Current Treatment of Age Related Macular Degeneration

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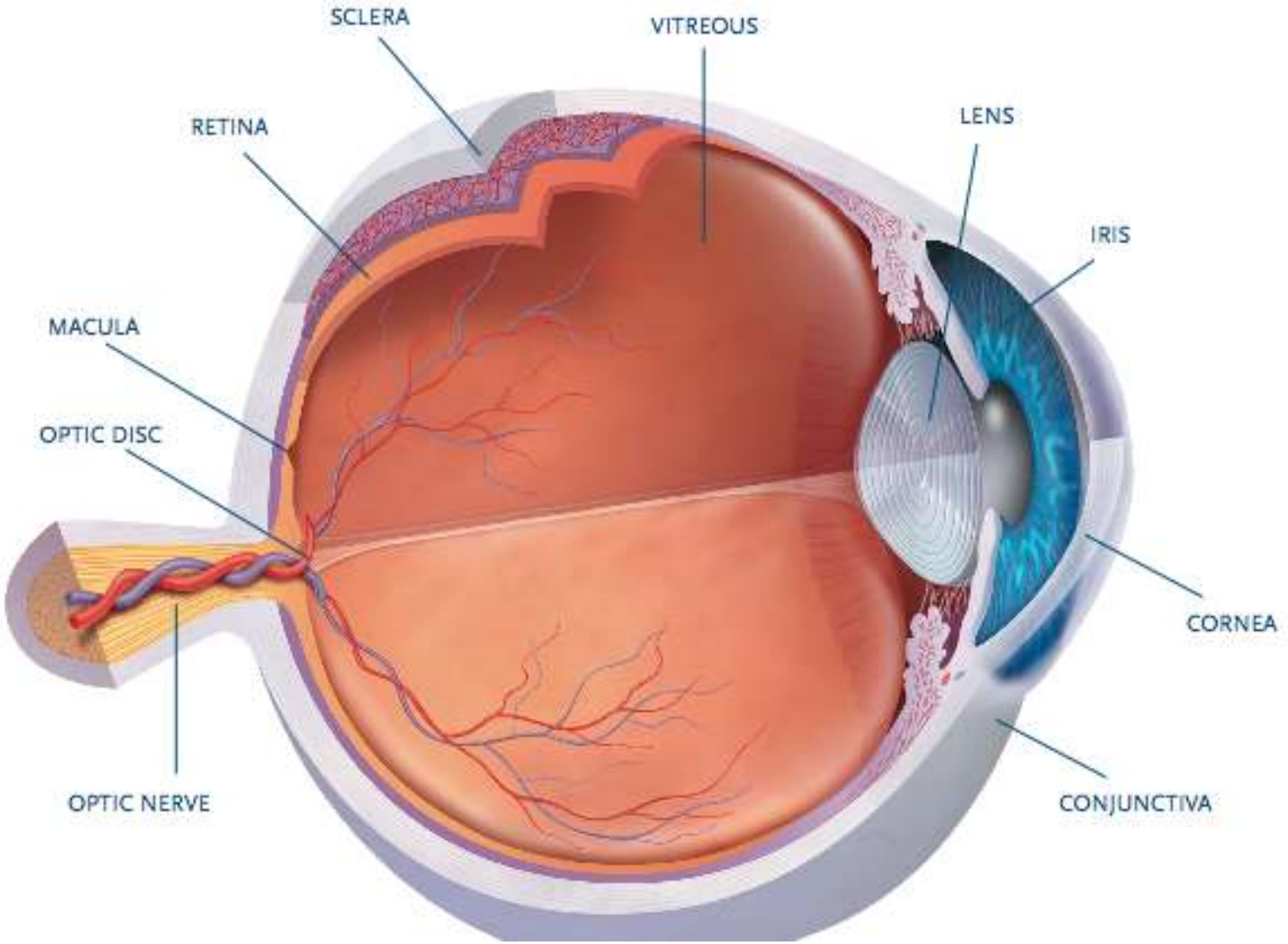
Financial Disclosure

I have financial interest/agreement or affiliation with Lansing Ophthalmology, where I am a shareholder and employed as a retina specialist.


SCLERA
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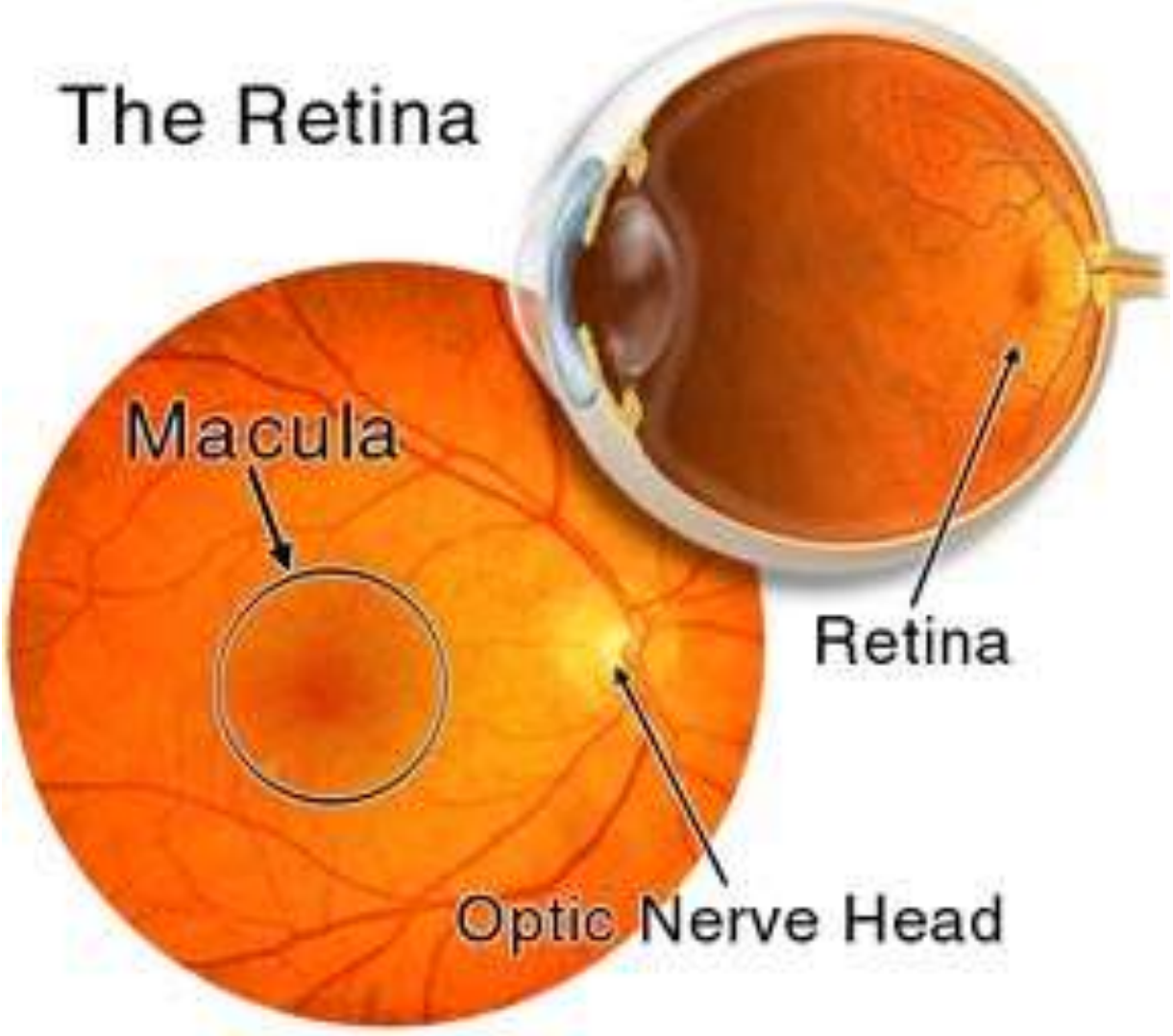
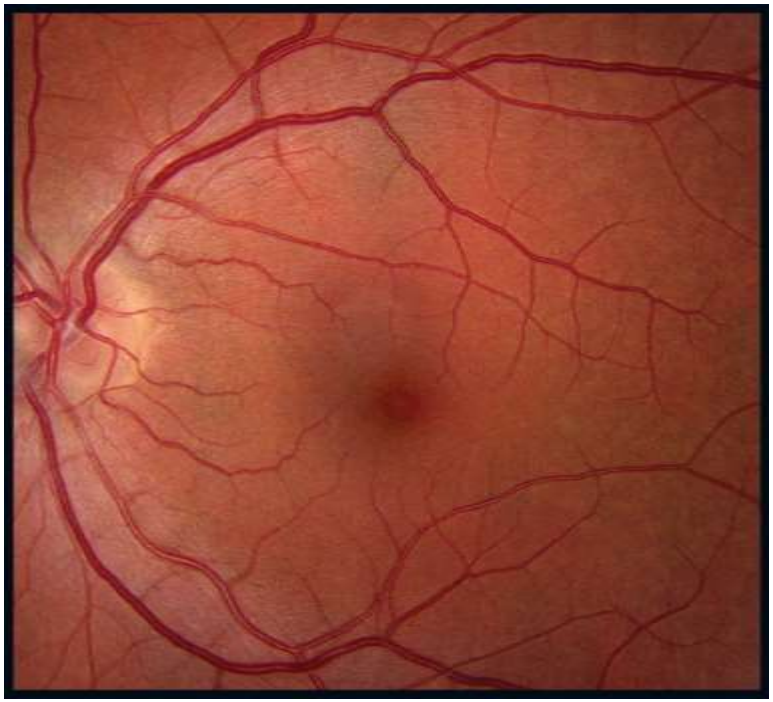
CONJUNCTIVA

Macular

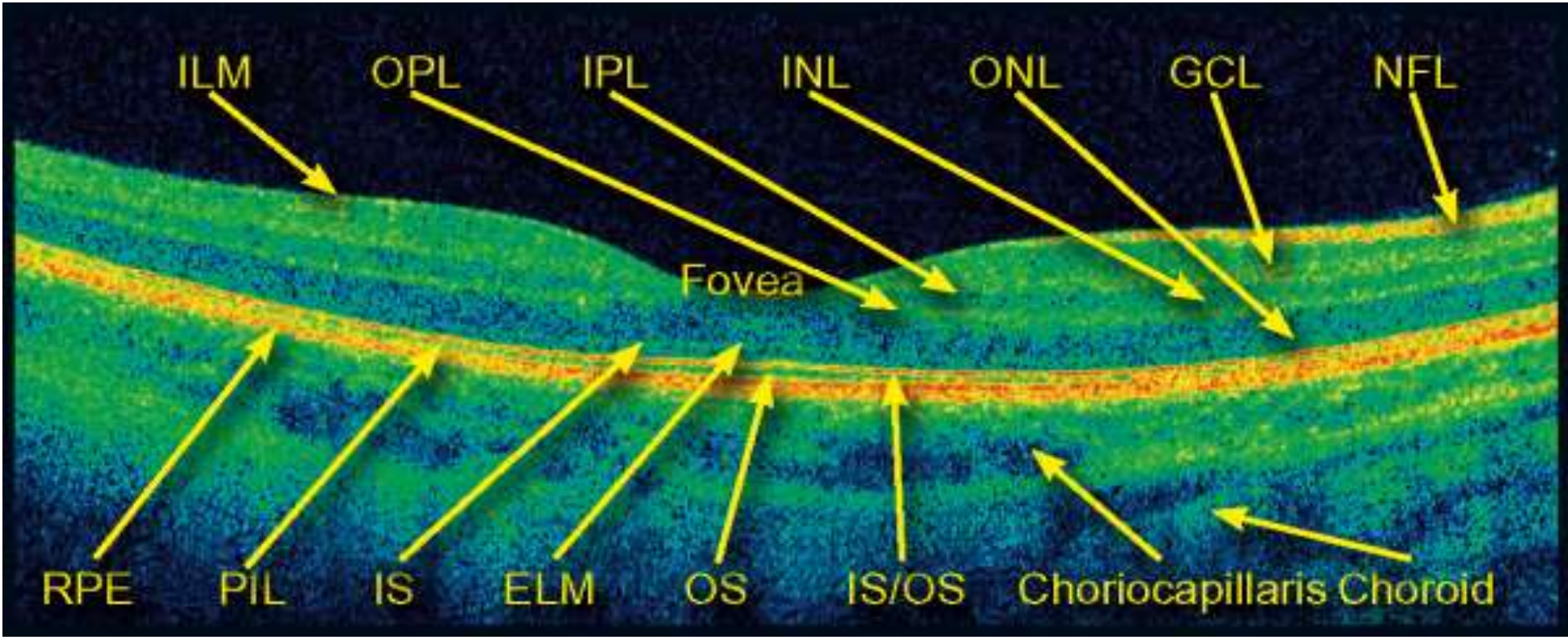


Macular

- Center of retina
- Small – 5-6 mm in diameter
- Responsible for detailed central vision/fine details



Optical coherence Tomography



Age related macular degeneration (AMD)

- Chronic condition
- Affects the macular
- Causes central vision loss
- Leading cause of vision loss among adults over age 60 in the US

Epidemiology

National Health and Nutrition Examination Survey (NHANES)

- Total prevalence over 40 yrs old
  - Any AMD -6.5% (7.2 million people)
  - Late stage of AMD – 0.8% – (809 000)
  - Statistically significant lower prevalence of any AMD in blacks cp to whites

Klein R, Chou CF, Klein BE, et al: Prevalence of age-related macular degeneration in the US population. *Arch Ophthalmol 2011; 129:75-80.*

Age Related Macular Degeneration (AMD)

- Spectrum of diseases
- Two major subtypes

  - **Dry AMD**
    - Atrophic
    - Non-exudative
    - Non-neovascular

  - **Wet AMD**
    - Neovascular

  - There is also a group of patients who experience exudation without neovascularization

DRY- Non-exudative AMD

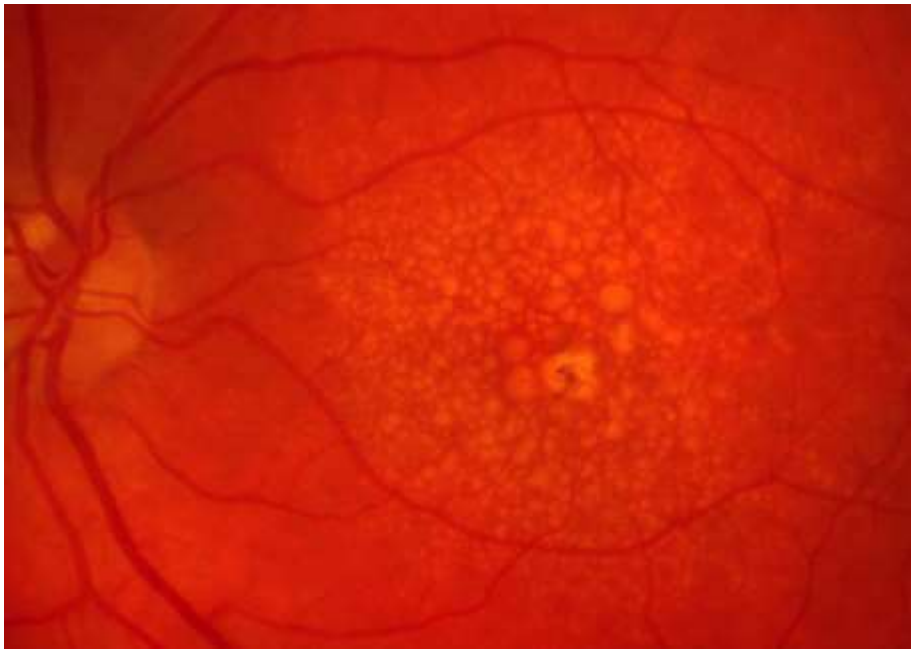
- Drusen
- Pigmentary alterations,
- Atrophy of the RPE and choroid.

DRY- Non-exudative AMD

- **Drusen**
  - small or hard drusen
  - large or soft/exudative drusen
  - basal laminar or cuticular drusen
  - mineralized or calcified drusen
  - reticular pseudodrusen

Drusen

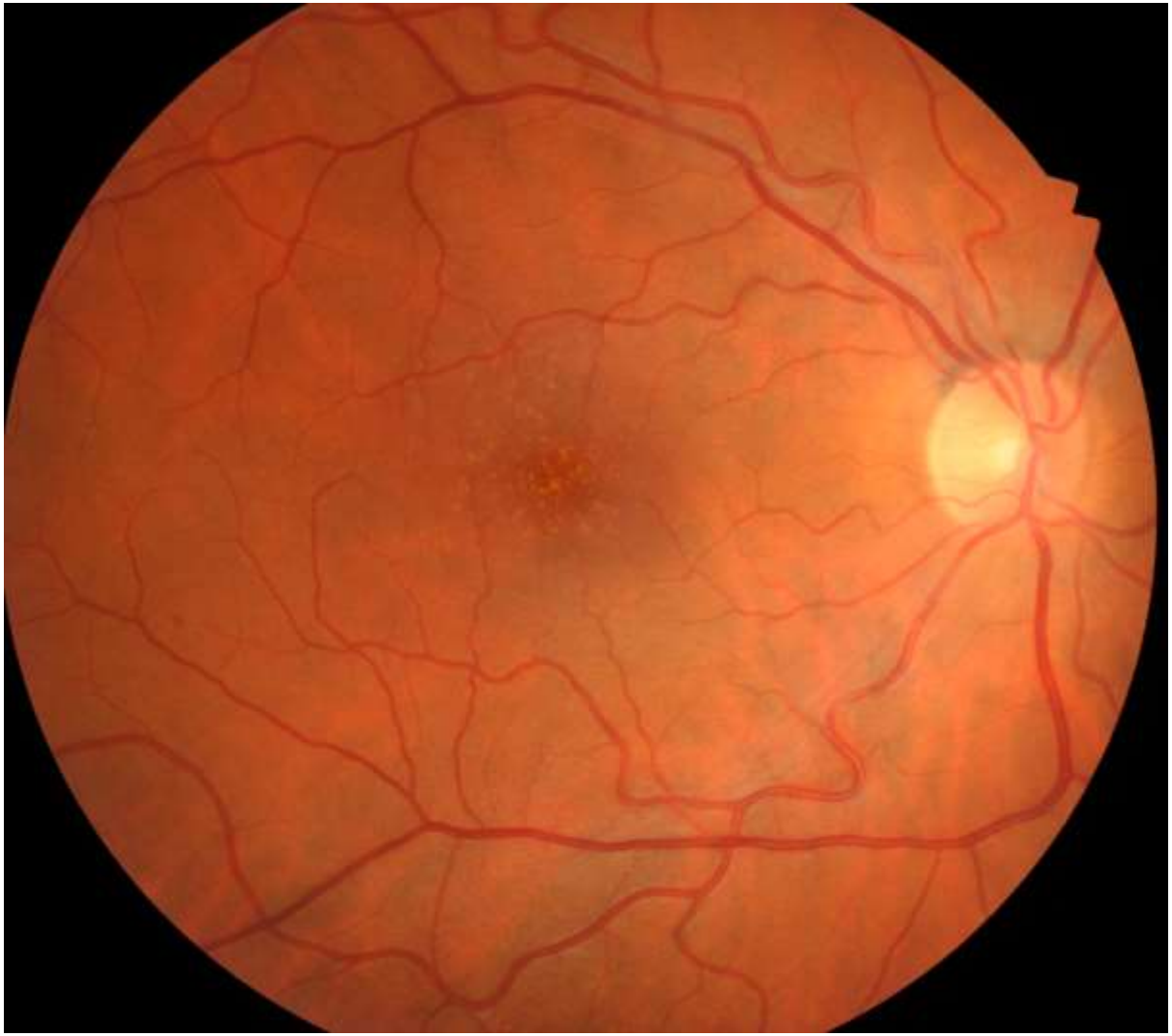
- Clinically, drusen size can be compared to the width of a major vein at the disc edge (approximately 125 μm).



DRY- Non-exudative AMD

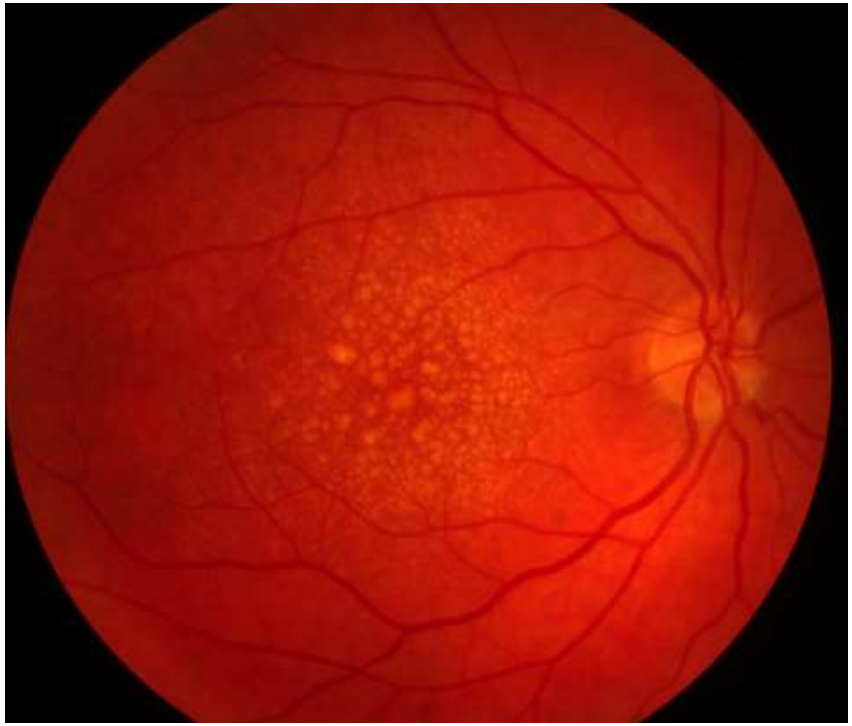
- **Small or hard drusen**
  - <63 μm in size (< 0.5 major vein width)
  - Small yellow-white lesions
  - Distinct borders
  - Located at the level of Bruch's membrane
  - Common in people over 40 years of age and by
  - Not high risk for progressive loss of central vision.

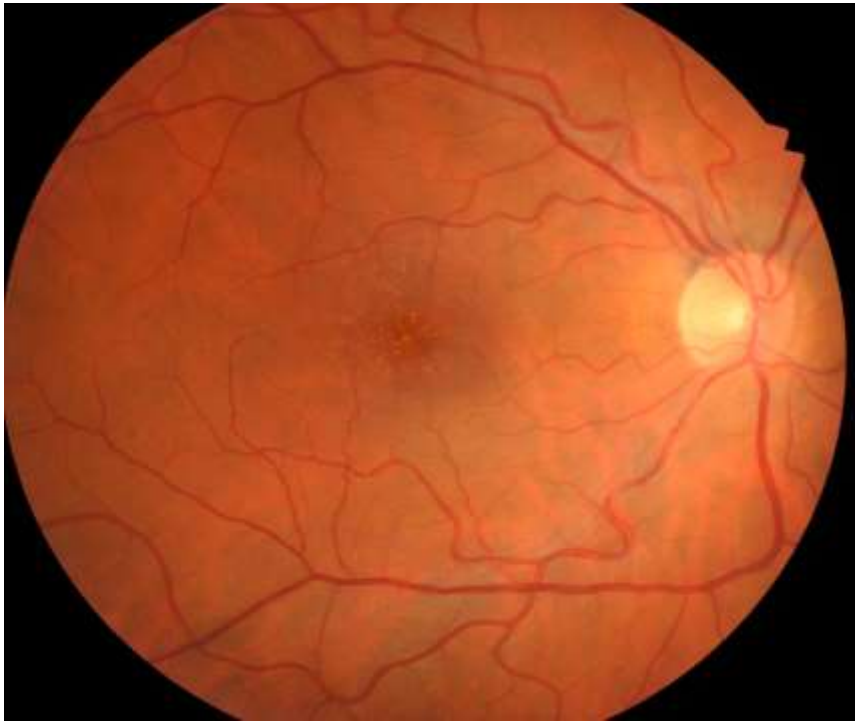
Small Drusen



DRY- Non-exudative AMD

- **Medium-sized drusen**
  - 63–124 μm in size.
  - > 0.5 < 1.0 major vein width

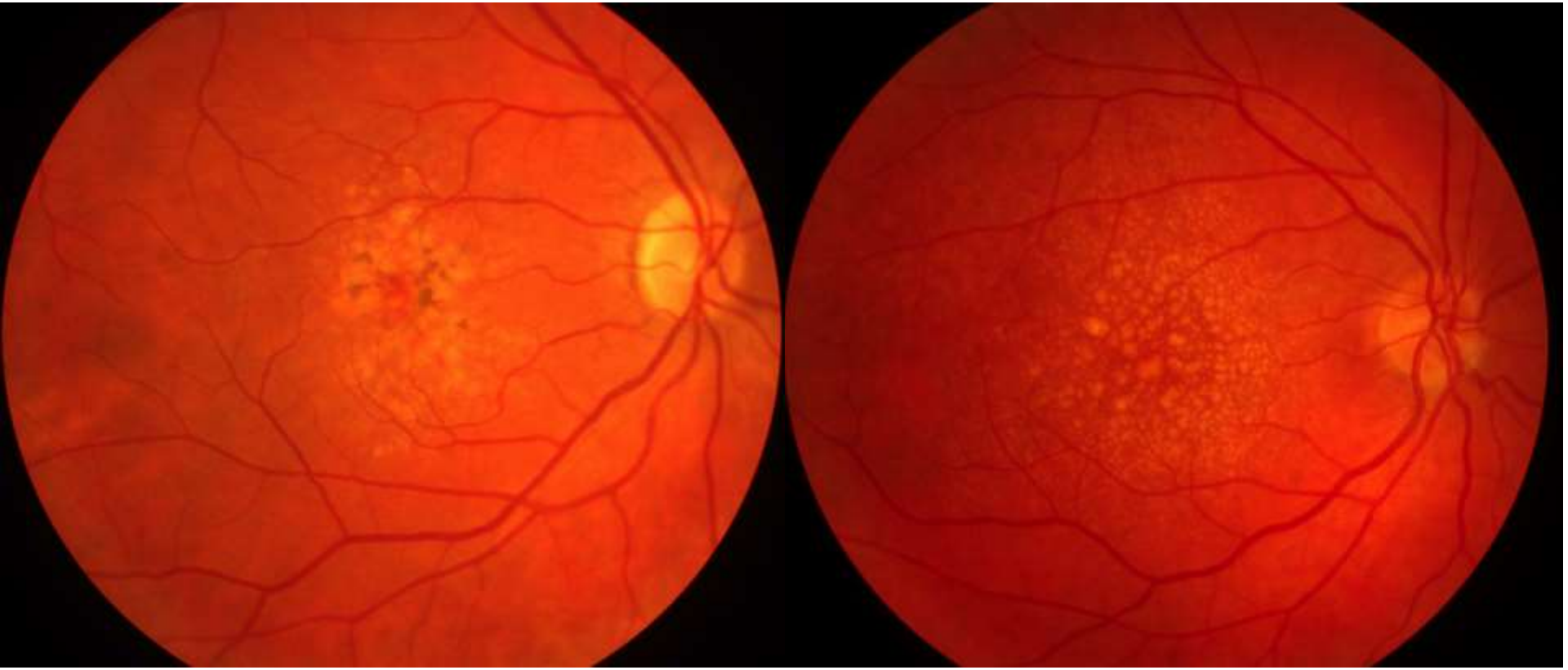




DRY- Non-exudative AMD

- **Large or soft drusen**
  - 125 μm or greater
  - Indistinct borders
  - Associated with an increased risk of pigment abnormalities, geographic atrophy, and choroidal neovascularization.

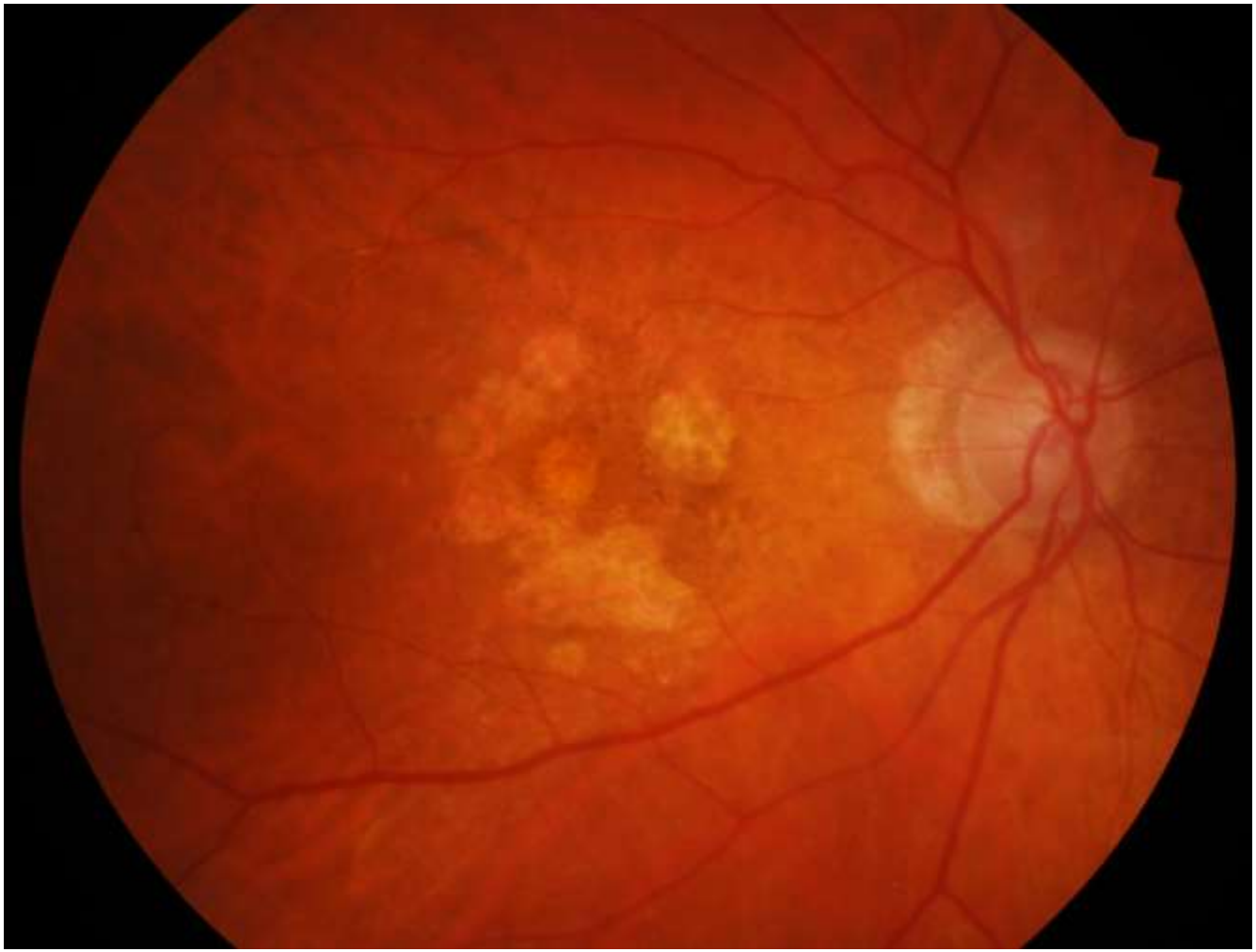
Large Drusen



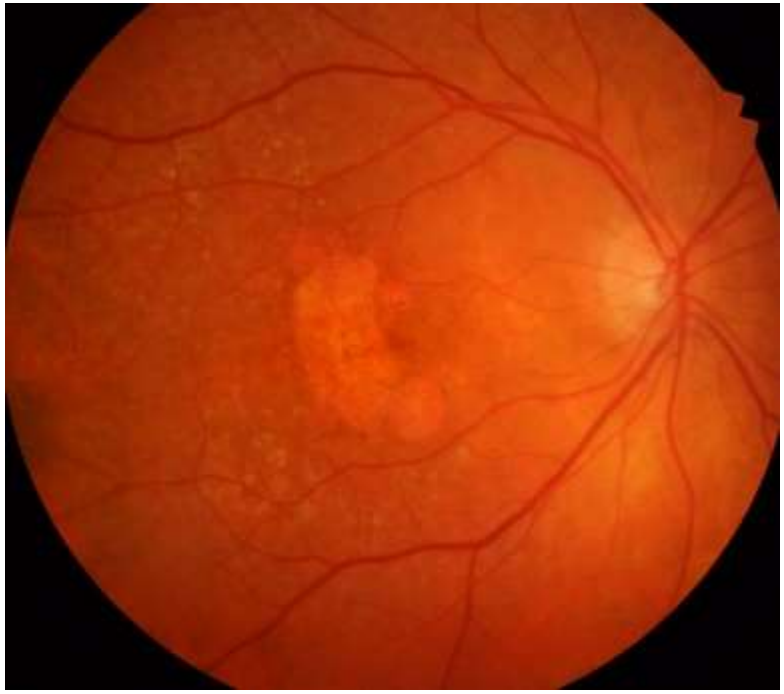
DRY- Non-exudative AMD

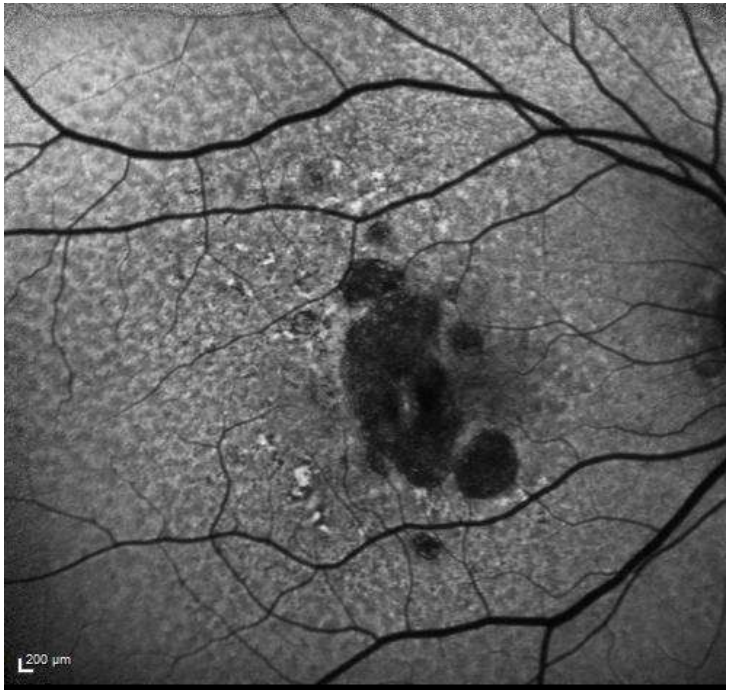
- **Geographic atrophy (GA)**
  - Discrete areas of RPE and choriocapillaris loss
  - At least 175 μm in diameter
  - Choroidal vessels are often visible
  - Window defect on FA
  - Dark on FAF

Geography Atrophy (GA)

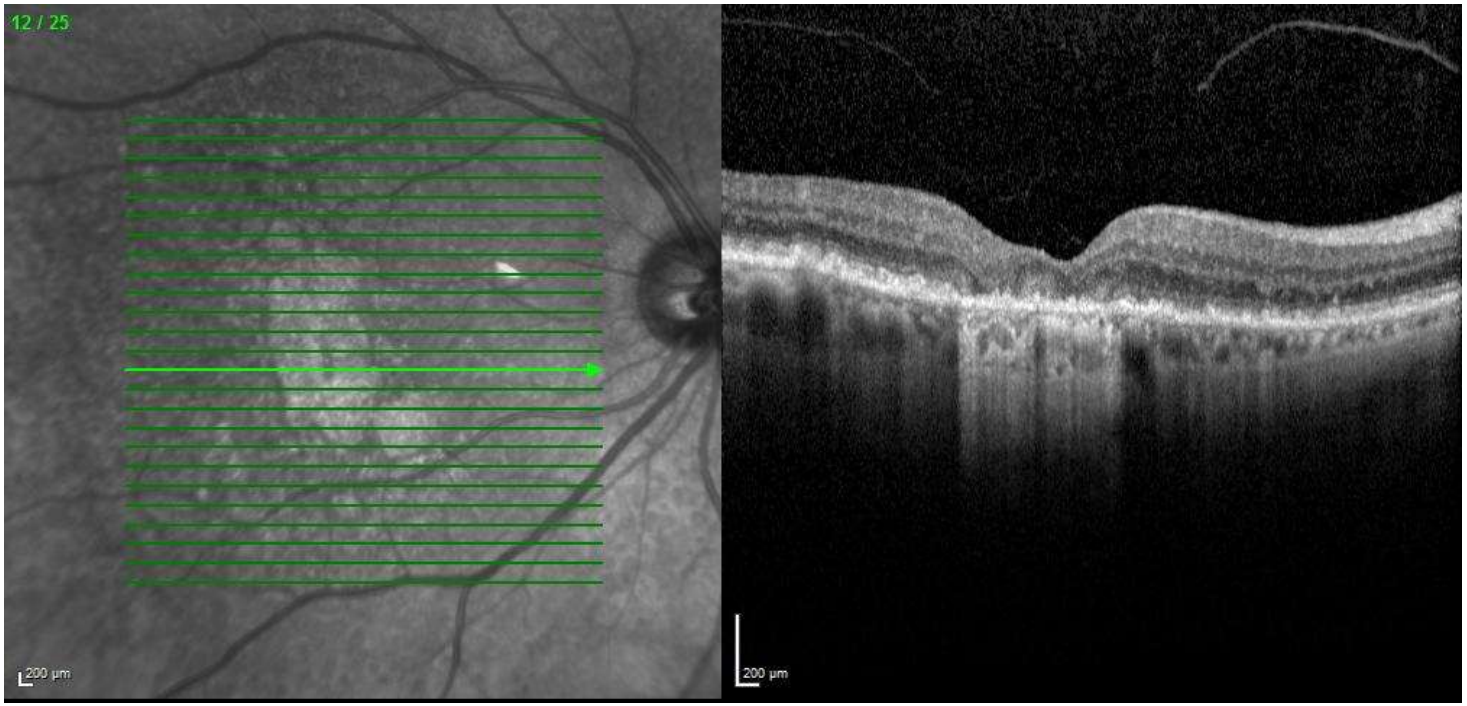


GA



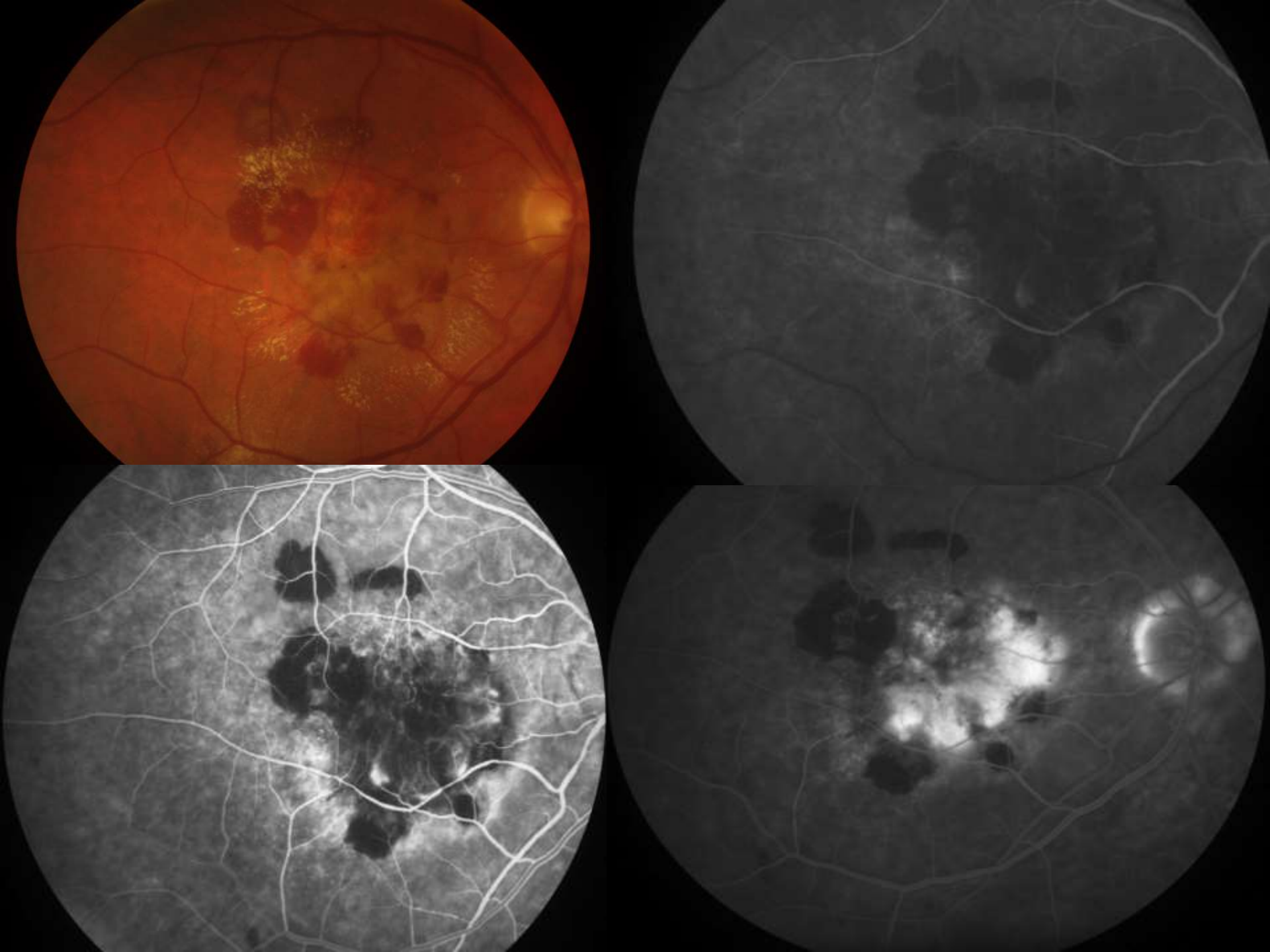


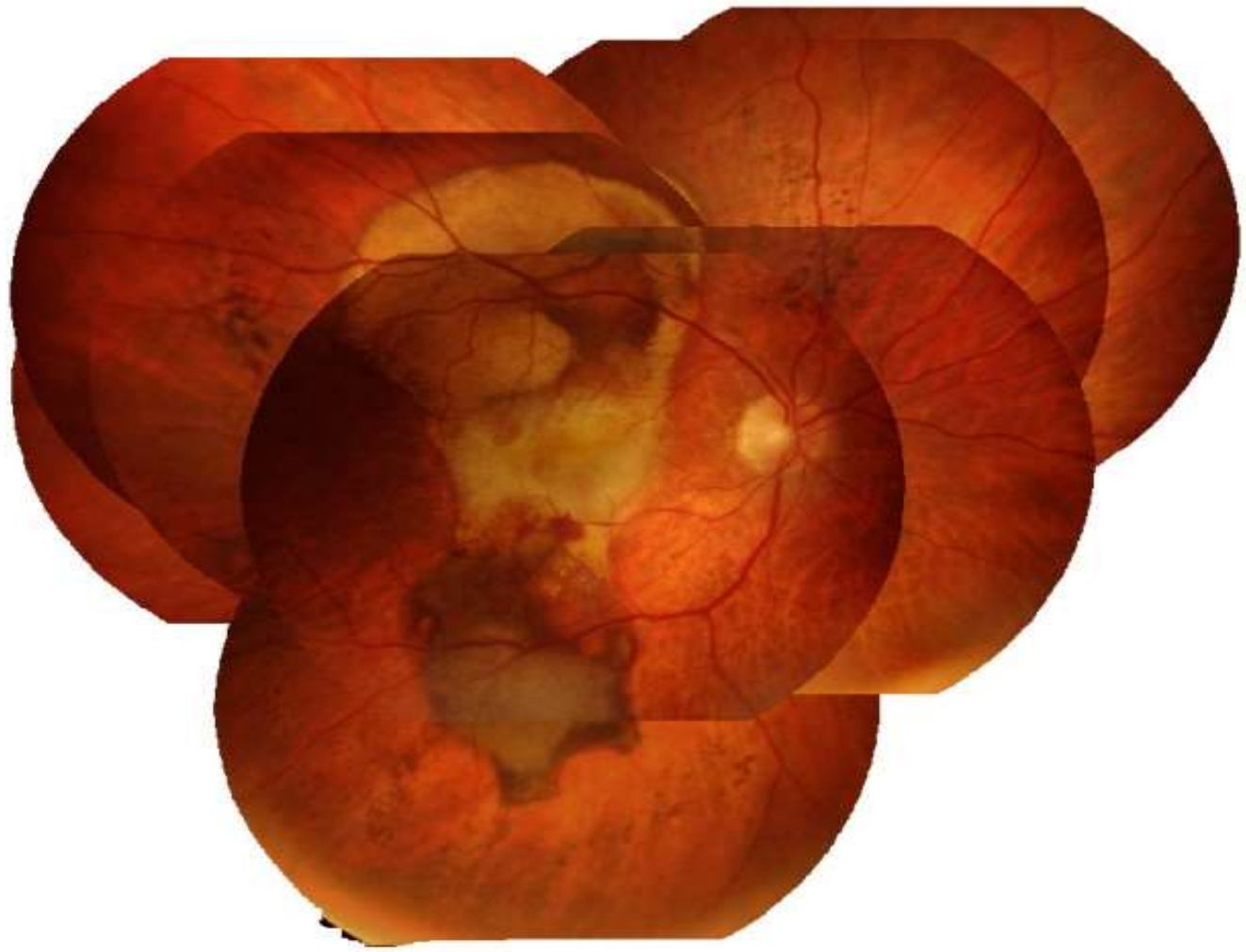
GA

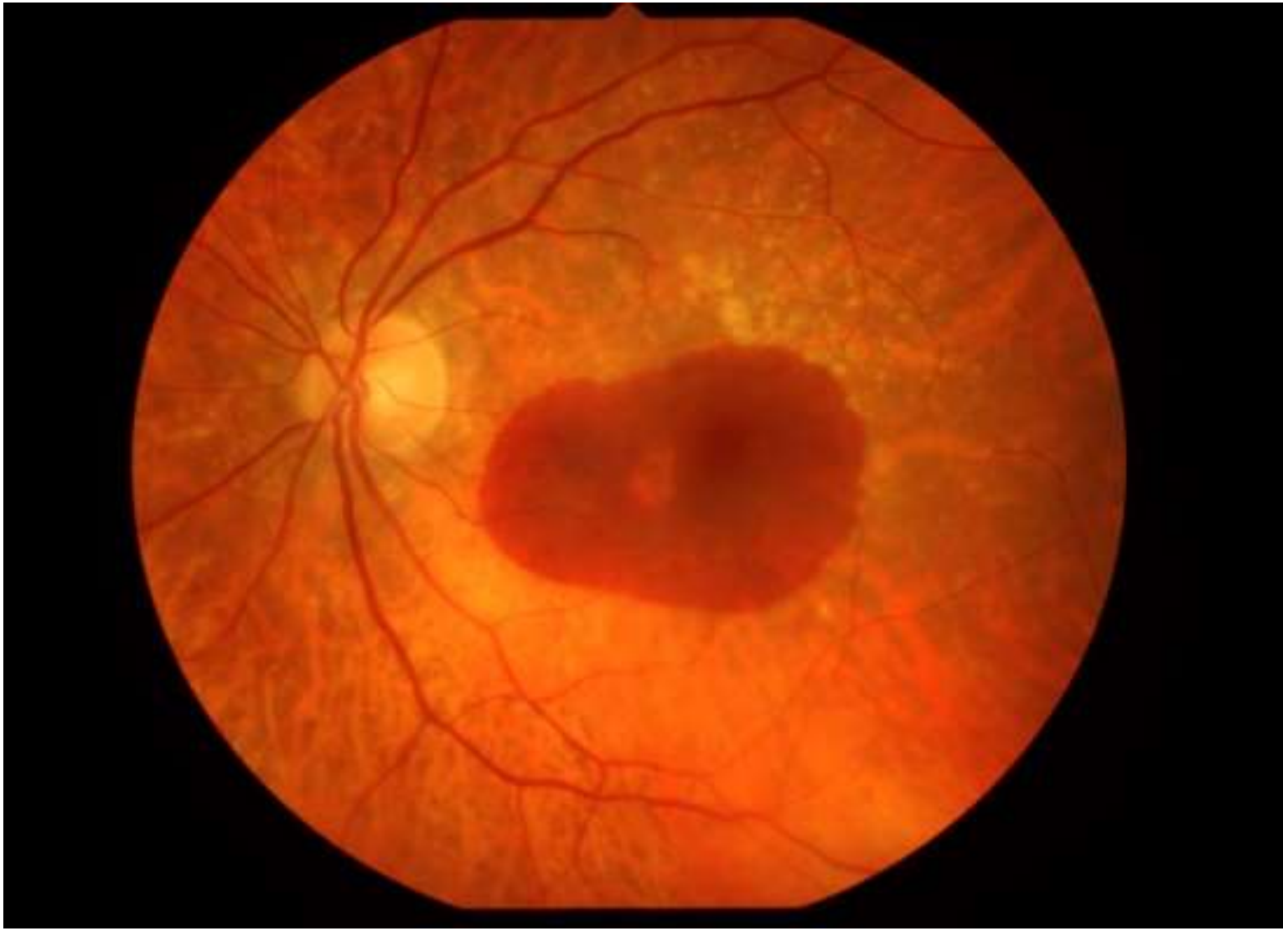


Wet - Neovascular AMD

- Retinal neovascularization
- Choroidal neovascularization (CNV)
- Serous and hemorrhagic complications.







Pathogenesis

- CNV appears as a neovascular sprout growing under or through the RPE through breaks in Bruch's membrane

Green WR, Enger C: Age-related macular degeneration histopathologic studies. The 1992 Lorenz E. Zimmerman lecture. *Ophthalmology 1993; 100:1519-1535.*

Pathogenesis

- Usually this occurs in association with evidence of fibroblasts, myofibroblasts, lymphocytes, and macrophages.

- Various growth factors are suspected to be involved in the development of this CNV, such as vascular endothelial growth factor (VEGF).

Killingsworth MC, Sarks JP, Sarks SH: Macrophages related to Bruch's membrane in age-related macular degeneration. *Eye 1990; 4:613-621.*

Ambati J, Ambati BK, Yoo SH, et al: Age-related macular degeneration: etiology, pathogenesis, and therapeutic strategies. *Surv Ophthalmol 2003; 48:257-293*

Classification of CNV

- **Type 1 (occult) CNV**
  - Under the retinal pigment epithelium (RPE)
  - Less distinct
  - Less permeable
  - Less actively proliferating
  - Poorly defined leakage on FA

Classification of CNV

- **Type 2 (classic)**
  - Choroidal vessels have penetrated the retinal pigment epithelial complex gaining access to the subretinal space.
  - Actively proliferates beneath the neurosensory retina
  - Well-demarcated intense leakage associated with dye pooling on FA
  - Intensely fluorescent during the recirculation phase.
  - Lacy bright pattern of early angiographic filling

Mixed Neovascularization

- Majority of cases
- Predominantly occult and classic
- Minimally occult and classic

Classification of CNV

- **Type 3 –Retinal angiomatous proliferation (RAP)**
  - Third anatomic subtype of neovascularization
  - New vessels within the retina itself
  - Compensatory telangiectatic response,
  - A perfusing arteriole,
  - A draining venule,
  - Retinal–choroidal anastomosis.

Yannuzzi LA, Negrao S, Iida T, et al: Retinal angiomatous proliferation in age-related macular degeneration. *Retina 2001; 21:416-434.*

Polypoidal Choroidal Vasculopathy (PCV)

- Variant of type 1
- Sub-pigment epithelial area
- Branching inner choroidal vessels
- Terminal aneurysmal changes

Yannuzzi LA, Wong DW, Sforzolini BS, et al: Polypoidal choroidal vasculopathy and neovascularized age-related macular degeneration. *Arch Ophthalmol 1999; 117:1503-1510.*

Clinical grading of AMD

- Features are evaluated within 3000 µm of the center of the macula

The Age-Related Eye Disease Study Research Group: A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. *Arch Ophthalmol 2001; 119:1417-1436*

Clinical grading of AMD

- **No AMD**
  - No Drusen or few < 15 small drusen in the absence of any other stage of AMD

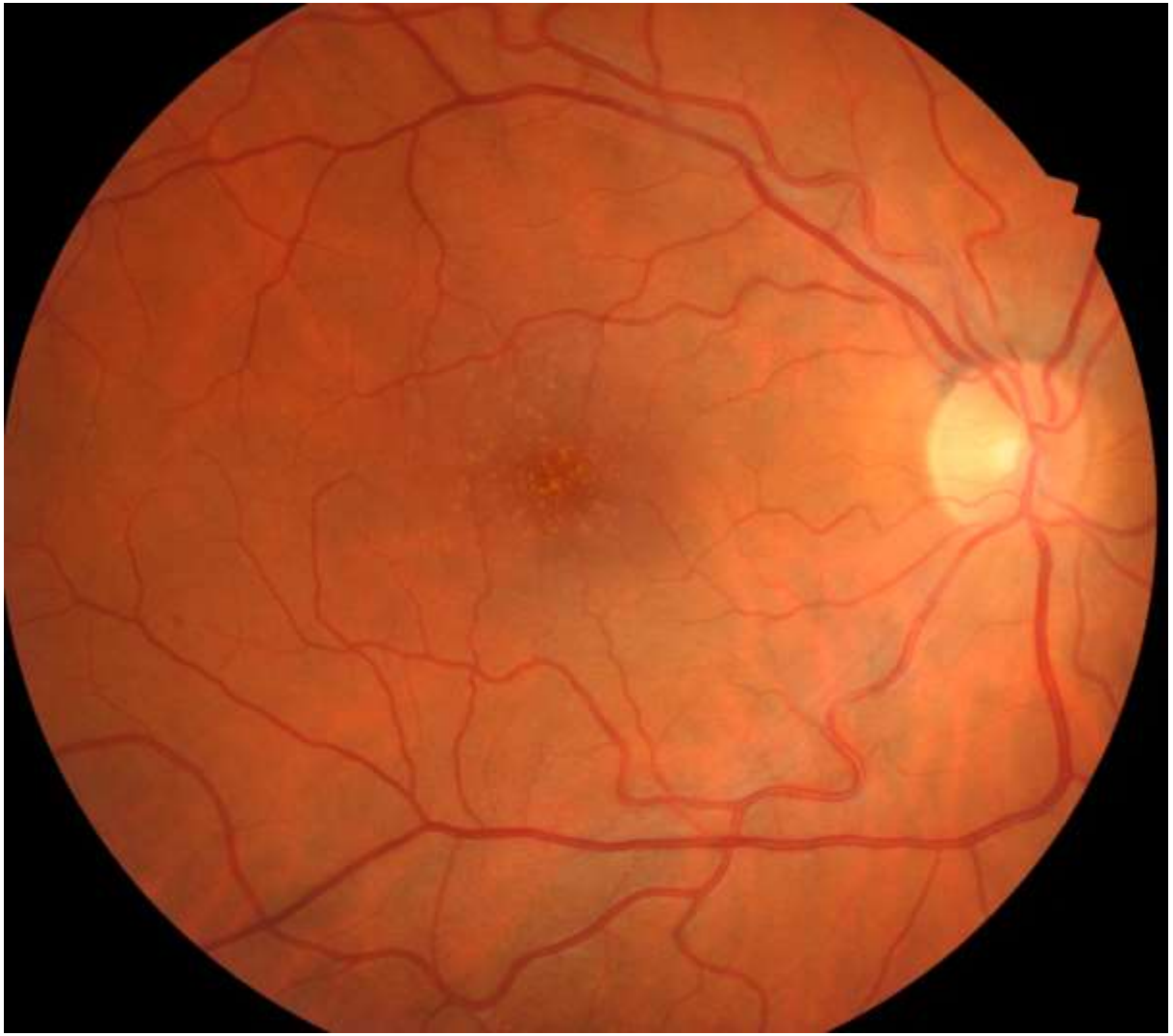
The Age-Related Eye Disease Study Research Group: A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. *Arch Ophthalmol 2001; 119:1417-1436.*

Clinical grading of AMD

- **Early AMD**
  - Extensive (>15) small drusen
  - Few (approximately <20) medium-size indistinct drusen (soft borders)
  - Pigment abnormalities (increased pigmentation or depigmentation but not geographic atrophy) and no other stage of AMD.

The Age-Related Eye Disease Study Research Group: A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. *Arch Ophthalmol 2001; 119:1417-1436.*

Early AMD

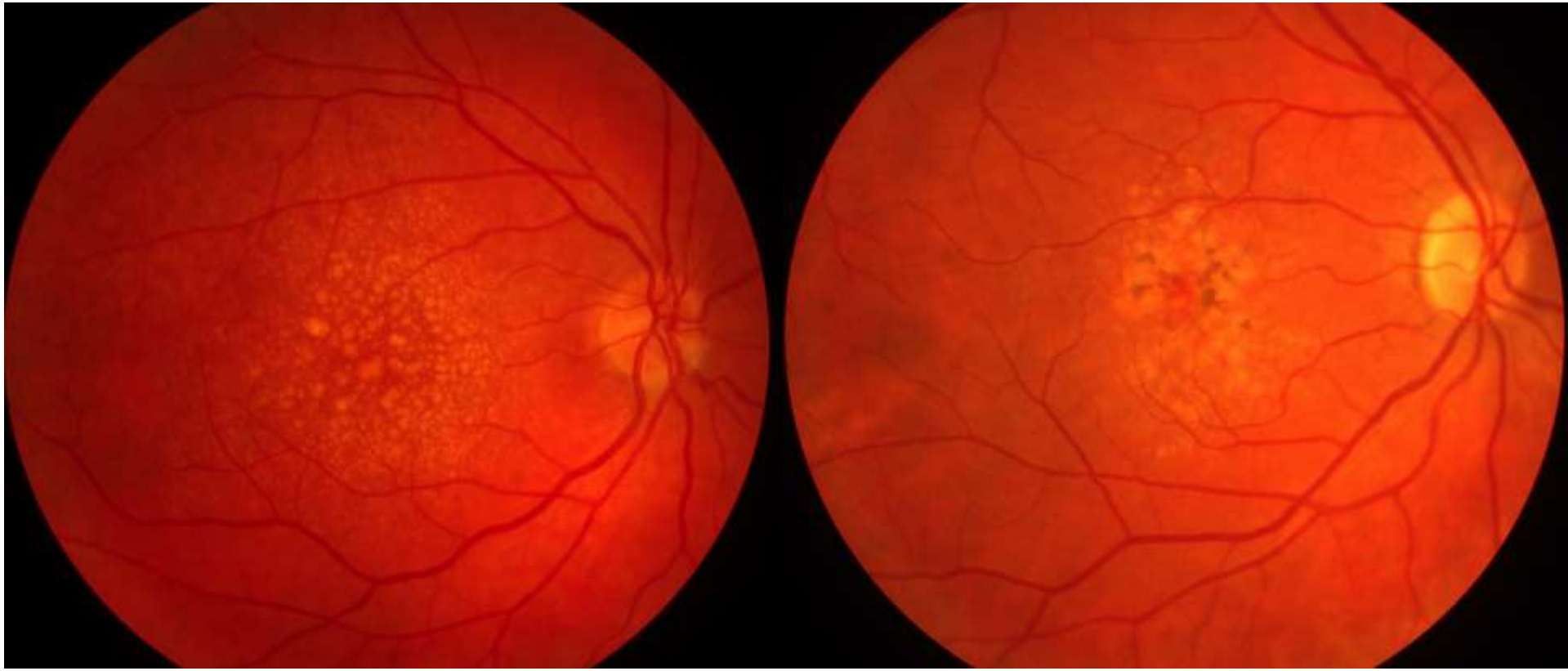


Clinical grading of AMD

- **Intermediate AMD**
  - Presence of at least one large druse
  - Numerous medium-size drusen
    - 20 or more when the drusen boundaries are amorphous
    - 65 or more when the drusen boundaries are distinct, sharp or hard
  - Geographic atrophy that does not extend under the center of the macula (noncentral GA).

The Age-Related Eye Disease Study Research Group: A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. *Arch Ophthalmol 2001; 119:1417-1436.*

Intermediate AMD



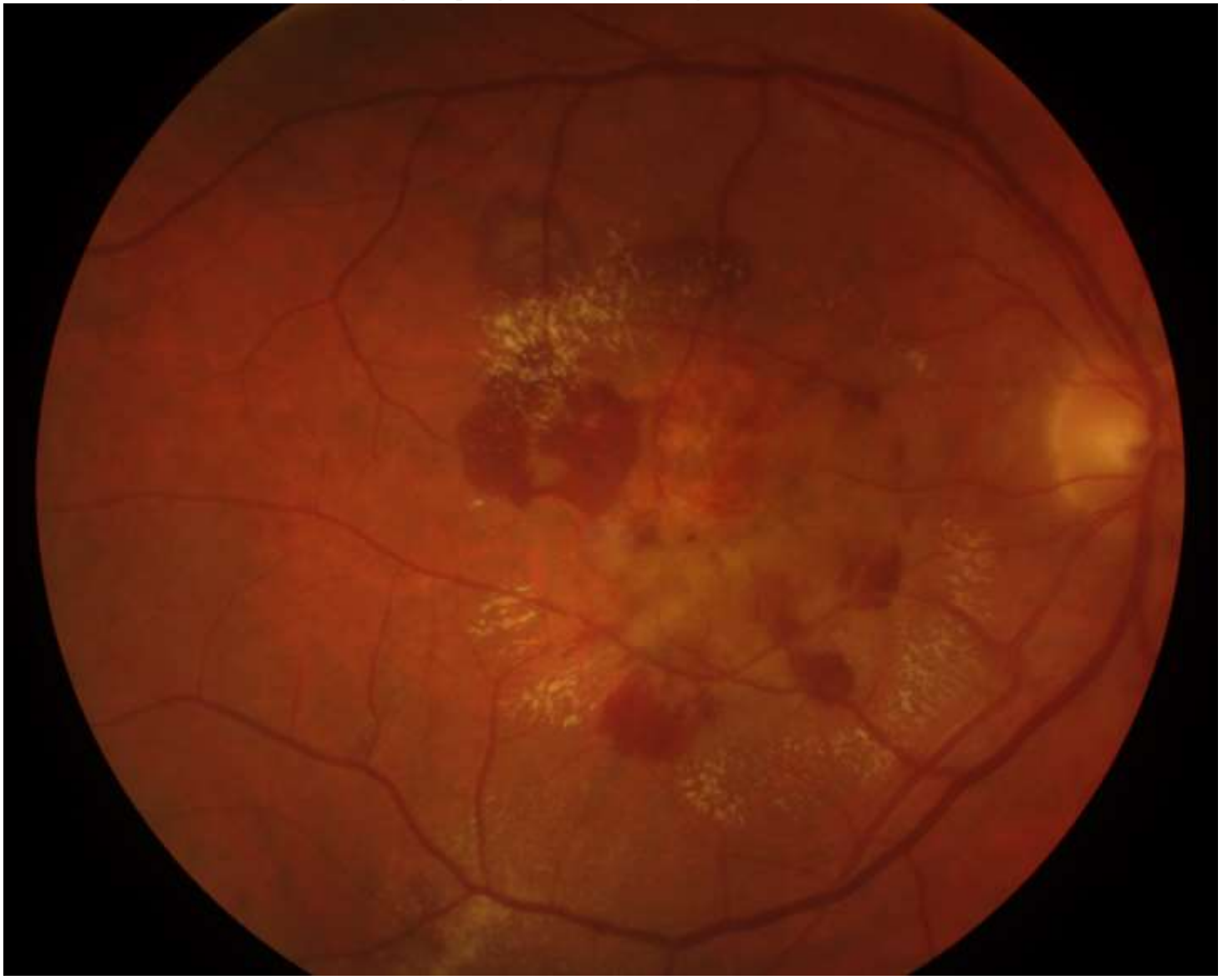
Intermediate AMD

Clinical grading of AMD

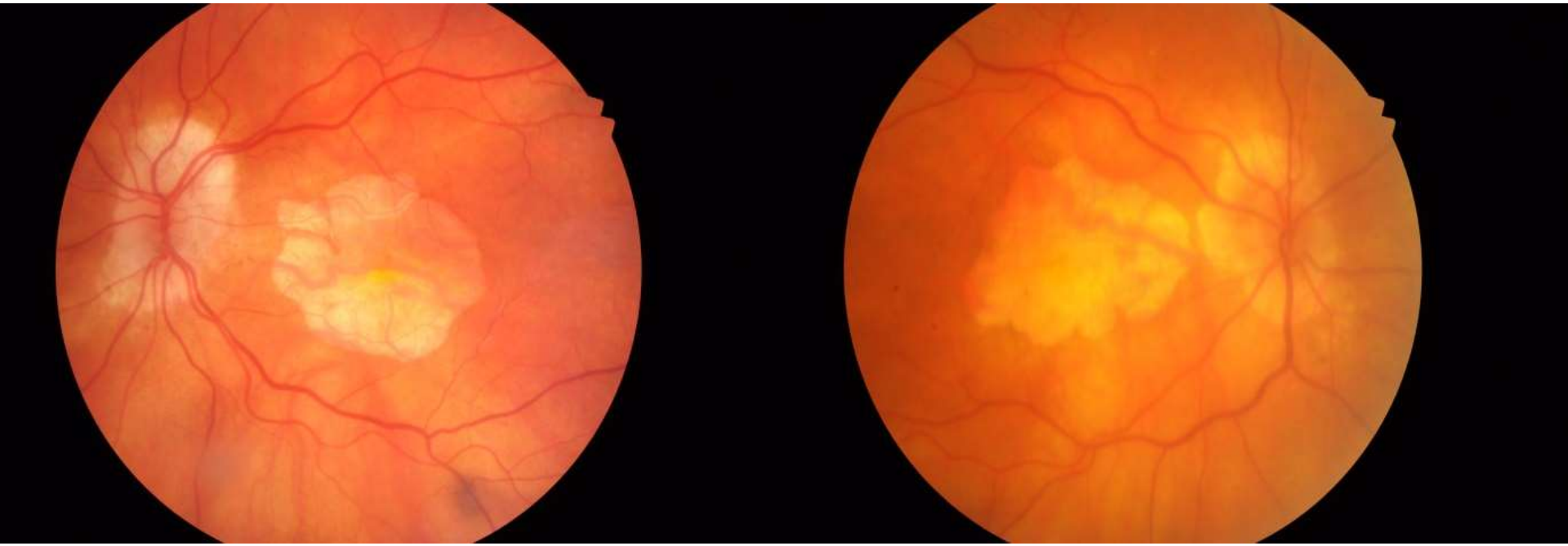
- **Advanced stage of AMD**
  - Geographic atrophy extending under the center of the macula
  - Neovascular AMD.

The Age-Related Eye Disease Study Research Group: A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. *Arch Ophthalmol 2001; 119:1417-1436.*

Advanced AMD



Advanced AMD



Diagnostic Tools

- Fundus photography (FP)
- Fluorescein angiography (FA)
- Optical Coherence Tomography (OCT)
- Fundus Auto Fluorescence (FAF)
- Indocyanin green Angiography (ICG)

Fundus photography (FP)

Fluorescein angiography (FA)

Optical Coherence Tomography (OCT)

Fundus Auto Fluorescence (FAF)

Indocyanin green Angiography (ICG)

MANAGEMENT OF NON-NEOVESCULAR AMD

Management Of Non-Neovescular AMD

- Annual evaluation of the retina to determine the presence and stage of AMD.

Management Of Non-Neovescular AMD

- If **no AMD** then no intervention
- If **early AMD** then annual follow up
  - One third progress to intermediate AMD in first 5 yrs of follow up
  - Vitamin supplements not beneficial

The Age-Related Eye Disease Study Research Group: A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. *Arch Ophthalmol 2001; 119:1417-1436.*

Management Of Non-NeovescularAMD

- If **intermediate AMD**
  - Consider AREDS type dietary supplement (if no medical contraindication)
    - Daily dose of
      - 500 mg vitamin C
      - 400 international units of vitamin E
      - 15 mg beta carotene (non-smokers)
      - 80 mg zinc oxide
      - 2 mg cupric oxide (to reduce the risk of a copper-deficiency anemia).

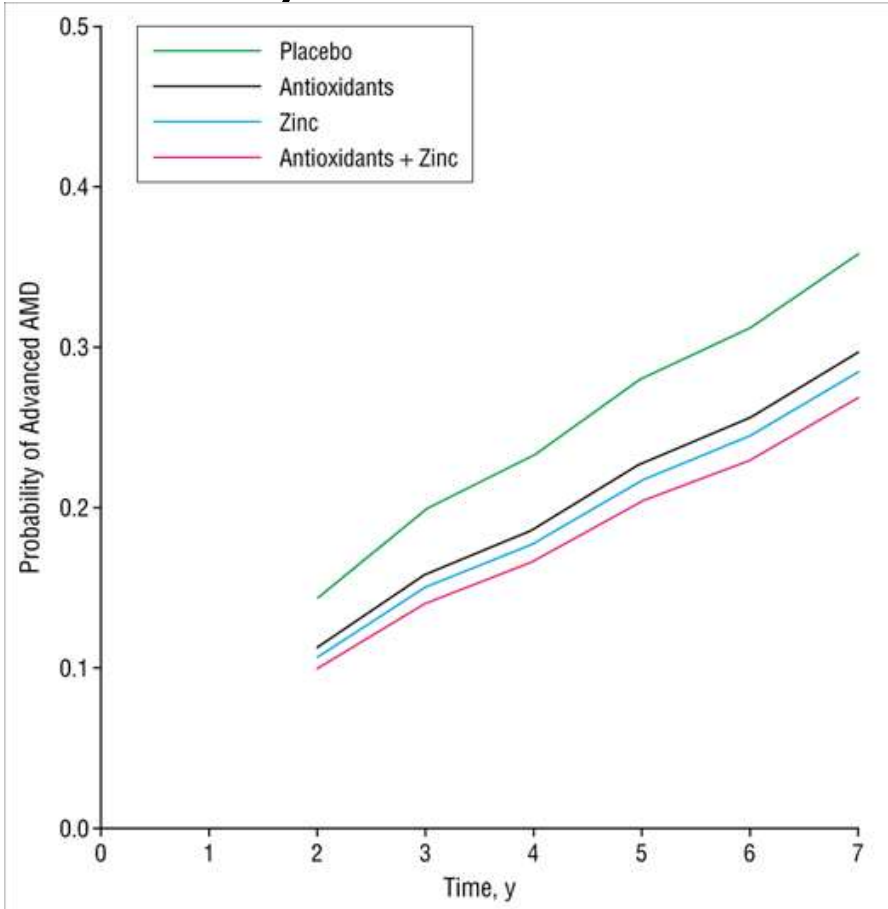
The Age-Related Eye Disease Study Research Group: A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. *Arch Ophthalmol 2001; 119:1417-1436.*

Management Of Non-Neovescular AMD

- Unilateral intermediate AMD on the AREDS 1 formulation
  - Decreased risk of progression to advanced AMD
  - Decreased risk of vision loss through at least 10 years

The Age-Related Eye Disease Study Research Group: A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. *Arch Ophthalmol 2001; 119:1417-1436.*

Probability of Advanced AMD



Probability of AMD Event by Year

Treatment	2	3	4	5	6	7
Placebo	.142	.197	.231	.278	.311	.357
Antioxidants	.112	.157	.185	.226	.254	.296
Zinc	.106	.149	.177	.216	.243	.284
Antioxidants + Zinc	.098	.139	.165	.202	.229	.267

Management Of Non-Neovescular AMD

- **AREDS 2**
  - Oral supplementation with
    - Lutein
    - Zeaxanthin
    - Omega-3 fatty acids
    - Among individuals with bilateral intermediate AMD or those with unilateral advanced AMD with large drusen in the healthier contralateral eye

Management Of Non-Neovescular AMD

- No additional benefit over AREDS 1 (non smokers)
- Safe for smokers
- Possible standardization benefit (1/2 of AMD pts are former smokers)

LuteinZeaxanthin and Omega-3 Fatty Acids for Age-Related Macular Degeneration
The Age-Related Eye Disease Study 2 (AREDS2) Randomized Clinical Trial : http://jama.jamanetwork.com

AREDS and Advanced AMD

- If **unilateral advanced AMD**
  - GA
  - Neovascular AMD
  - Disciform scar
  - fellow eye is at high risk of progression to advanced AMD
  - Consider AREDS vitamin to decrease anatomic progression and functional impairment.

The Age-Related Eye Disease Study Research Group: A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. *Arch Ophthalmol 2001; 119:1417-1436.*

AREDS and Advanced AMD

- Unilateral advanced AMD on the AREDS 1 formulation
  - Decreased risk of progression to advanced AMD
  - Decreased risk of vision loss through at least 10 years

The Age-Related Eye Disease Study Research Group: A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. *Arch Ophthalmol 2001; 119:1417-1436.*

AREDS and Advanced AMD

- If **bilateral advanced AMD**
  - Consider AREDS type supplement if visual acuity is relatively good (20/100 or better) in at least one eye **in the presence of CNV.**
  - Decreased risk of at least 3 additional lines of visual acuity in the eye with neovascular AMD among the advanced AMD participants with unilateral CNV at baseline.

The Age-Related Eye Disease Study Research Group: A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. *Arch Ophthalmol 2001; 119:1417-1436.*

MANAGEMENT OF NEOVASCULAR AMD

HISTORY

- LASER
- SURGERY
- PDT
- Anti VEGF

LASER

- Laser photocoagulation has been shown to be beneficial for some lesions
  - well-defined lesions not involving the foveal center

- Additional visual acuity loss can occur
  - recurrent CNV
  - treatment will destroy retinal tissue (and corresponding function).

Macular Photocoagulation Study Group: Persistent and recurrent choroidal neovascularization after laser photocoagulation for subfoveal choroidal neovascularization of age-related macular degeneration. Arch Ophthalmol 1994; 112:489-499

SURGERY

- Submacular surgery
- Macular translocation
- Vitrectomy
  - Tpa
  - Gas

Submacular surgery

- Visual acuity outcomes with submacular surgery are no different compared with observation for subfoveal CNV in patients with AMD in which a majority of the lesion is CNV and there is evidence of classic CNV.

Hawkins BS, Bressler NM, Miskala PH, et al: Surgery for subfoveal choroidal neovascularization of age-related macular degeneration: ophthalmic findings. SST report no. 11. *Ophthalmology 2004; 111:1967-1980.Submacular Surgery Trials (SST) Research Group*

Macular translocation

- No strong evidence on
  - Effectiveness
  - Technique
- Significant rate of complications
- Randomized clinical trials are needed

American Academy of Ophthalmology : Macular translocation. Ophthalmic procedure preliminary assessment. *Ophthalmology 2000; 107:1015-1018.*

Subretinal Recombinant Tissue Plasminogen Activator (rt-PA)

- Useful in displacing thick submacular hemorrhage

- More controlled studies needed.

Olivier S, Chow DR, Packo KH, MacCumber MW, Awh CC. Subretinal recombinant tissue plasminogen activator injection and pneumatic displacement of thick submacular hemorrhage in Age-Related macular degeneration. Ophthalmology. 2004 Jun;111(6):1201-8.

Photodynamic Therapy (PDT)

- Intravenously injected photosensitizing drug
- Low-intensity laser light
- Photochemical reaction
- Direct cellular injury, including damage to vascular endothelial cells and vessel thrombosis
- Damage of choroidal neovascular tissue

Miller JW, Schmidt-Erfurth U, Sickenberg M, et al: Photodynamic therapy for choroidal neovascularization due to age-related macular degeneration with verteporfin: results of a single treatment in a phase I and II study. *Arch Ophthalmol 1999; 117:1161-1173.*

PDT

- **The TAP Study Group**
  - PDT with verteporfin (Visudyne) can reduce the risk of moderate and severe visual acuity loss for at least 2 years
  - Predominantly classic subfoveal lesions

Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group: Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: Two year results of 2 randomized clinical trials – TAP report no. 2. *Arch Ophthalmol 2001; 119:198-207.*

PDT

Verteporfin In Photodynamic therapy (VIP) Trial

- Occult with no classic lesions with recent progression
  - blood associated with CNV
  - Definite loss of visual acuity within the past 3 months
  - Growth of the lesion on fluorescein angiography

- PDT could reduce the risk of moderate (3 lines) and severe visual acuity loss (6 lines) by 2 years after randomization compared with a sham treatment

Verteporfin in Photodynamic Therapy (VIP) Study Group: Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: Two year results of a randomized clinical trial including lesions with occult but no classic neovascularization – VIP report no. 2. *Am J Ophthalmol 2001; 131:541-560.*

ANTI-VEGF

- Interferon-alpha-2a
- Pegaptanib sodium (Macugen)
- Ranibizumab (Lucentis)
- Bevacizumab (Avastin)
- Aflibercept (Eylea)

Anti-VEGF

- Various growth factors are suspected to be involved in the development of this CNV, such as vascular endothelial growth factor (VEGF).

Ambati J, Ambati BK, Yoo SH, et al: Age-related macular degeneration: etiology, pathogenesis, and therapeutic strategies. *Surv Ophthalmol 2003; 48:257-293*

Anti-VEGF

- Anti-VEGFdrugs have been shown to reduce the risk of vision loss
- Vision loss still occurred in many treated cases
- Antiangiogenic effect or antipermeability effect?

Interferon-alpha-2a

- Weak inhibitor of angiogenesis
- Commercially available
- When tested in a randomized clinical trial, however, the treatment was found to be of no benefit, and possibly harmful, compared to placebo treatment.

Pharmacological Therapy for Macular Degeneration Study Group: Interferon alfa-2a is ineffective for patients with choroidal neovascularization secondary to age-related macular degeneration: results of a prospective, randomized, placebo-controlled clinical trial. *Arch Ophthalmol 1997; 115:865-872.*

Pegaptanib sodium (Macugen)

- Modified oligonucleotide
- Binds to an isoform of vascular endothelial growth factor (VEGF)
- Injections were given every 6 weeks
- Primary endpoint
  - Proportion of patients losing less than 3 lines of visual acuity by week 54
  - 15% in favor of treatment (70% vs 55%; *P <0.001) for the 294 patients receiving pegaptanib 0.3 mg.*

Gragoudas ES, Adamis AP, Cunningham Jr ET, et al: Pegaptanib for neovascular age-related macular degeneration. *N Engl J Med 2004; 351:2805-2816.for the VEGF Inhibition Study in Ocular Neovascularization Clinical Trial Group*

Ranibizumab (lucentis)

- A recombinant humanized IgG1 kappa isotype monoclonal antibody fragment designed for intraocular use
- Binds to and inhibits the biologic activity of human vascular endothelial growth factor A (VEGF-A)
- Molecular weight of approximately 48 kilodaltons

Ranibizumab

- Ranibizumab binds to VEGF-A
- Prevents the interaction of VEGF-A with its receptors (VEGFR1 and VEGFR2) on the surface of endothelial cells
- Reducing endothelial cell proliferation, vascular leakage, and new blood vessel formation.

Ranibizumab Trials

- **MARINA**
  - Efficacy of ranibizumab vs sham treatment for **minimally classic or occult** with **no classic subfoveal** choroidal neovascular lesions and presumed recent disease progression
- **ANCHOR**
  - Efficacy of ranibizumab vs PDT with verteporfin for **predominantly classic subfoveal** CNV lesions.

ANCHOR

- Efficacy of ranibizumab vs PDT with verteporfin for **predominantly classic subfoveal** CNV lesions.

- Monthly ranibizumab for 24 months

Brown DM, Kaiser PK, Michels M, et al: Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med 2006; 355:1432-1444.*

ANCHOR- Outcomes 12 months

Outcome Measure	Verteporfin PDT N=143	Lucentis 0.5mg N=140	Estimated difference
Loss of < 15 letters in VA (%)	64.3 %	96.4%	33%
Gain of ≥ 15 letters in VA (%)	5.6%	40.3%	35%
Mean change in VA (letters)	-9.5	+11.3	21.1

Brown DM, Kaiser PK, Michels M, et al: Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med 2006; 355:1432-1444.*

ANCHOR- Outcomes 24 months

Outcome Measure	Verteporfin PDT N=143	Lucentis 0.5mg N=140	
Loss of < 15 letters in VA (%)	65.7 %	89.9%	
Gain of ≥ 15 letters in VA (%)	6.3%	41.0%	
Mean change in VA (letters)	-9.8	+10.7	

Brown DM, Kaiser PK, Michels M, et al: Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med 2006; 355:1432-1444.*

ANCHOR Outcomes

- PDT outcomes likely were better than the natural course of the disease

- Monthly intravitreal ranibizumab persisted through at least 2 years compared with standard applications of PDT.

Brown DM, Kaiser PK, Michels M, et al: Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med 2006; 355:1432-1444*

MARINA

- Efficacy of ranibizumab vs sham treatment for **minimally classic or occult** with **no classic subfoveal** choroidal neovascular lesions and presumed recent disease progression

Rosenfeld PJ, Brown DM, Heier JS, et al: Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med 2006; 355:1419-1431*.

Marina outcomes
12 months

Outcome Measure	Sham N=238	Lucentis 0.5mg N=240	Estimated difference
Loss of < 15 letters in VA (%)	62.2 %	94.6%	32%
Gain of ≥ 15 letters in VA (%)	5.0%	33.8%	35%
Mean change in VA (letters)	-10.4	+7.2	17.5

Rosenfeld PJ, Brown DM, Heier JS, et al: Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med 2006; 355:1419-1431.*

Marina outcomes
24 months

Outcome Measure	Sham N=238	Lucentis 0.5mg N=240	Estimated difference
Loss of < 15 letters in VA (%)	52.9 %	90.0%	33%
Gain of ≥ 15 letters in VA (%)	4.0%	33%	29%
Mean change in VA (letters)	-14.9	+6.6	21.4

Rosenfeld PJ, Brown DM, Heier JS, et al: Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med 2006; 355:1419-1431.*

Bevacizumab (Avastin)

- AVASTIN® (Bevacizumab) is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF).

- Molecular weight of approximately 149 kilodaltons.

Bevacizumab (Avastin)

- Bevacizumab binds VEGF and prevents the interaction of VEGF to its receptors (Flt-1 and KDR) on the surface of endothelial cells.

Comparison of Age-related Macular Degeneration Treatments Trial (CATT)

- Designed to answer two questions

Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) Research Group: Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration; N Engl J Med 2011;364:1897-908

CATT Question 1

- Does bevacizumab (Avastin) injected every 4 weeks provide visual acuity results which are equivalent (noninferior) to ranibizumab (Lucentis) injected every 4 weeks with an acceptable safety profile?

CATT Question 2

- Does either bevacizumab or ranibizumab when provided as needed result in visual acuity outcomes equivalent to those following ranibizumab provided every 4 weeks?

CATT Results

- **First year**
- **Answer 1**
  - Visual acuity outcomes when using bevacizumab every 4 weeks were equivalent (not inferior) to those when using ranibizumab every 4 weeks?

CATT Results

- **First year**
- **Answer 2**
  - Visual acuity outcomes when using ranibizumab as needed, based on examinations every 4 weeks, were equivalent to those when ranibizumab was given every 4 weeks

CATT Results

- **First year**
- **Answer 2**
  - Visual acuity outcomes when bevacizumab as needed was compared with ranibizumab every 4 weeks were inconclusive.

CATT Results

- Average as needed treatments
  - Ranibizumab - seven treatments in the first year
  - Bevacizumab - eight treatments in first year

CATT

- No difference between ranibizumab and bevacizumab
  - Myocardial infarction
  - Cerebrovascular accidents
  - Endophthalmitis,

CATT

- Systemic serious AE
  - Ranibizumab 19%
  - Bevacizumab 24%

- Systemic serious adverse events was higher in the bevacizumab as-needed group than the bevacizumab every-4-weeks group; and

CATT

- First year average cost of drug per patient
  - Ranibizumab every-4-weeks $23 ,400
  - Ranibizumab as-needed $13 ,800
  - Bevacizumab every-4-weeks $595

CATT

- **Two-year results**
  - Monthly bevacizumab was equivalent to ranibizumab
  - Treatment as needed resulted in less gain in visual acuity both groups,
  - No differences between drugs in rates of death or arteriothrombotic events
  - The increased risk of serious systemic adverse events with bevacizumab was sustained and still requires further study

Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) Research Group: Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology 2012; 119:1388-1398.*

Aflibercept (Eylea)

- Fusion protein
  - Key domains of human VEGF receptors 1,2 (VEGFR1,VEGFR2)
  - human IgGFc
- Binds VEGF-A and Placental growth factor (PLGF)
  - Prevent their interaction with native VEGF receptors

VIEW 1,2

- Compared monthly and every-2-month dosing of intravitreal aflibercept injection with monthly ranibizumab.

VIEW 1,2

- Active, subfoveal, choroidal neovascularization (CNV) lesions

- Juxtafoveal lesions with leakage affecting the fovea

VIEW 1,2

- Randomized to
  - Intravitreal aflibercept
    - 0.5 mg monthly
    - 2 mg monthly
    - 2 mg every 2 months after 3 initial monthly doses
    - Ranibizumab 0.5 mg monthly

VIEW 1,2

- Primary end point
  - Noninferiority of the aflibercept regimens to ranibizumab in the proportion of patients maintaining vision at week 52
  - Other key end points included change in best-corrected visual acuity (BCVA) and anatomic measures.

View 1,2 Results

- All aflibercept groups were noninferior and clinically equivalent to monthly ranibizumab
- All aflibercept regimens were within 0.5 letters of the reference ranibizumab for mean change in BCVA
- All aflibercept regimens also produced similar improvements in anatomic measures.
- Ocular and systemic adverse events were similar across treatmentgroups.

View 1,2 Conclusions

- Intravitreal aflibercept dosed monthly or every 2 months after 3 initial monthly doses produced similar efficacy and safety outcomes as monthly ranibizumab.

View 1,2 Conclusions

- Aflibercept is an effective treatment for AMD
- Every-2-month regimen
  - Potential to reduce
    - Risk from monthly intravitreal injections
    - Burden of monthly monitoring.

Review Questions

- Name the two major categories of Age Related Macular degeneration.

- What are the clinical stages of Age Related Macular Degeneration

- Name the three injectable anti- VEGF medications available for treating Age related macular degeneration