocapillaris
  - Fed by posterior ciliary artery branches
    - Compartmentalized blood supply

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Choroidal Vasculature

- Choroid
  - Larger blood vessels, nerves, melanocytes, immune cells
    - Presence of immunological cells represent source for inflammatory retinal disease

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OCT Angiography

- The only thing that moves in the retina over time are red blood cells
- Take the 'difference' between multiple B scans at the same location to produce a 'decorrelation signal'

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OCT Angiography

- En face flow formation and cross sectional structural information
- Not a replacement for FA/OCT
  - Provides new information
- Important in diagnosis of NV and macular ischemia

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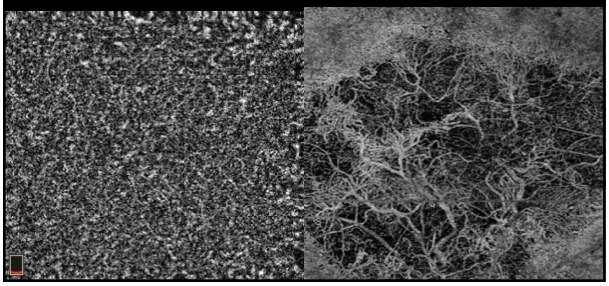
Choriocapillaris on OCTA



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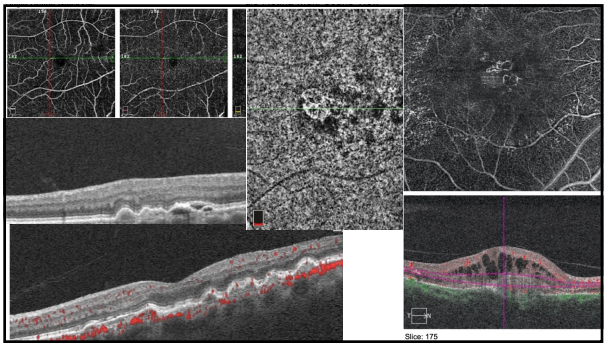

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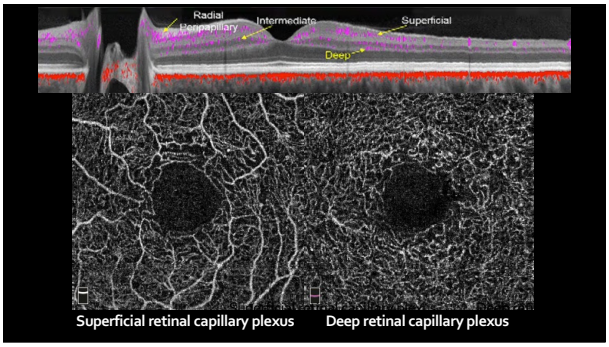

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Challenges in OCTA

Static blood flow information
No leakage, pooling or staining

Small field of view 3x3mm; 6x6mm; 8x8mm with current systems

Motion artifacts are a big deal

Sensitivity is a challenge in eyes with pathology

Quantification of blood flow-not yet

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Vascular Response to Disease

- **1) Exudation**
  - Loss of blood retinal barrier
    - Accumulation of plasma fluid and lipid
    - Hard exudate and intraretinal edema
- **2) Ischemia**
  - Capillary drop out leads to hypoxia
    - Microaneurysms, capillary drop out, neovascularization
- **3) Both**

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Diabetic Retinopathy

- End organ response to systemic disease
- Multifactorial condition
  - Hyperglycemic component
    - Free-radical formation
    - Oxidative stress
  - Vascular component
  - Inflammation
  - Compromised autoregulation
- Tissue damage to metabolically active sites

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Diabetic Retinopathy

- Type II: High incidence of DR at the time of presentation
  - Annual exam
  - Insulin-dependent type II patients are considered to be of higher risk
- Type I: No matter how poorly controlled, typically no retinopathy for 5-7 years
  - Examine 5 years after diagnosis—or at age ten, then annually
- Gestational DM
  - Do not seem to have increased risk of DR; no examination recommendation during pregnancy
- But—for individuals with diabetes who are pregnant:
  - Diabetic retinopathy worsens during pregnancy

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DR Severity Scale

TABLE 1 Diabetic Retinopathy Disease Severity Scale and International Clinical Diabetic Retinopathy Disease Severity Scale

Disease Severity Level	Findings Observable upon Dilated Ophthalmoscopy
No apparent retinopathy	No abnormalities
Mild NPDR (see Glossary)	Microaneurysms only
Moderate NPDR (see Glossary)	More than just microaneurysms but less than severe NPDR
Severe NPDR	
U.S. Definition	Any of the following (4-2-1 rule) and no signs of proliferative retinopathy: • Severe intraretinal hemorrhages and microaneurysms in each of **four** quadrants • Definite venous beading in **two** or more quadrants • Moderate IRMA in **one** or more quadrants
International Definition	Any of the following and no signs of proliferative retinopathy: • More than 20 intraretinal hemorrhages in each of **four** quadrants • Definite venous beading in **two** or more quadrants • Prominent IRMA in **one** or more quadrants
PDR	One or both of the following: • Neovascularization • Vitreous/preretinal hemorrhage

IRMA = intraretinal microvascular abnormalities; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy

NOTE:
- Any patient with two or more of the characteristics of severe NPDR is considered to have very severe NPDR.
- PDR may be classified as high-risk and non-high-risk. See Table 6 for more information.

Adapted with permission from Wilkinson CP, Ferris FL III, Klein RE, et al. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology 2003;110:1679.

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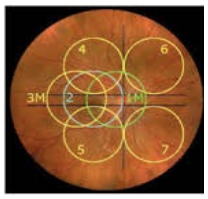
DR Severity Scale (DRSS)

- Modified Airlie House-defined by ETDRS in 1981
- Very mild NPDR
  - MA only (level 20)
- Mild NPDR
  - Hard exudate, cotton wool spots, and/or mild retinal hemorrhages (level 35)



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Retinal Imaging

- Color fundus photography
  - Great for documentation
- Fundus autofluorescence
  - Few indications that alter management
- FA
  - Evolved to be a test of retinal periphery-wider field of view
- ICG
  - Limited availability and utility
- OCT
  - **THE** most important ancillary test in retinal disease
    - Important for determining need for retreatment
- OCT angiography

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Diabetic Retinopathy

- **Vision loss occurs secondary to:**
  - 1) Diabetic macular edema
  - 2) Macular ischemia
  - 3) Proliferative diabetic retinopathy

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Diabetic Macular Edema

- Caused by microvascular occlusion or leakage
- 'CSME' defined by ETDRS
  - Hard exudate within 500µm of the center of the macula
  - Hard exudates at or within 500µm of the center of the macula with adjacent retinal thickening
  - Retinal thickening of 1DD of larger within 1DD of the center of the macula

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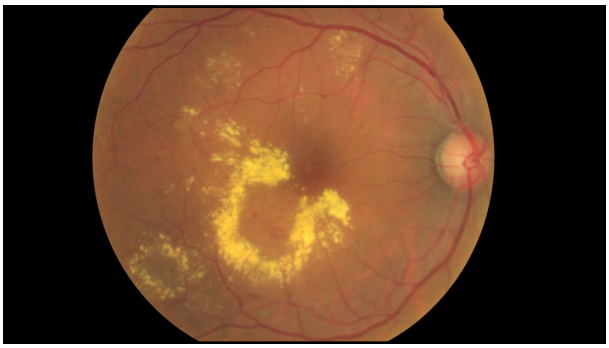

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Now

- Is macular edema present?
- Yes, or no?
  - *Sometimes OCT is needed to aid in diagnosis*

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And if DME is Present…

- Further classify based on OCT findings

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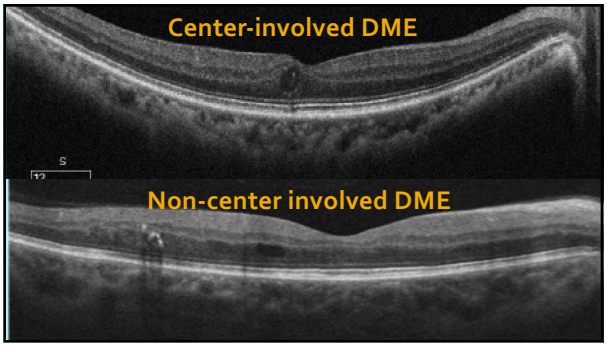

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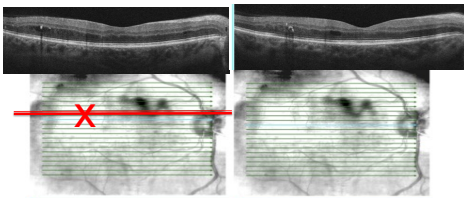
Focal Diabetic Macular Edema



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Microaneurysms

- Early clinical feature of non-proliferative diabetic retinopathy
  - Thickening of basement membrane, pericyte loss, MAs, increased permeability
    - Leads to loss of vessel perfusion, hypoxia, increased VEGF, neovascularization

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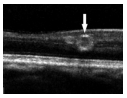
Microaneurysms

- Weakening of capillary wall
- Large MAs visible clinically
- Leak
  - Cause intraretinal edema



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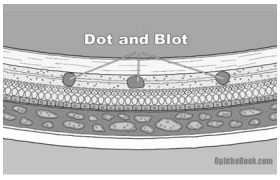
Dot and Blot Hemorrhages

- Deep retinal hemorrhages
  - Inner nuclear layer, outer plexiform layer, outer nuclear layer
  - From pre-venular capillaries
    - DM, RVO
  - Represent ruptured microaneurysms
    - Do not leak on FA



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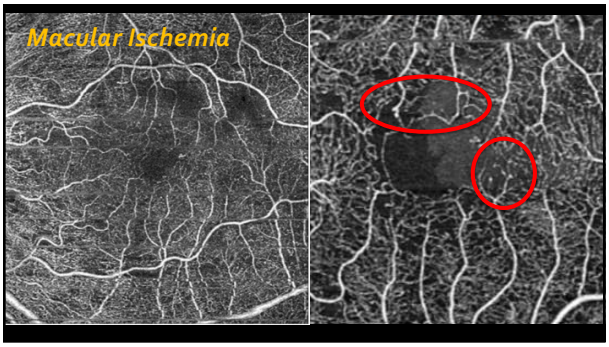

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Macular Ischemia

- Vision loss either due to fluid within in the macula or a poorly perfused macula
  - **Macular ischemia** in the absence of DME/hemorrhage/exudate

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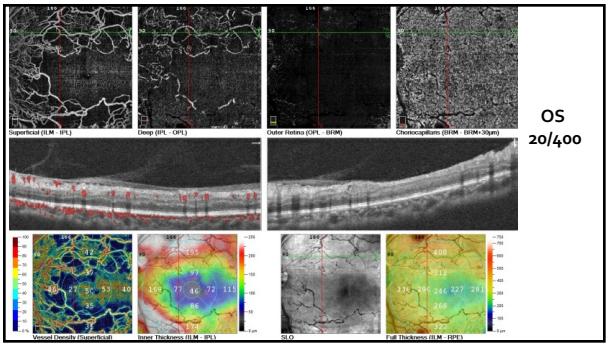

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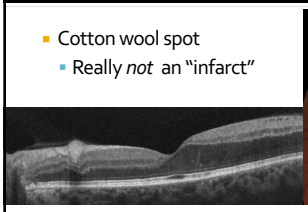
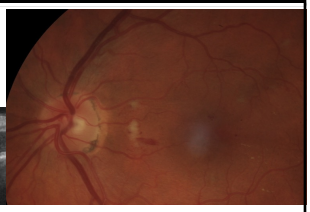
Ischemia in Diabetic Retinopathy

- Cotton wool spot
  - Really *not* an "infarct"





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Pharmacology in Retinal Vascular Disease

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Vascular Endothelial Growth Factor

- Signaling protein for vasculogenesis and angiogenesis
  - Secreted by RPE cells, pericytes, astrocytes and endothelial cells
- Produced in response to ischemia
  - Ultimately leads to neovascularization
- Anti-VEGF is the typical first line treatment

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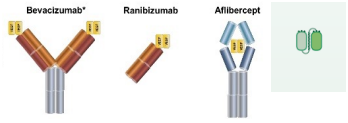
Currently Available Anti-VEGF Agents

- Ranibizumab (Lucentis)
- Bevacizumab (Avastin)
- Aflibercept (Eylea)
  - VEGF trap—inhibits VEGF receptor expression
- And…



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New Agents in AMD

- Brolucizumab (Beovu)-approved October 8, 2019
  - Single chain antibody fragment inhibitor of VEGF
  - Molecular weight half of ranibizumab
    - Smaller molecule = better penetration, faster clearance, lower systemic exposure
  - Phase 3 trials-top line results
    - HAWK/HARRIER trials showed non-inferiority to Eylea in visual acuity and fluid reduction in patients with wet AMD
    - Improved acuity vs. aflibercept
    - Improved central thickness and fluid on OCT vs. aflibercept
  - **12 week duration (after 3 monthly loading doses) for AMD**
  - **On label for neovascular (or exudative) AMD;** *KITE and KESTREL (DME) in progress; ~~RAPTOR~~ and ~~RAVEN~~ & ~~MERLIN~~*

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Beovu

- February, 2020: 14 cases of vasculitis (11 were occlusive retinal vasculitis)
- Through June 26, 2020
  - 7.92 events/10,000 injections (retinal vasculitis, retinal vascular occlusion-or both)
    - As high as 4.6% incidence of inflammation—**and 0.7% of IOI and loss of 15+ letters**
- *Contraindicated in patients with active intraocular inflammation (uveitis)*
  - *But…so is Eylea*
- *KITE and KESTREL (DME)*
  - *Does diabetes impact the risk of intraocular inflammation?*

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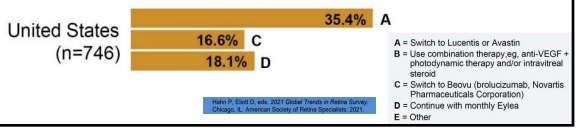
Beovu

- Current guidance:
  - **Look at the AC**; look at the retina, look at imaging

How do you manage persistent CNV (AMD) activity after 8 monthly Eylea injections, VA = 20/50?



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Faricimab (Vabysmo)

Permanent J-code as of October 1, 2022

- FDA approved January 28, 2022
- Bispecific antibody
  - Targets angiopoietin-2 (Ang-2) and VEGF-A
    - Ang-2 and VEGF work in concert-increases permeability and inflammation
- TENAYA and LUCERNE (nAMD)
  - Vs. aflibercept
  - Treated every 3-4 months (after 4 monthly doses)
    - 80% of individuals were able to go 3+ months between treatments in the first year
  - YOSEMITE and RHINE (DME)

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Cost Effectiveness of Anti-VEGF

- $2190 faricimab (6mg/0.05mL)
- $1850 brolucizumab (6mg/0.05mL)
- $1850 aflibercept (2.0mg/0.05mL)
- $1170 ranibizumab (0.3mg/0.05mL)
- $60 bevacizumab (1.25mg/0.05mL)

- **Bevacizumab is a typically the first line anti-VEGF in the USA**

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Pharmacology in Diabetic Retinopathy

- Injectable Steroids
  - Ozurdex-dexamethasone 0.7mg
    - DRCRnet Protocol U
    - Initially indicated for RVO; now indicated for DME and non-infectious posterior uveitis
    - Causes cataract; must have an intact posterior capsule
  - Iluvien (fluocinolone 0.19mg)
  - Triesence (intravitreal triamcinolone acetonide-PF)

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Neovascularization in DR

- PRP is considered the gold standard of DR-related neovascularization
  - Supported by ETDRS
- PRP associated with increased macular edema (initially)

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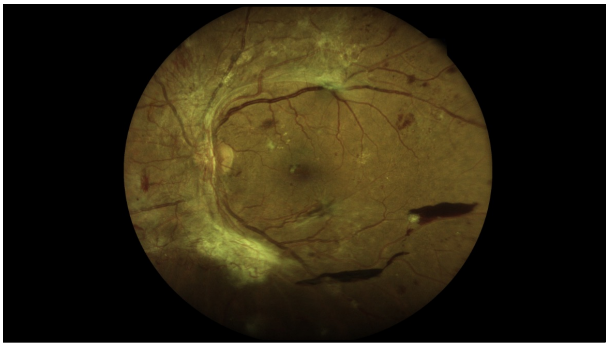

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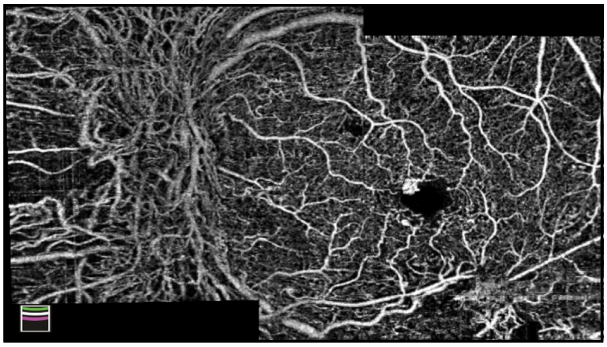

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Brief Lit Review (Because it Matters)

- DRCRnet (Diabetic Retinopathy Clinical Research Network)
  - Protocol S:
    - 2 year results: Lucentis is non-inferior to PRP in PDR for maintenance of visual acuity in PDR
      - Less VF loss, fewer vitrectomies
    - Supported by CLARITY trial (RCT)
    - PRIDE: ranibizumab monotherapy = greater reduction of area of NV from baseline at 12 months vs. PRP
    - **THIS IS HUGE…**

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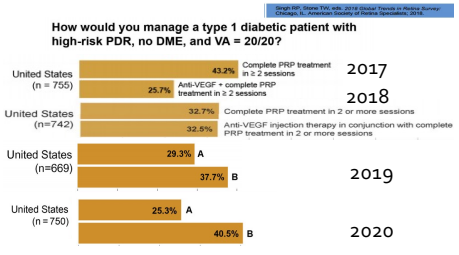
Impact of DRCRnet Protocol S



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Impact of DRCRnet Protocol S

- *Eyes lost to follow up?*
  - *Obeid et al. Ophthalmology 2018*
- *5 year results*

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DRCR.net Protocol T

- Head to head (to head) anti-VEGF comparison
- Aflibercept, bevacizumab, ranibizumab
- All three agents are effective in treatment of DME
  - Bevacizumab (Avastin) had worse central thickness-but same VA
- For worse levels of VA (20/50 or worse); Eylea is better at improving VA at one year
  - *Results maintained at 2 years*

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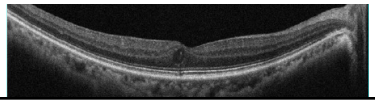
Recent Research

- Protocol V: "Very good vision"
  - Center involved DME with good vision (20/25 or better)
    - To treat or not to treat?
  - Similar vision between treated (anti-VEGF, laser) and observation at 2 years: 20/20 (2 letter difference)
    - 34% of observation, 25% of laser patients needed rescue
      - 18 visits-treated; 13 visits in observation/laser



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Recent Research

- Protocol AA
  - Ultra-widefield imaging and the ETDRS 7 standard field imaging for assessment of peripheral lesions, DR severity and worsening over 4 years
  - **70% of nonperfusion in diabetic eyes involves the periphery!**
    - **UWF FA**

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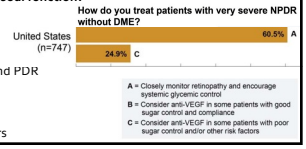
What About Patients Without DME?

- **Panorama**
  - Eylea for patients with moderately severe, or severe **NPDR** (DRSS)
    - **No** macular edema
- Sure, patients who received injections showed *regression* of DR
  - This makes sense
- But, did it result in long term improvement in **visual function?**
  - Not assessed.
- **Protocol W**
  - 2 year data
    - Reduced risk of development of CI-DME and PDR (16.3% vs. 43.5%)
    - Average of 8 injections over 2 years
  - No difference between visual acuity at 2 years



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Macular Degeneration

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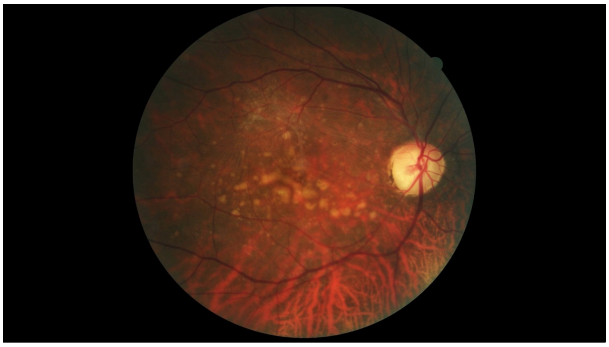

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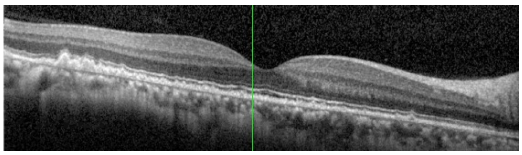
Cuticular Drusen

- Drusen subtype
  - AKA basal laminar deposits
    - Between the basal lamina of RPE and the inner collagenous layer of Bruch's membrane
- *Can progress to geographic atrophy and MNV*



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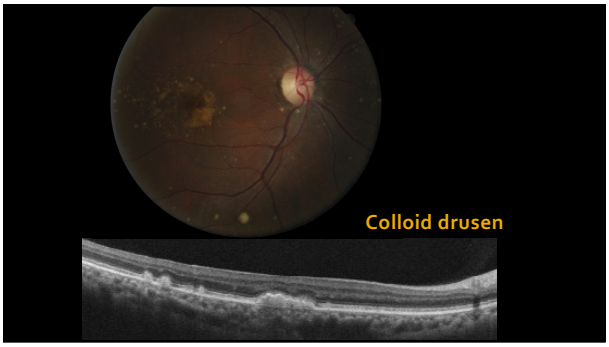

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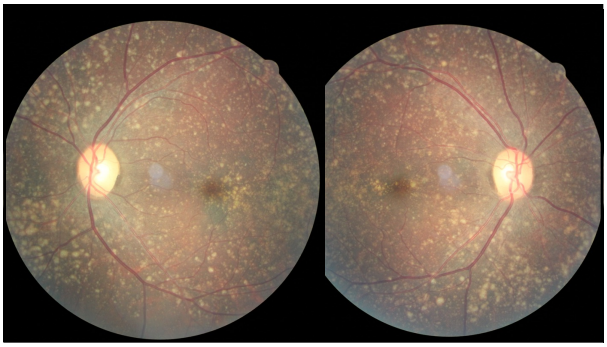

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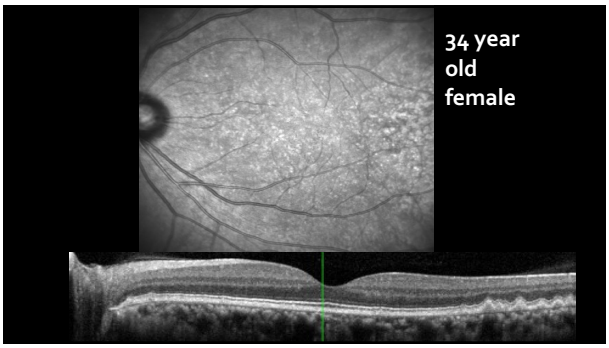

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Subretinal Drusenoid Deposits

- Abnormal material deposited internal to RPE on OCT (including en face); reticular pseudodrusen on OCT
- Often common with other hallmarks of AMD

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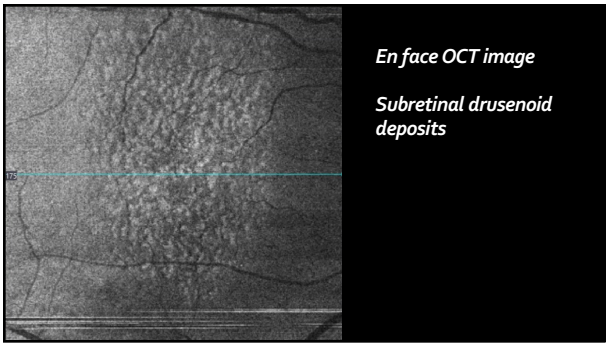

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Subretinal Drusenoid Deposits

- Distinctive type of drusen aka reticular pseudodrusen
  - Subretinal space extending to the outer segments of photoreceptors
- Not *just* drusen above the RPE
  - Include immune-reactive cells (macrophages, microglia)
    - Impact dark adaptation; choriocapillaris flow impairment
- Increased risk of progression to late stage AMD
  - Finger *et al. 2014*

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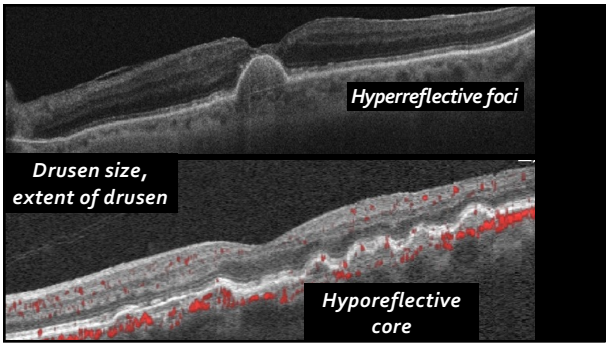

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Types of Neovascularization

- 1: subRPE
  - Less permeable, less actively proliferating
  - Minimal late leakage on FA
  - Historically "occult"….but now we can see them on OCTA
- 2: Has penetrated the BM/RPE complex
  - Active leakage associated with dye pooling
  - "Classic"
- 3:Intraretinal complex
  - Vascular activity within the retina with choroidal anastamoses

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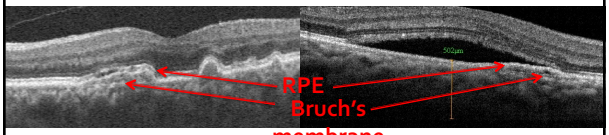
Double Layer Sign

- Highly suspicious for evidence of type 1 MNV on B-scan
  - AMD, CSCR, "PCV"
- Arise from choriocapillaris, penetrates Bruch's membrane
- Represents a splitting of the RPE-basal lamina-Bruch's membrane complex



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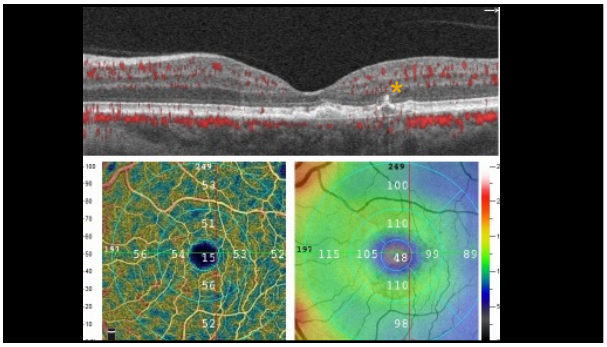

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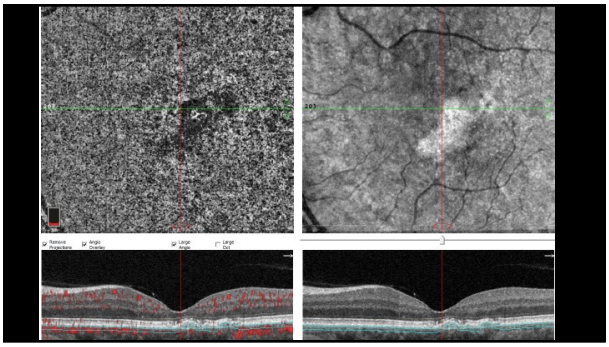

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Exudative AMD

- PRN protocol
  - OCT and clinical examination performed once per month
    - Is dilation necessary at every visit?
      - 1/10 patients had a new retinal hemorrhage, 7% missed on OCT
    - Inject only if there is a recurrence of fluid or hemorrhage
- Treat and extend**
  - Once macular fluid is cleared (at least 3 monthly injections), extend the interval between treatments by (typically) 2 week increments
    - Patients are treated on each visit-but at longer intervals
      - Compromise approach
    - **OCT-guided therapy**

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Geographic Atrophy

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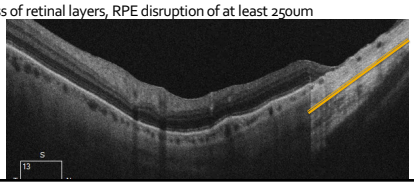
cRORA vs iRORA

- CAM (classification of atrophy meetings) classification
  - Consensus on nomenclature
- Complete RPE and retinal atrophy (cRORA) which occurs in AMD
  - >= 250 um choroidal hypertransmission on OCT B-scan
  - Loss of retinal layers, RPE disruption of at least 250um



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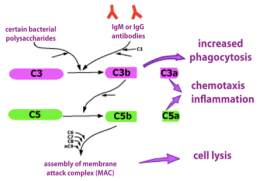
Complement in AMD

- CFH polymorphism increases risk of AMD
- Classical, alternative, lectin pathways converge to activate **C3**
  - C5 **activation** can lead to increased VEGF expression by the RPE
- Components of drusen and oxidative stress can trigger complement cascade→ **cell lysis**



Complement over-activation is implicated in pathogenesis of AMD

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Complement Inhibitors in GA

- ***Geographic atrophy doesn't get better-the goal is to slow progression***
- APL-2 (Pegcetacoplan)-C3 inhibitor
- Met phase 2 endpoints (FILLY) in September 2019-slows GA rate of progression **in a dose-dependent manner**
- Phase 3 trials (DERBY & OAKS)
  - Endpoints met in OAKS, very close in DERBY
  - Pooled data met endpoints
- **Slows the growth rate of geographic atrophy**
- *Fast track designation from FDA (GA)-Unmet clinical need*
  - *Interesting safety signal: increased risk of exudation*
- ***Whatever drives a druse towards GA is the same mechanism that seems to cause GA expansion***

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C5 Inhibition

- Zimura (avacincaptad pegol)
  - C5 inhibitor
  - Phase 2b/3 (GATHER1)-October 28, 2019-met primary endpoints
    - Also being investigated in Stargardt's disease
    - Reduction in growth rate of GA at month 12
  - Phase 3 (GATHER2) began June 30, 2020: monthly injection of 2mg dosing vs. sham
    - Phase 3 trial for **intermediate stage dry AMD** to begin late 2022
  - *Awarded fast track designation from FDA early 2023*

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Geographic Atrophy

- Elamipretide-subcutaneous injection (daily..ugh)
  - Reduces oxidative stress at the level of **mitochondria**
    - **Acts as a mitochondrial protector**
      - **Did not meet primary endpoints (May 2, 2022)—but enhanced ellipsoid zone preservation on OCT**
        - **Shows proof of proposed mechanism**
- Risuteganib (Luminate)
  - Also investigated in DR
  - Anti-integrin therapy
- ***All about oxidative stress***

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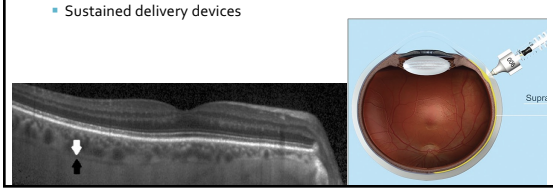
New Agents

- Beyond intravitreal injections
  - Triamcinolone acetonide in the suprachoroidal space (works well in uveitis)
  - Sustained delivery devices



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OPTIC & LUNA Trials

- Optic trial
  - September 2018-FDA awarded fast track designation to a gene therapy for exudative AMD
  - Aflibercept coding sequence + adenoviral associated vector (ADVM-022)
    - 30 patients
  - Coding sequence (cDNA) injected intravitreally
    - Replicates in deep retina producing detectable 'aflibercept' protein in vitreous, deep retina, and choroid
  - Durability up to 92 weeks (cohort 1-high dose)
    - High dose vs. low dose; 13 day oral steroid vs. 6 week topical ophthalmic steroid
  - **LUNA-Phase 2 in progress!**

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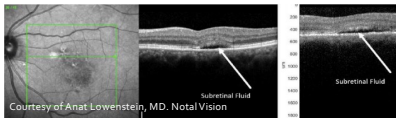
New Technology

- Home-based OCT system
  - Notal Vision
  - Generates an automated report, transmits data to prescriber



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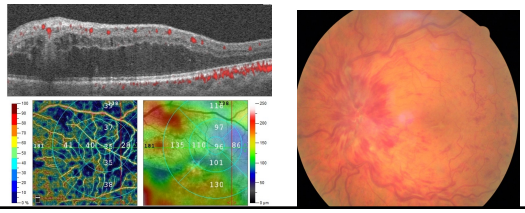
Retinal Vein Occlusion

- Central retinal vein occlusion
  - Obstruction at the level of the lamina cribrosa



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Retinal Vein Occlusion

- Arteriosclerosis
  - Loss of elasticity within the vessel wall
    - Arterioles and venules share common adventitia at crossings
    - Venular compression and turbulent blood blow
    - Thrombus formation and occlusion

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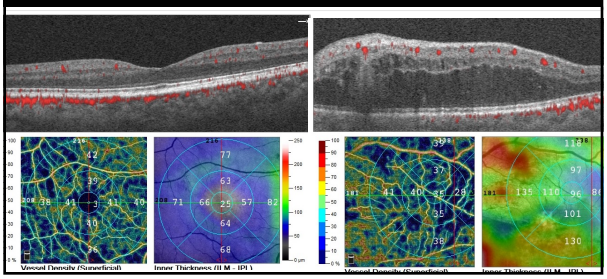
What's the Status of the Fellow Eye?



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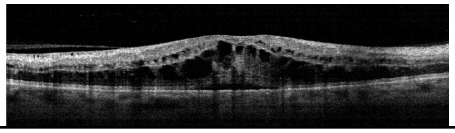
Treatment of Macular Edema Secondary to RVO

- Anti-VEGF
- Intravitreal steroid
- Dorzolamide-timolol?!
  - With injections
  - Aqueous suppressant-may have an effect on RPE pump function



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SCORE2

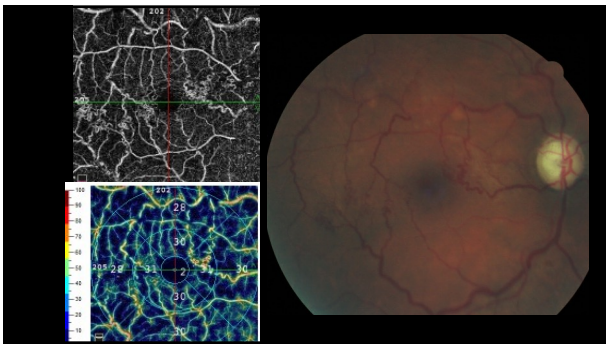
5 year data (April 2022)

No significant difference between Avastin and Eylea

66% had at least one treatment between year 4 and 5

RVO is a chronic disease

90



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Ischemic CRVO

- Believed that occlusion leads to increased resistance which causes stagnant blood and ischemia
  - **Leads to PR death, increased cytokine production, increased VEGF**
- Anterior and posterior neovascularization
  - Vitreous hemorrhage, anterior segment NV

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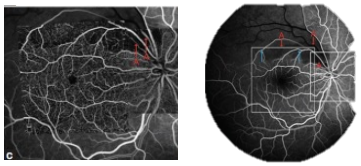
BRAO

- Treatment?
  - **Stroke evaluation on emergent *basis*-*where is your nearest 24 hour ER with stroke center?***



Bonnin, Kyiyosic, Cognat, Tadayoni. J Ophthalmic Vis Res 2018

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I have discussed elsewhere[4] why it is irrational to equate retinal artery occlusion with stroke.

Comment on: Retinal vein occlusion and the risk of dementia: A nationwide cohort study

per se. The presence of a particular associated systemic disease does not necessarily imply a cause-and-effect relationship. Thus, the authors' conclusion that "RVO may be a risk factor for dementia" has no scientific validity.

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Department of Ophthalmology & Visual Sciences, College of Medicine, University of Iowa, Iowa City, Iowa

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Re: Biousse et al.: Management of acute retinal ischemia
(*Ophthalmology.* 2018;125:1597-1607)

TO THE EDITOR: I was interested to read the article by Biousse et al[1] dealing with the management of acute retinal artery occlusion; this is a repetition of the views dealing with management of acute retinal ischemia they expressed some time ago.[2] I published an article on the same subject,[3] discussing a concept opposite to that of Biousse et al.[1,2] Our different views on the topic likely relate to coming at this from the viewpoint of our different specialties, which provide different perspectives on the subject. I have been dealing with acute retinal artery occlusion for >50 years and my studies on retinal artery occlusion are the largest studies reported (>500 cases). Biousse et al, being neuro-ophthalmologists and neurologists, have a neurologic bias. In support of their argument, they cite opinions expressed

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Finally…

- Angiogenesis and exudation are significant causes of vision loss in retinal vascular disease
- Treatment targets, treatment modalities, and imaging strategies are rapidly changing
- Driving forces behind retinal vascular disease are multifactorial
- Anti-VEGF agents are the mainstay of treatment in retinal vascular disease
- *We're very close to a therapeutic for GA—how will we identify patients who may qualify for treatment?*

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Thank You!

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