Intravitreal Aflibercept (VEGF Trap-Eye) in Patients with Neovascular Age-Related Macular Degeneration:

Our the first experience in Turkey

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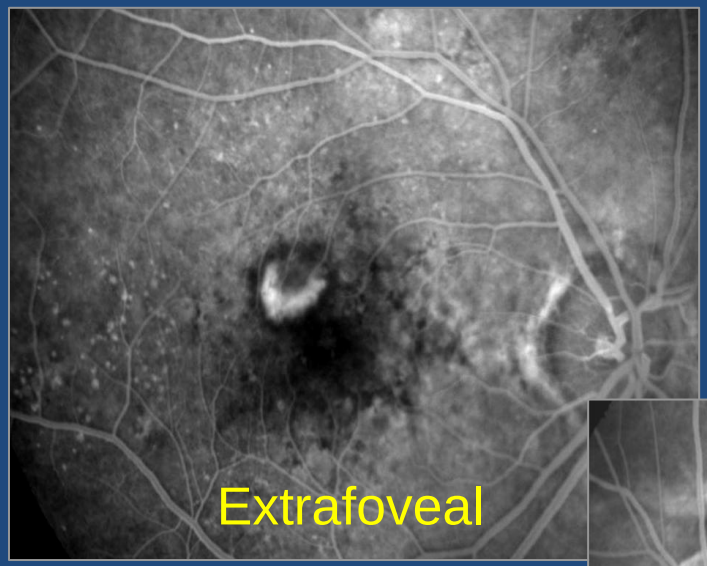
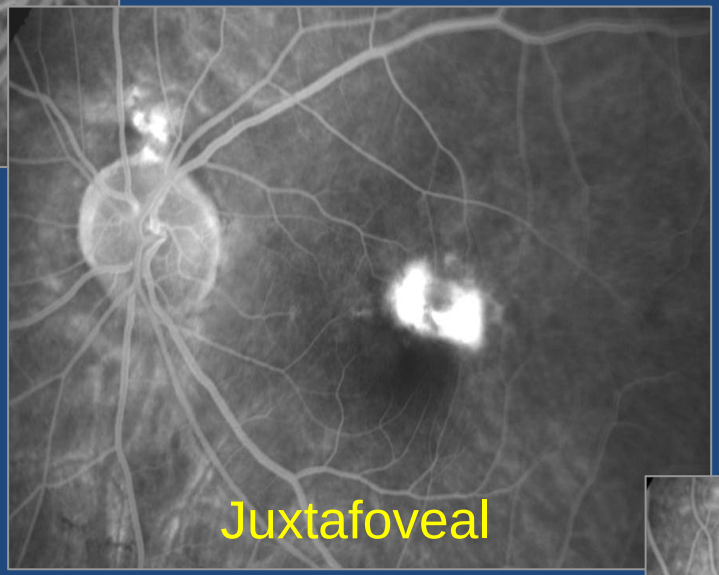
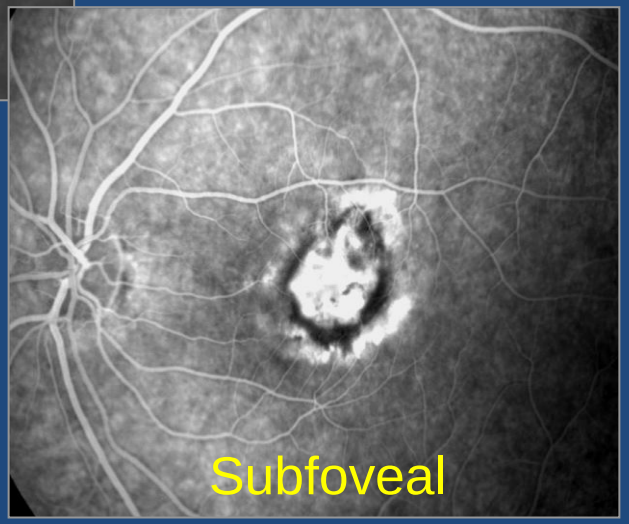
AMD is a leading cause of visual loss over 65 years old







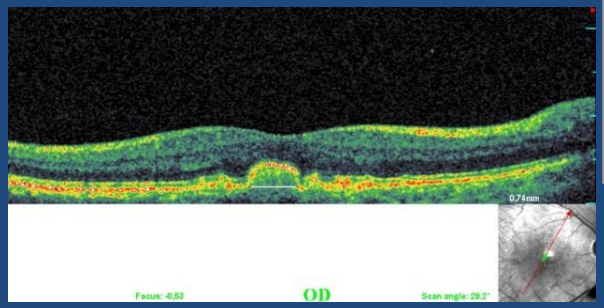
Although neovascular disease comprises only 15 % of AMD, it is responsible for the majority of visual loss
(Ferris 1984)

The International Epidemiological Age-related Maculopathy Study Group (1995)

Age-related Maculopathy (ARM): Early

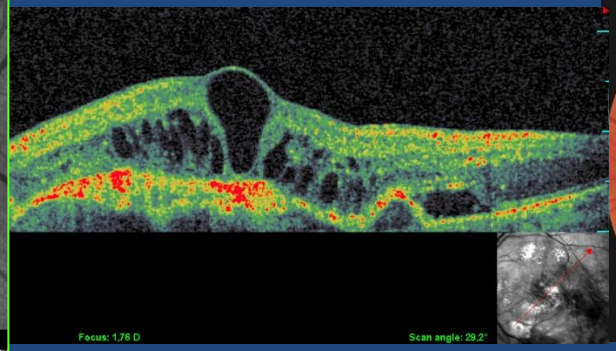
Presence of drusen larger than 63 µ (soft indistinct)

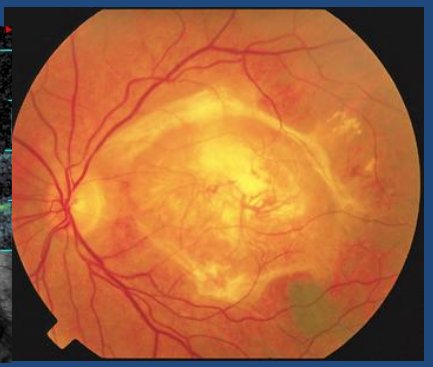
RPE abnormalities + any type of drusen



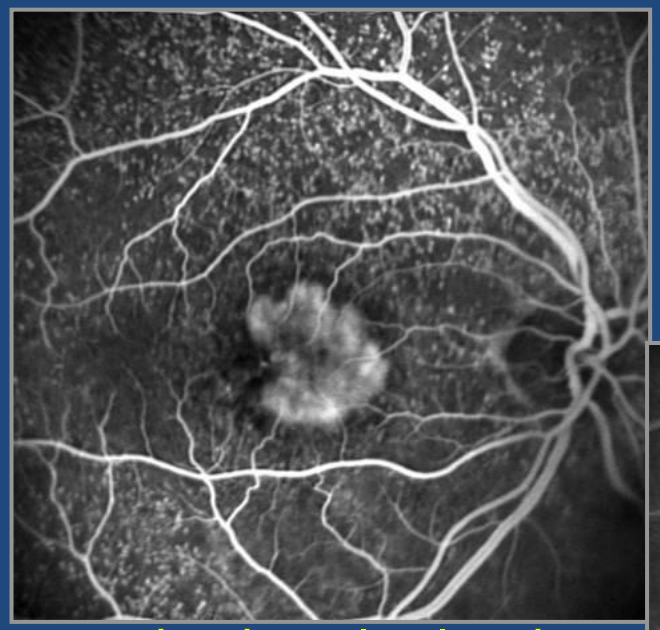
Age-related Macular Degeneration (AMD): Late

Geographic atrophy, choroidal neovascularization, scar





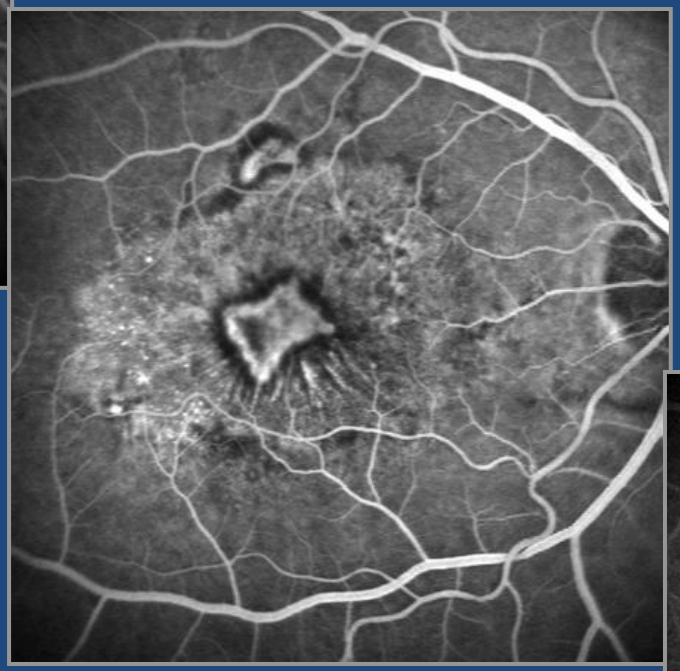
TAP Study



Predominantly classic

Classic CNV component

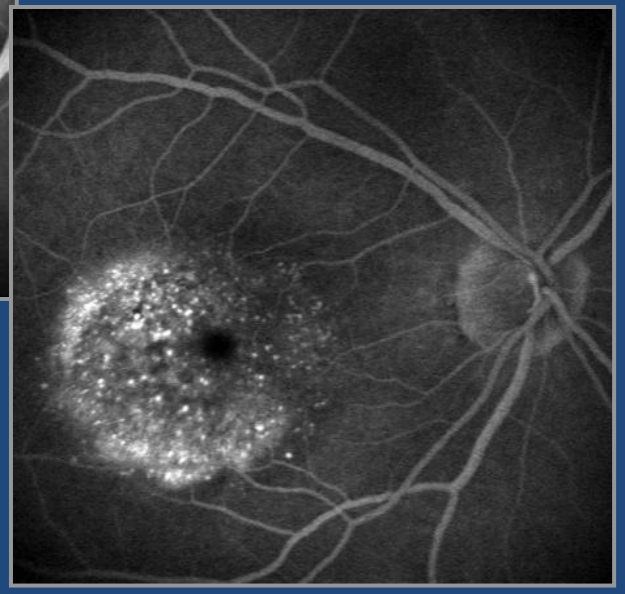
≥ 50% of the total lesion area



Minimally classic

Classic CNV component

>0% - <50% of the total lesion area

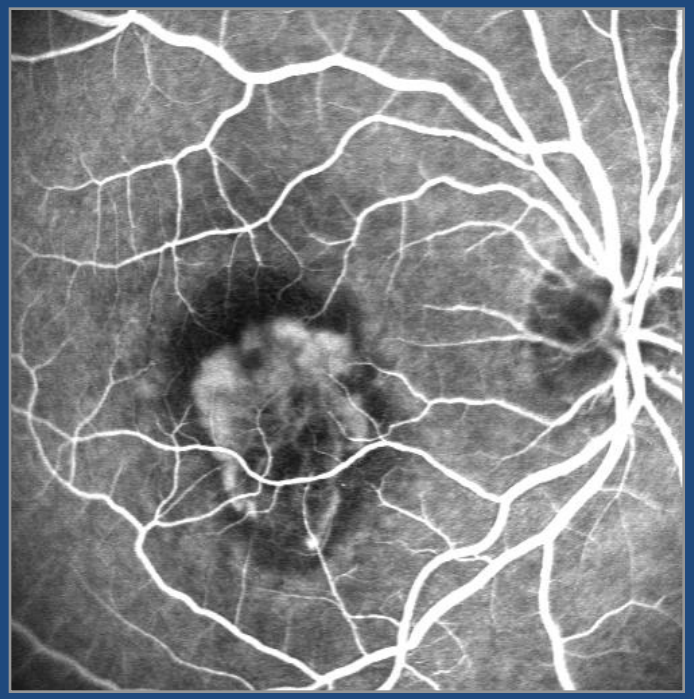


Purely occult

No classic CNV component

Classic CNV - FA

Early phase



Bright hyperfluorescence with well-demarcated boundaries

Middle-late phase

Increasing leakage obscures the boundaries of CNV

Classic CNV - ICGA

Hyperfluoresecent area on ICG similar to that of FA pattern

Occult CNV / MPS Classification (1988)

Occult CNV displays three principal subtypes:

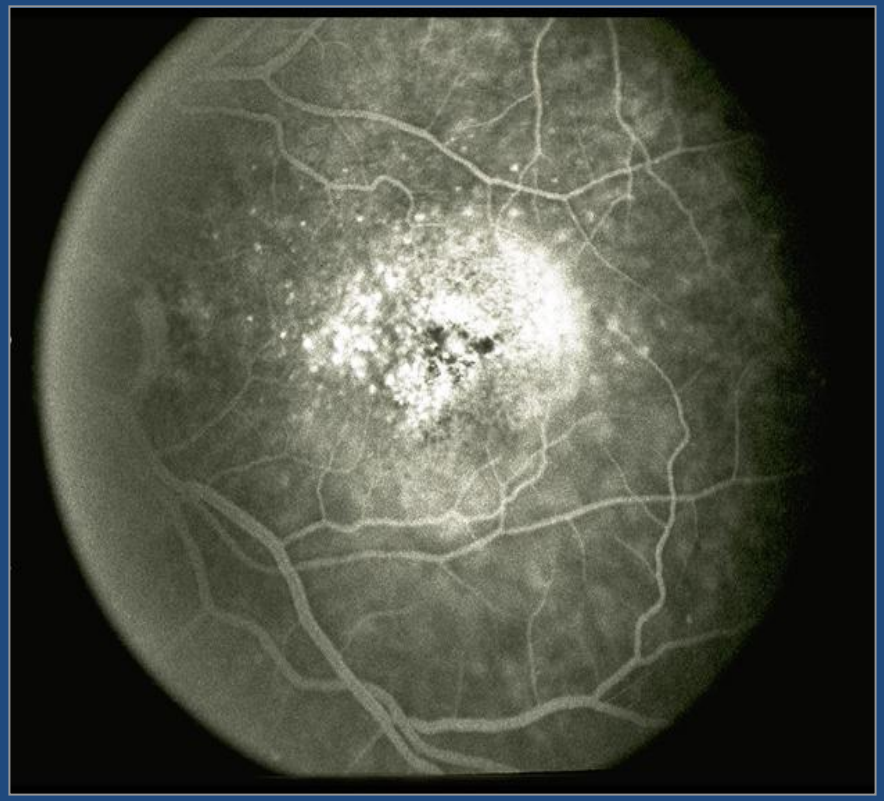
1. Fibrovascular PED (Type 1) :
2. Late leakage of an undetermined source (Type 2)
3. Serous pigment epithelial detachment:

   Serous PED is defined as uniform, early, bright hyperfluorescence beneath a dome-shaped elevation of the retinal pigment epithelium.

Occult CNV (Type I)

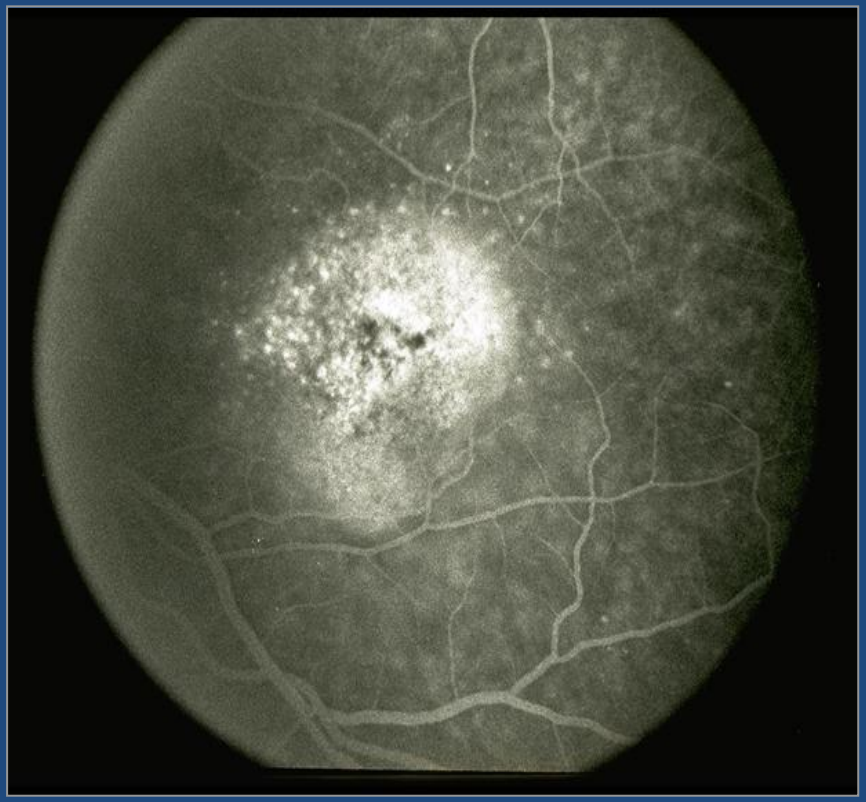
Fibrovascular PED

Middle



An area of stippled hyperfluorescence noted within 1-2 minutes after fluorescein injection.

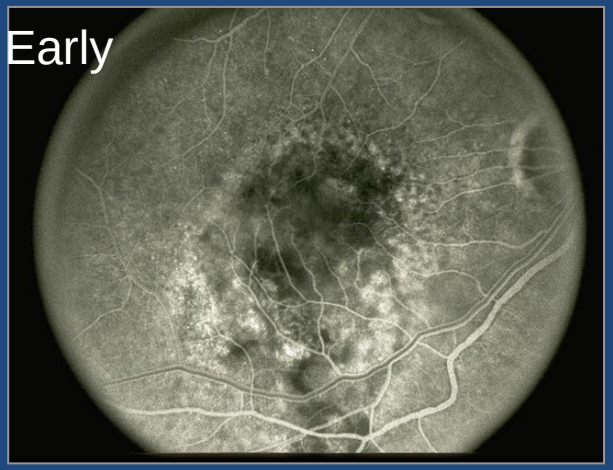
Late phase

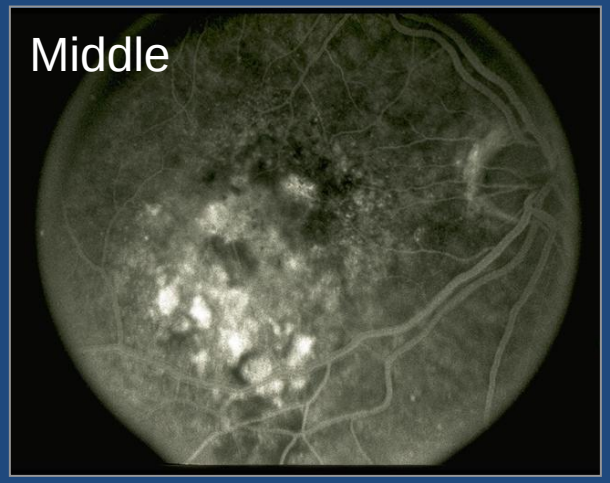


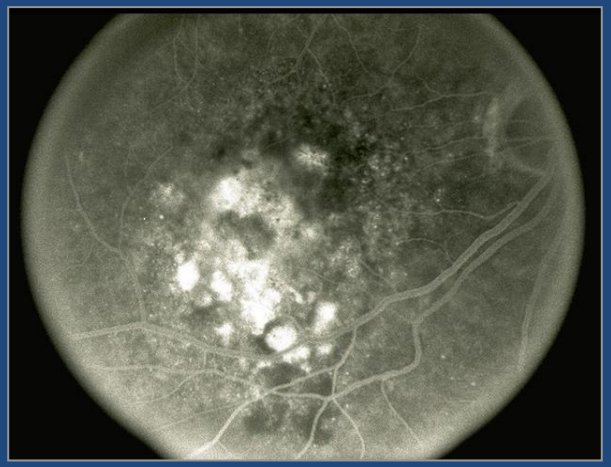
Persistence of fluorescein staining or leakage in this area occurs within ten minutes after injection.

Occult CNV (Type 2)

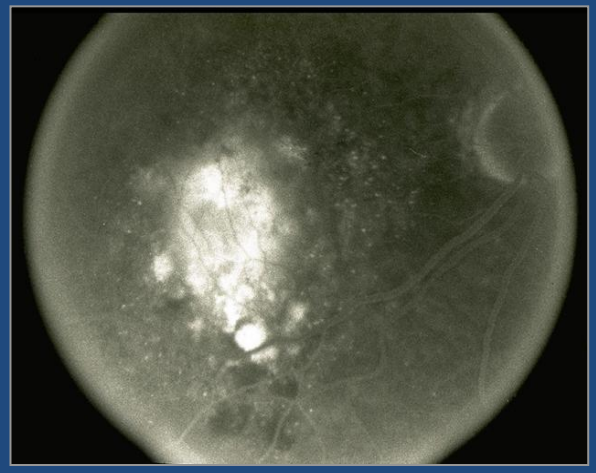
Late leakage of an undetermined source





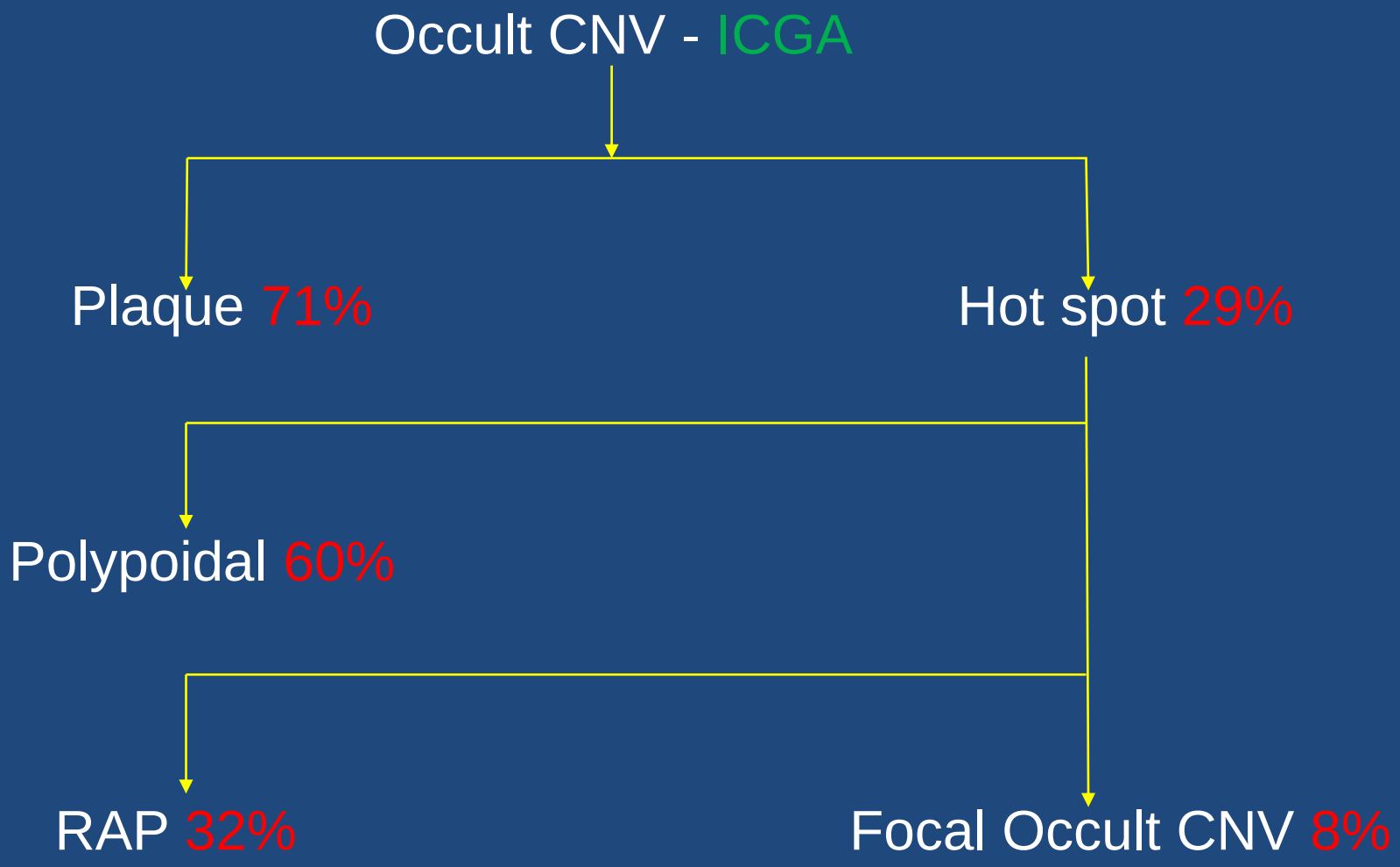


Late



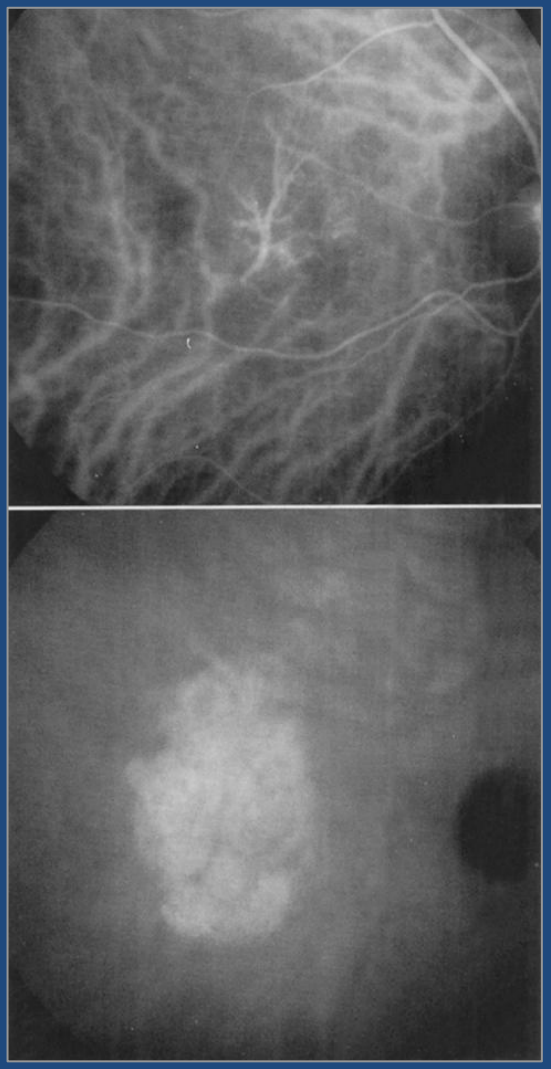
Areas of leakage at the level of the retinal pigment epithelium in the late phase of the angiogram are without well-demarcated areas of hyperfluorescence

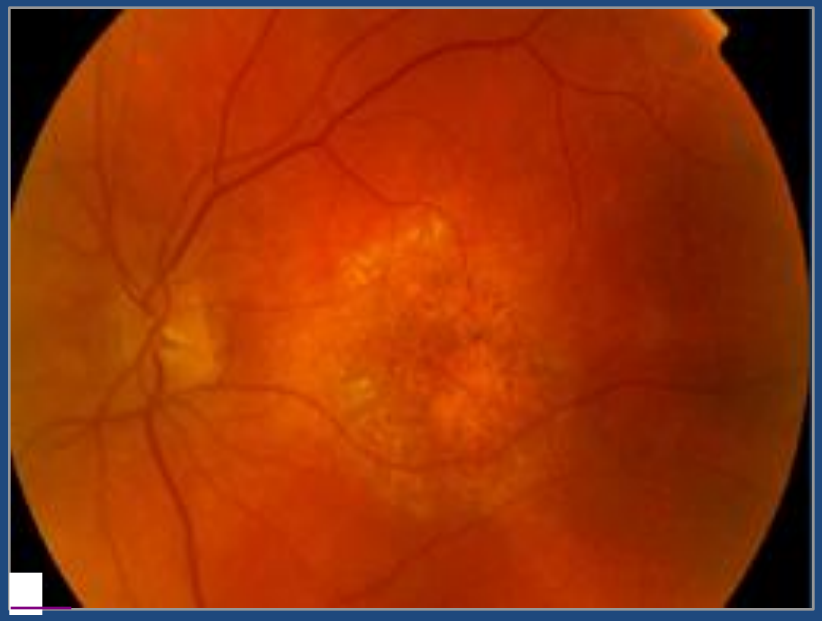
Occult CNV 87% / Classic CNV 13%

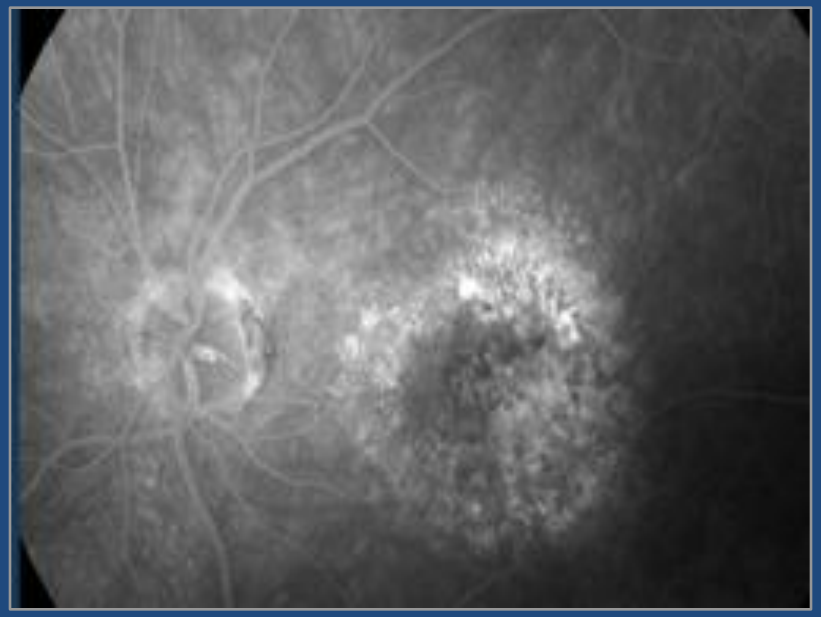


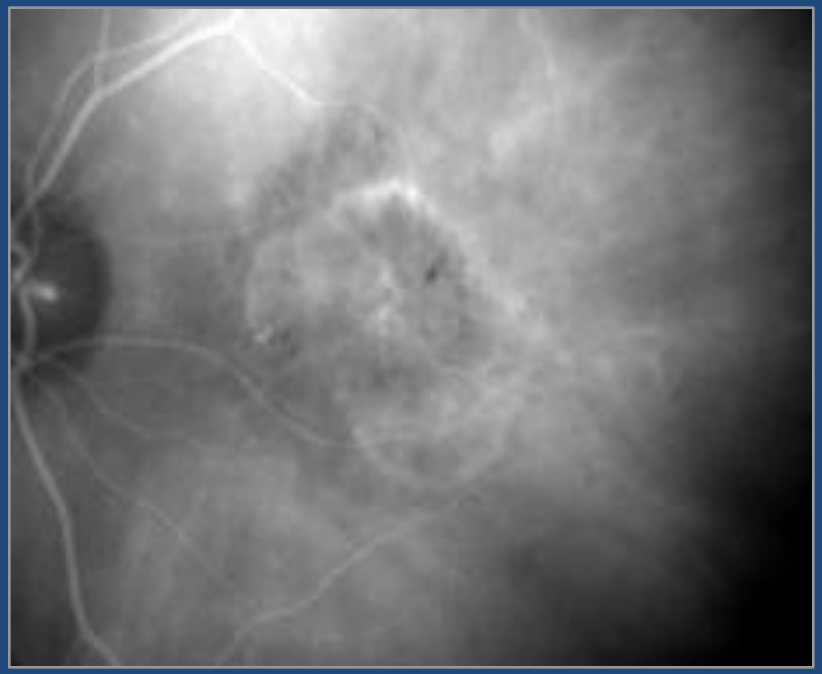
Occult CNV / Plaque CNV

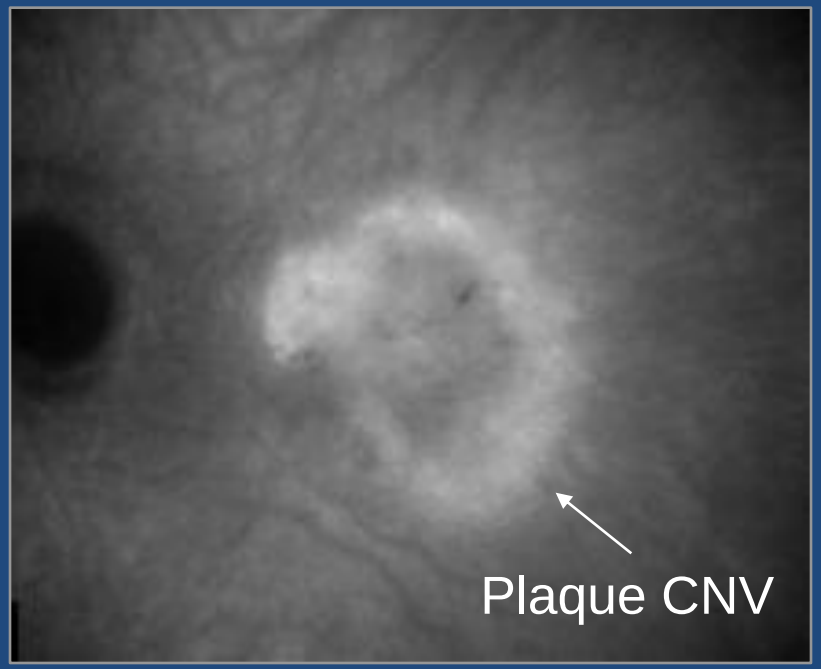
Larger than 1 DD



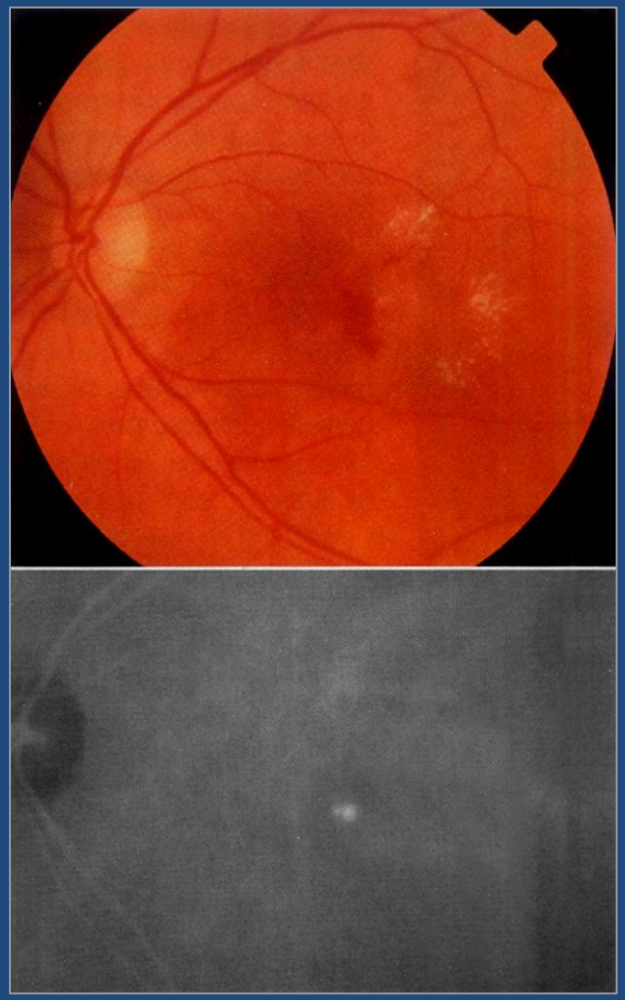


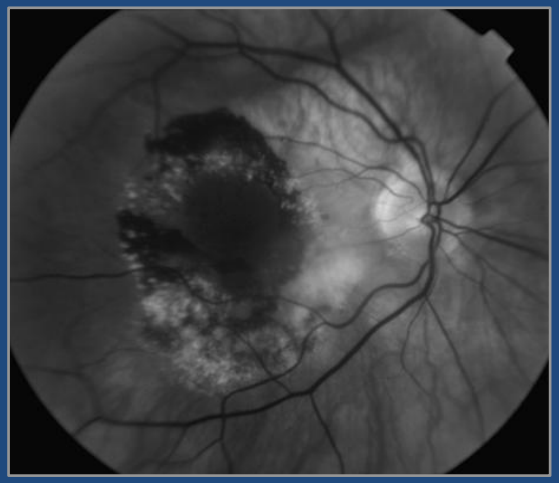


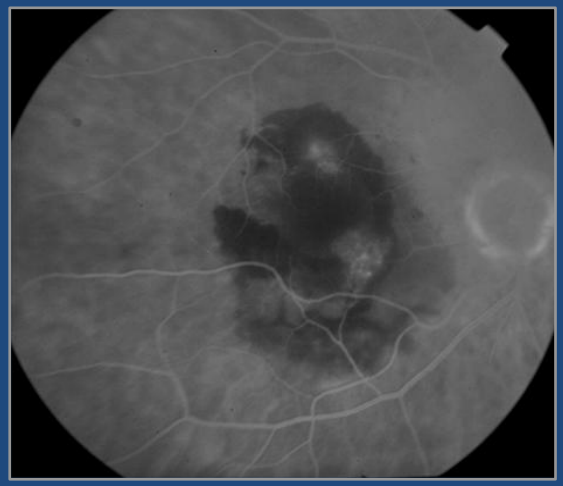


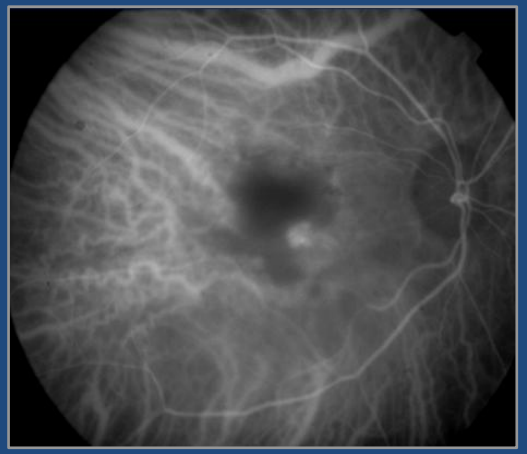

Plaque CNV

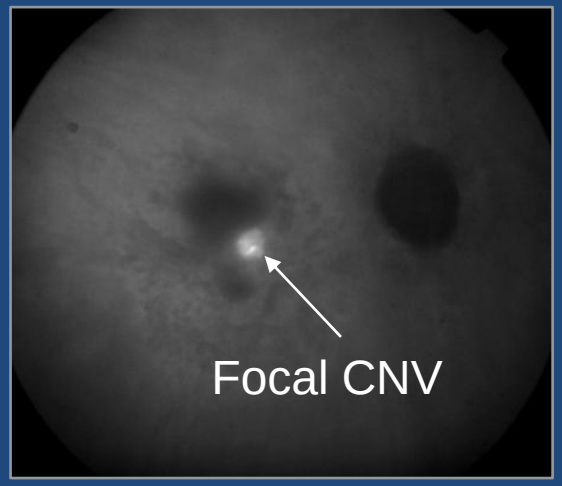
Hot Spot / Focal Occult CNV









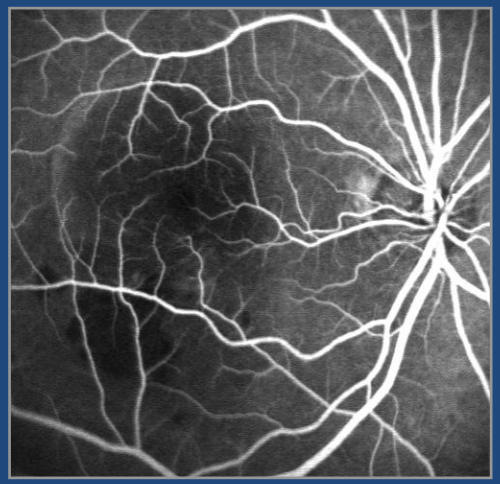
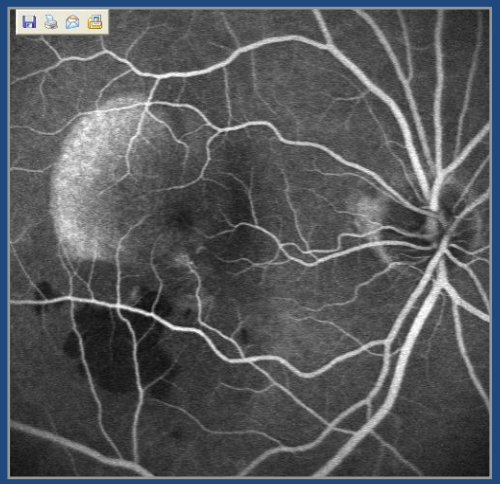
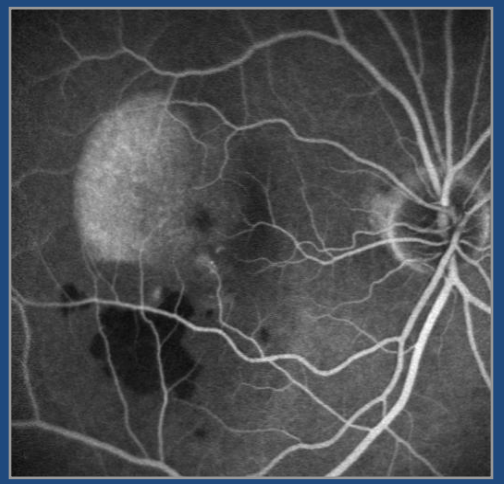
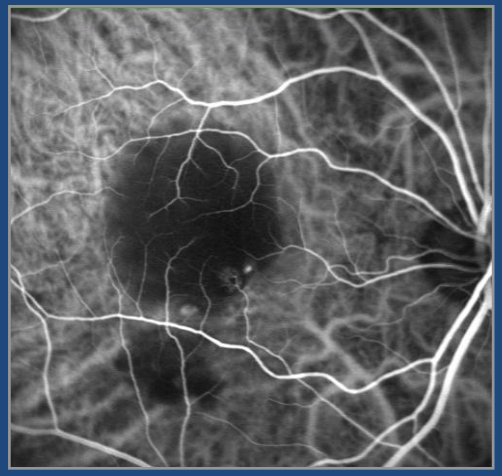
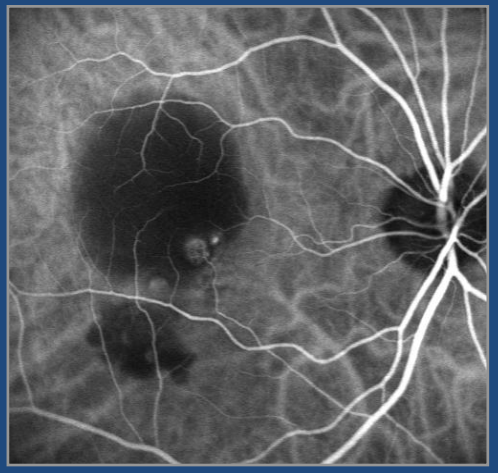


Smaller than 1 DD

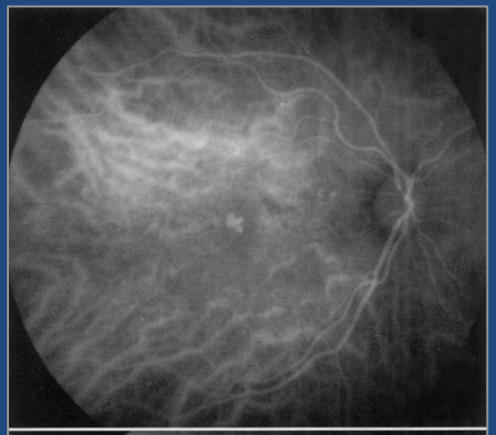
AMD– Notched PED

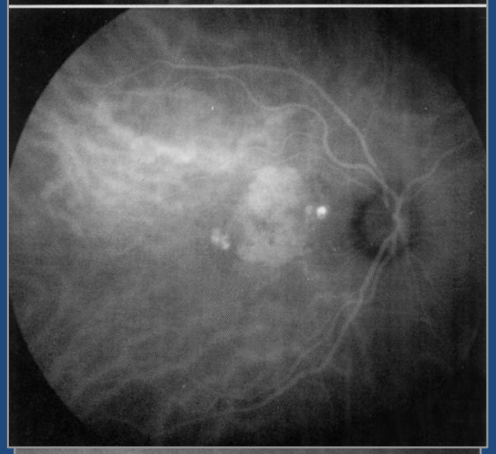
Serous PED + notch ➔ CNV

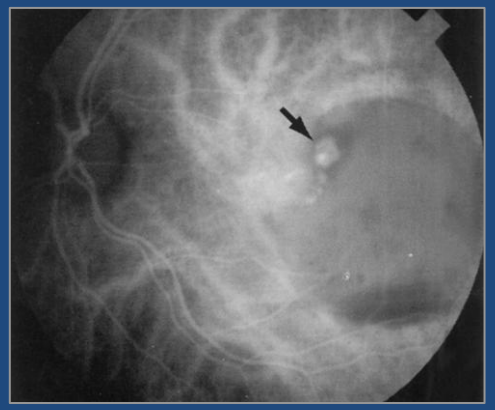
Fibrovascular PED

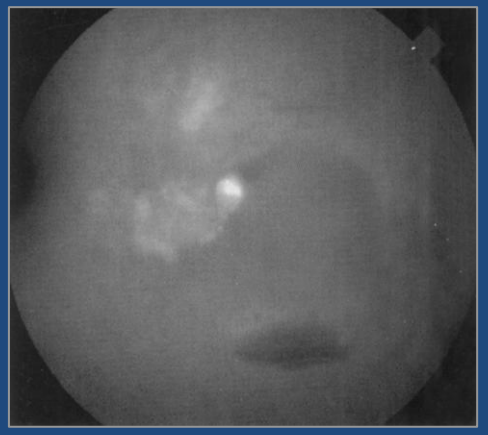







Combined focal and plaque Occult CNV







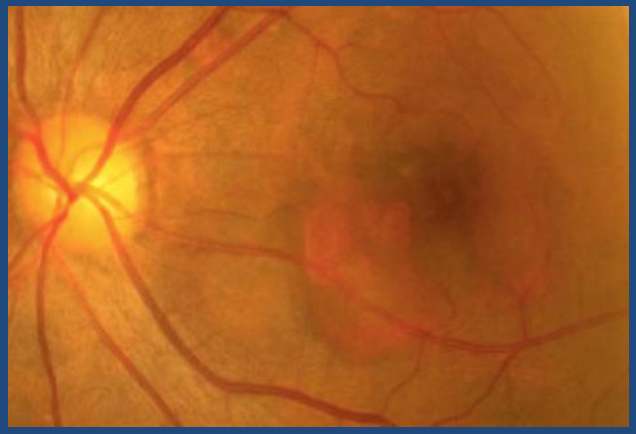


Other reasons of hot spot on ICGA

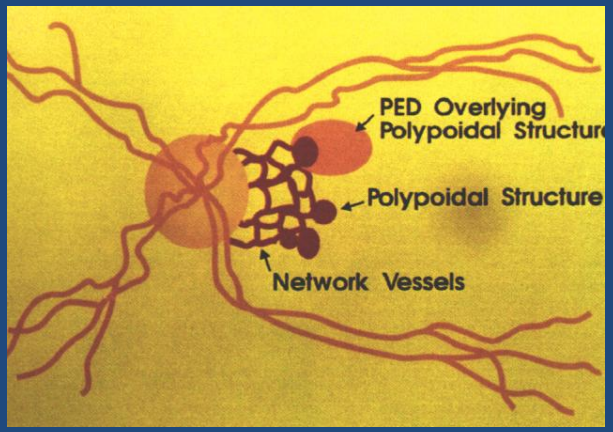
Polypoidal Choroidal Vasculopathy (PCV)
&
Retinal Angiomatous Proliferation (RAP)

PCV & RAP

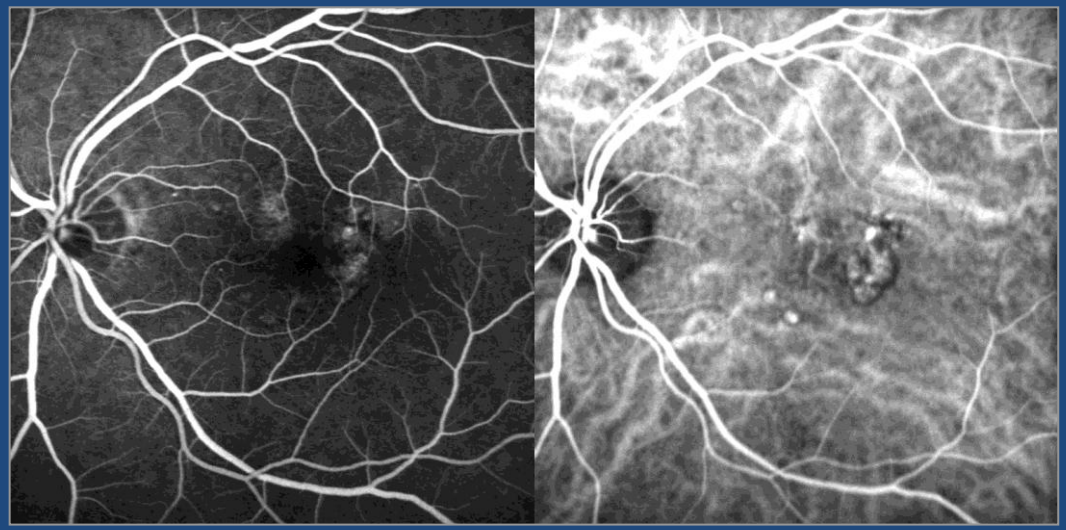
- Distinct forms of AMD
- Misdiagnosed as CNV
- Prognosis, treatment and response to treatment differs from CNV in AMD
- Accurate diagnosis is important

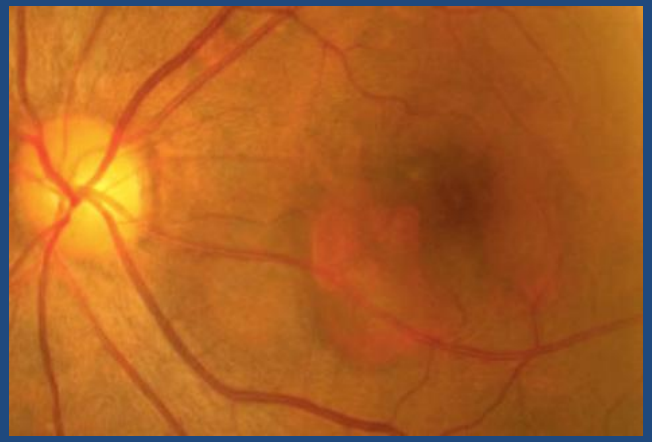


PCV

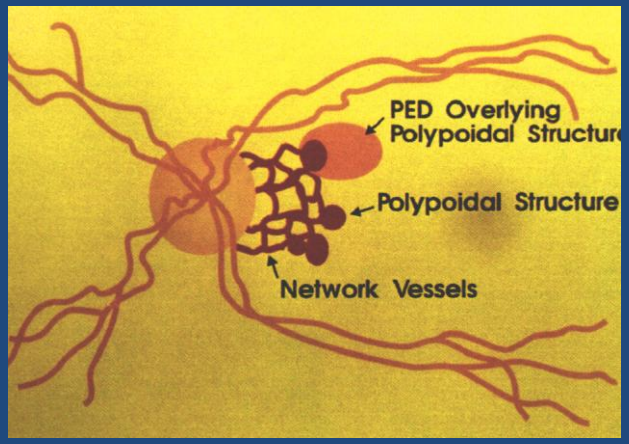


- 7.8 -13.9% of the cases with AMD
- Aneurysmal dilatations of inner choroidal vascular network
- Visible as reddish-orange, spheroid, polyp-like structure
- Most commonly found in the peripapillary area, also in the central macula and in the midperiphery
- Single or cluster of lesions

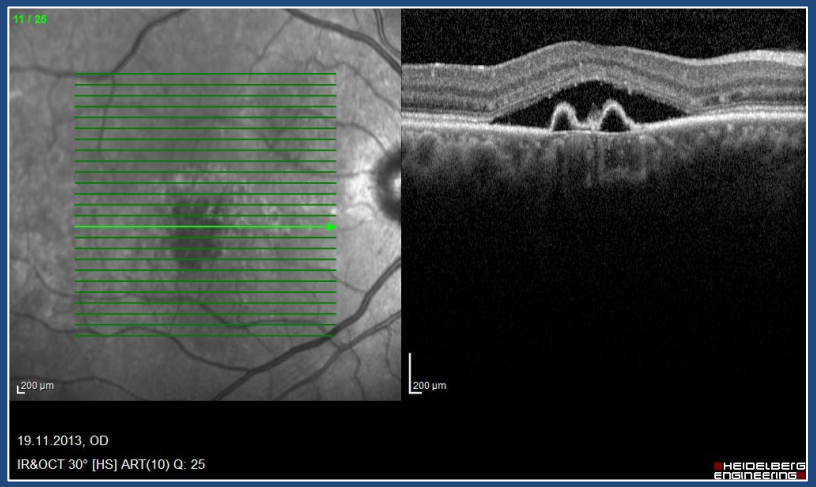




PCV

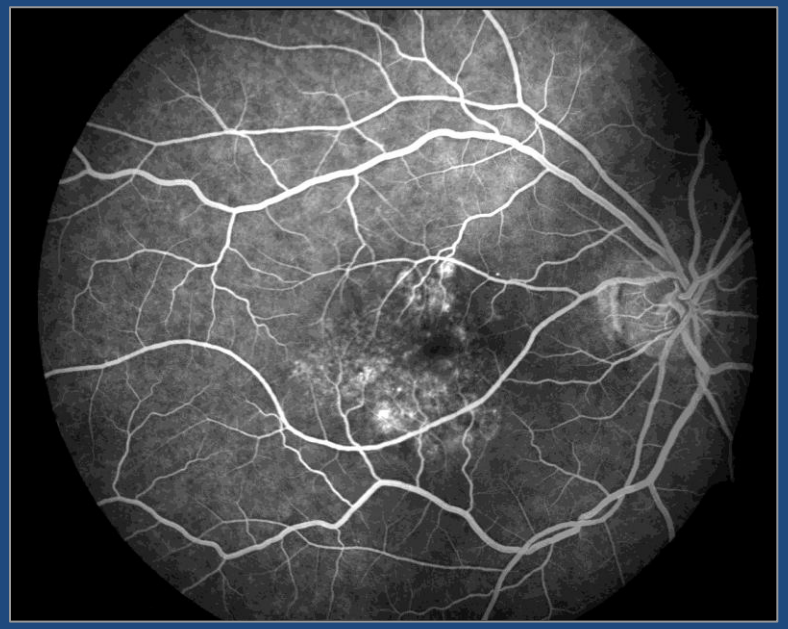


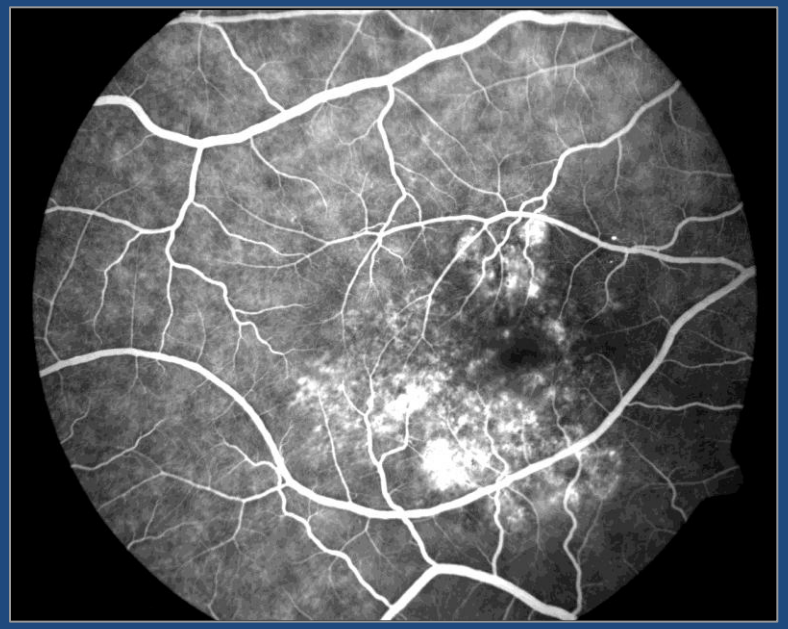
- Chronic / multiple / recurrent PED, neurosensory RD, massive subretinal hemorrhage, hemorrhagic PED, sub-retinal exudation, CSR and CSR-like lesions (remitting-relapsing course)



- Long-term preservation of good vision, minimal fibrous scarring, no drusen
- Natural course is variable

Diagnosis - 1

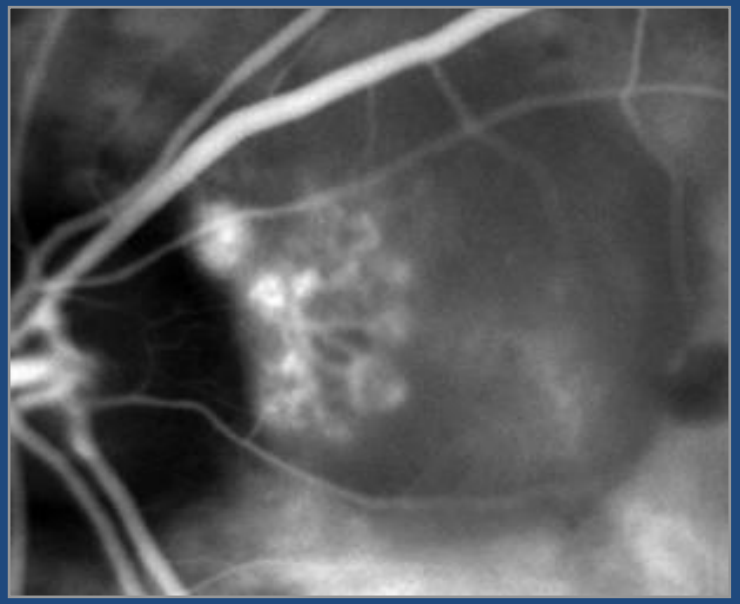




Fluorescein Angiography
Limited value in PCV

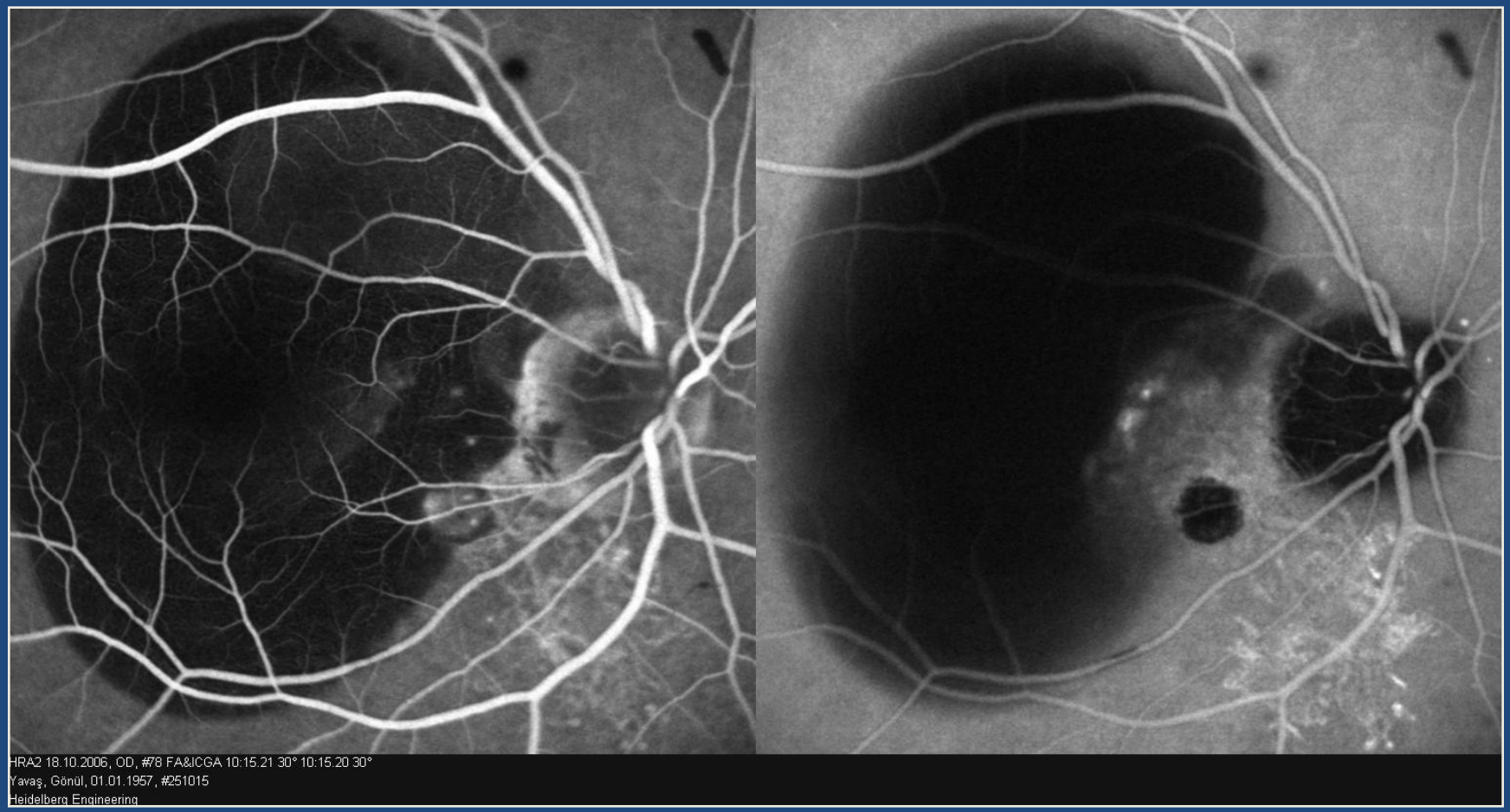
Diagnosis-2

ICG angiography



- Gold standart for the diagnosis
- Filling of branching vascular network earlier than retinal vessels
- Shortly after, small hyperfluorescent polyps appear
- Late phase discloses reversal of pattern:

  - Surrounding hyperfluorescence with central hypo
  - Washout of network and polyps (non-leaking)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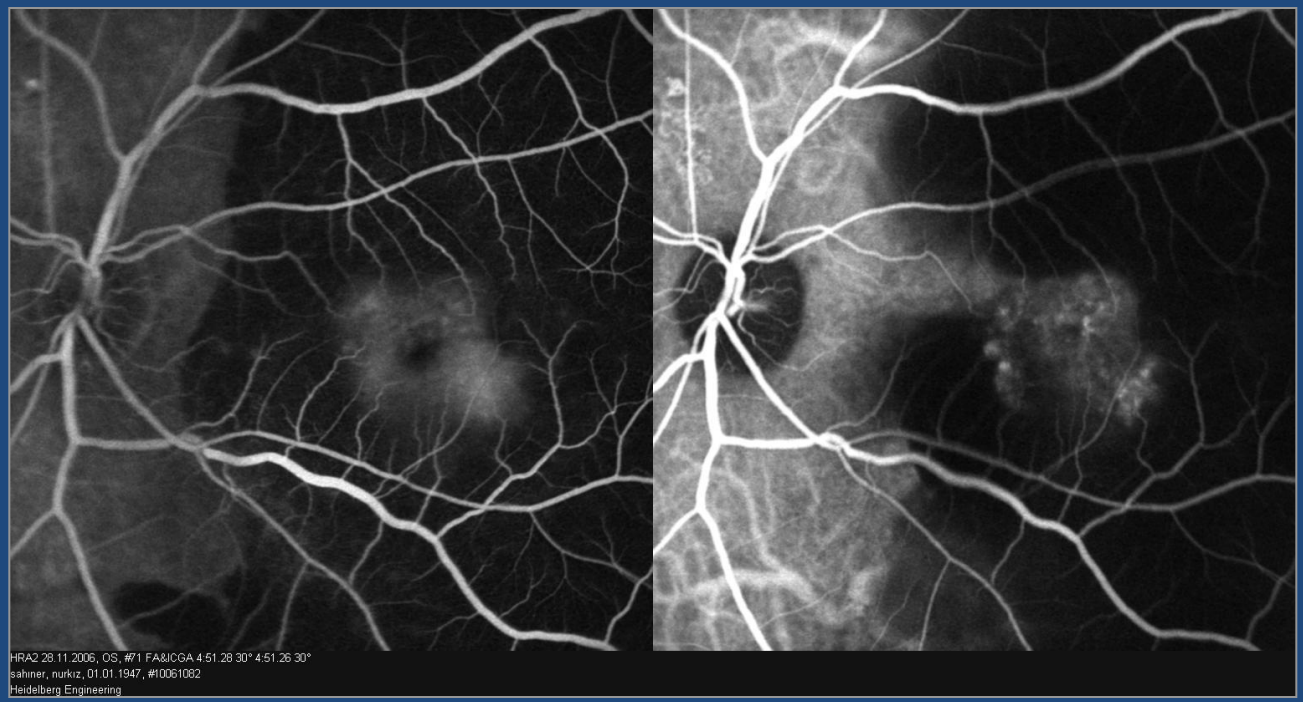
Yavaş, Gönül, 01.01.1957, #251015
Heidelberg Engineering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sahiner, nurkız, 01.01.1947, #10061082
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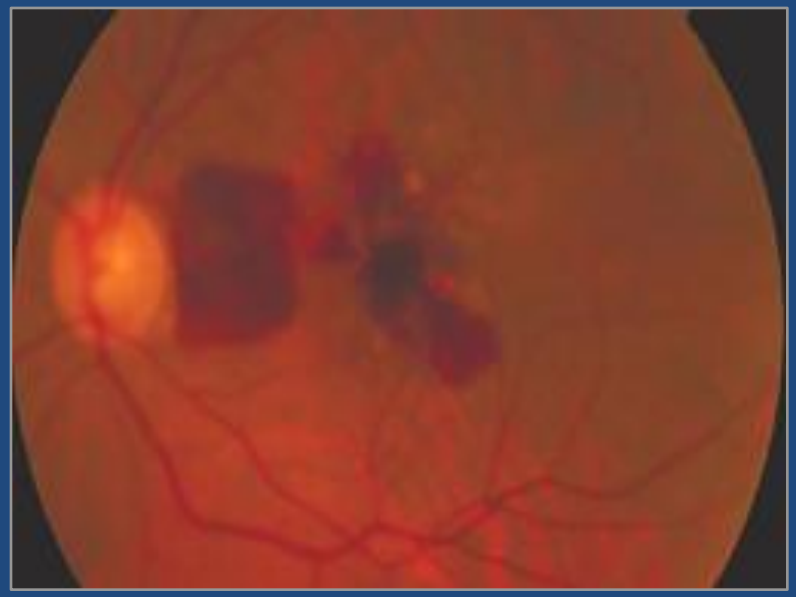
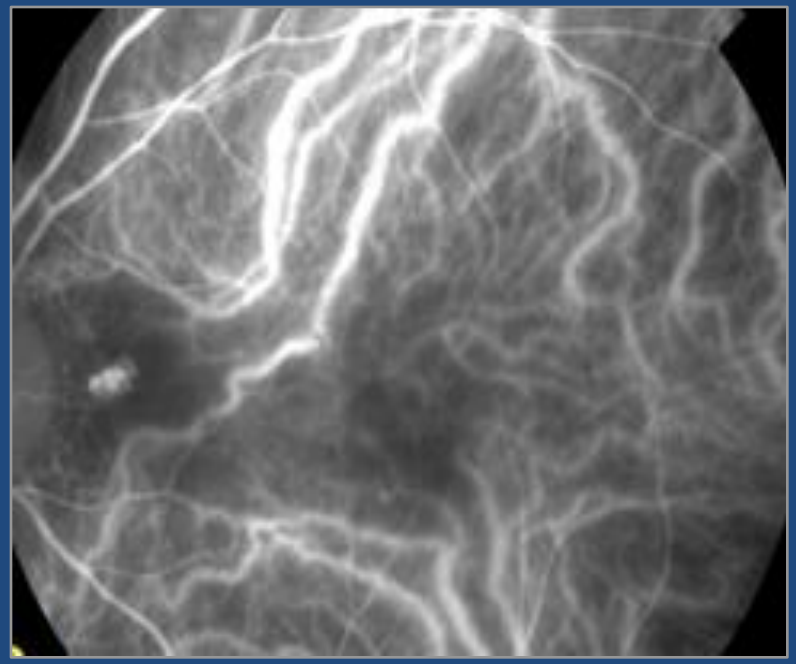
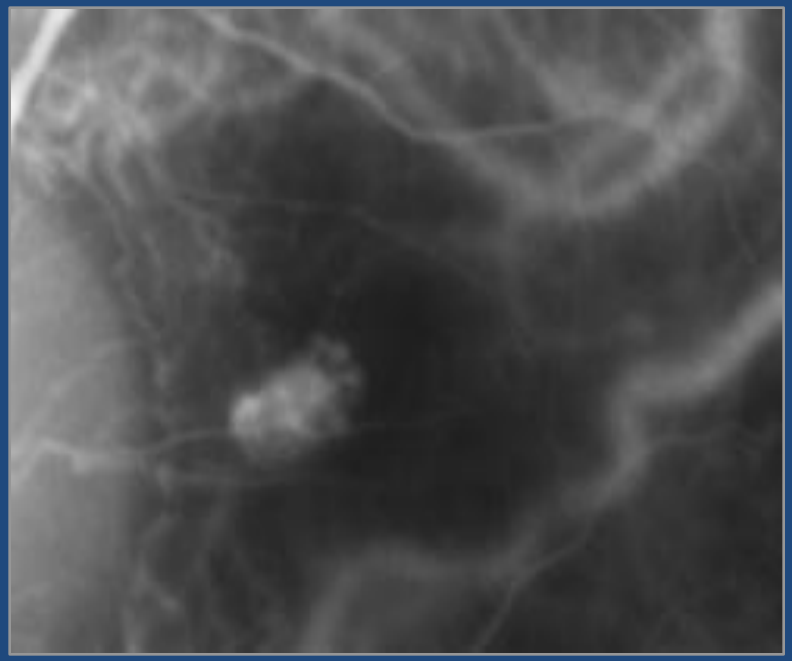
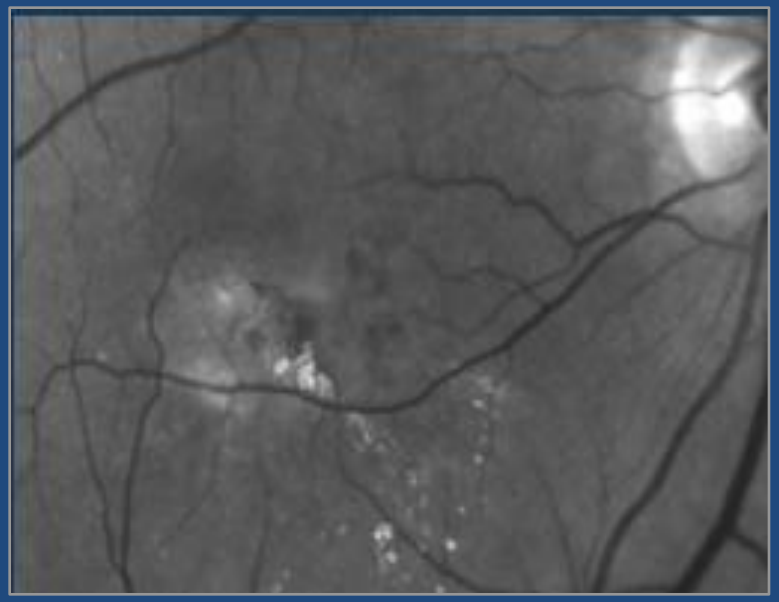
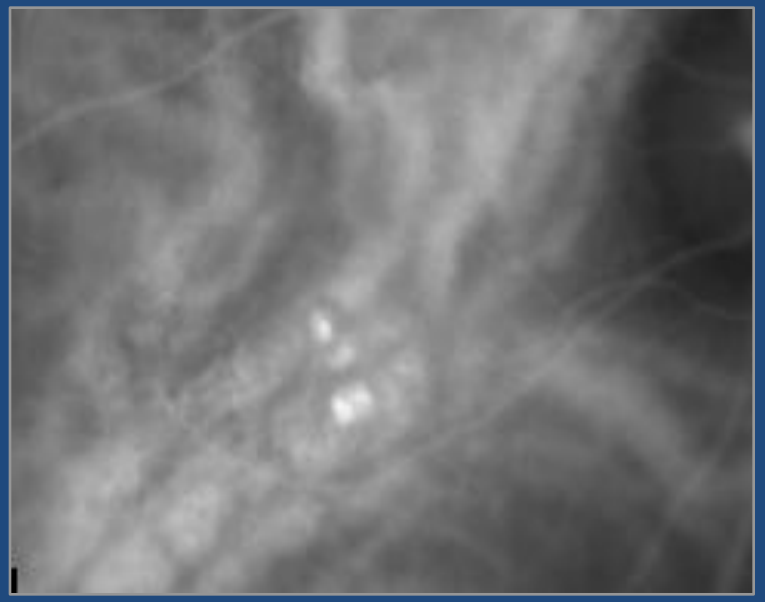
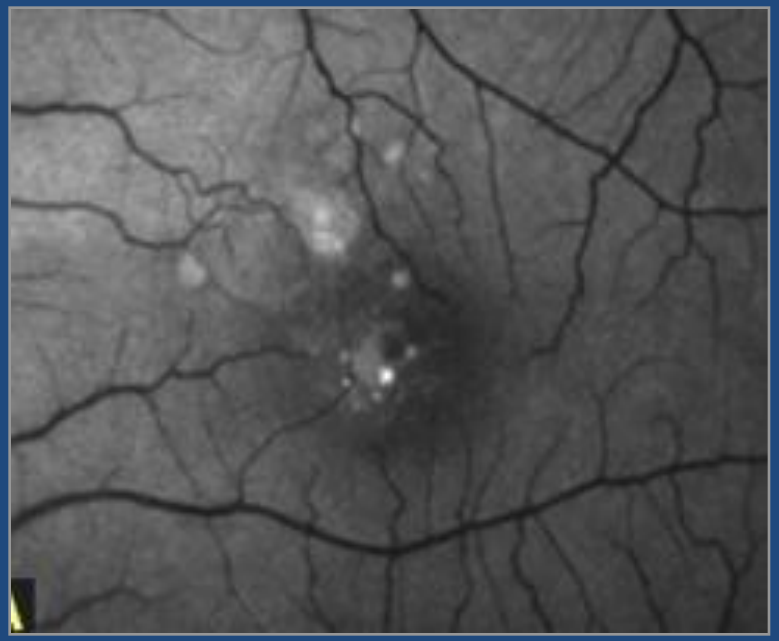
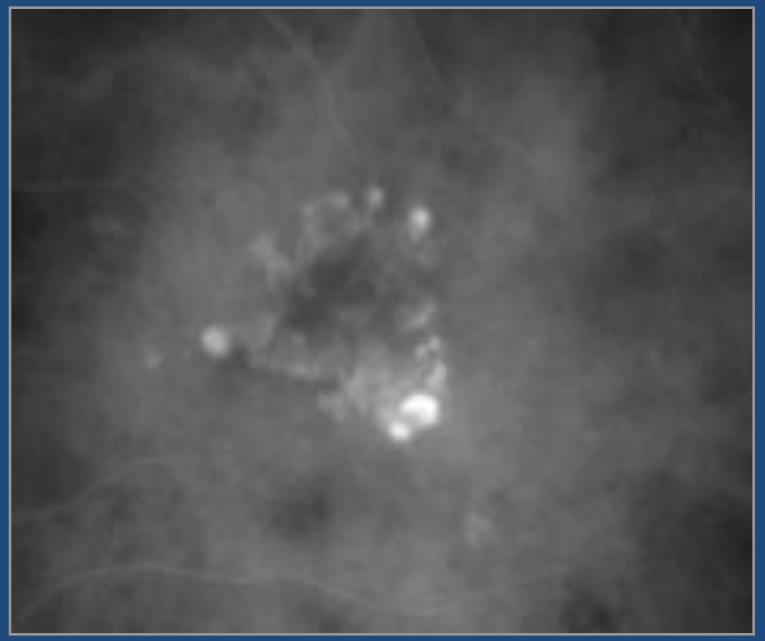


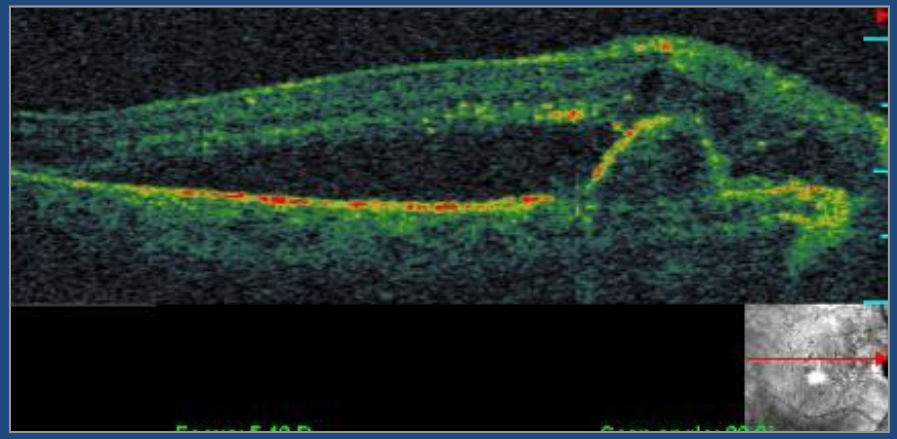



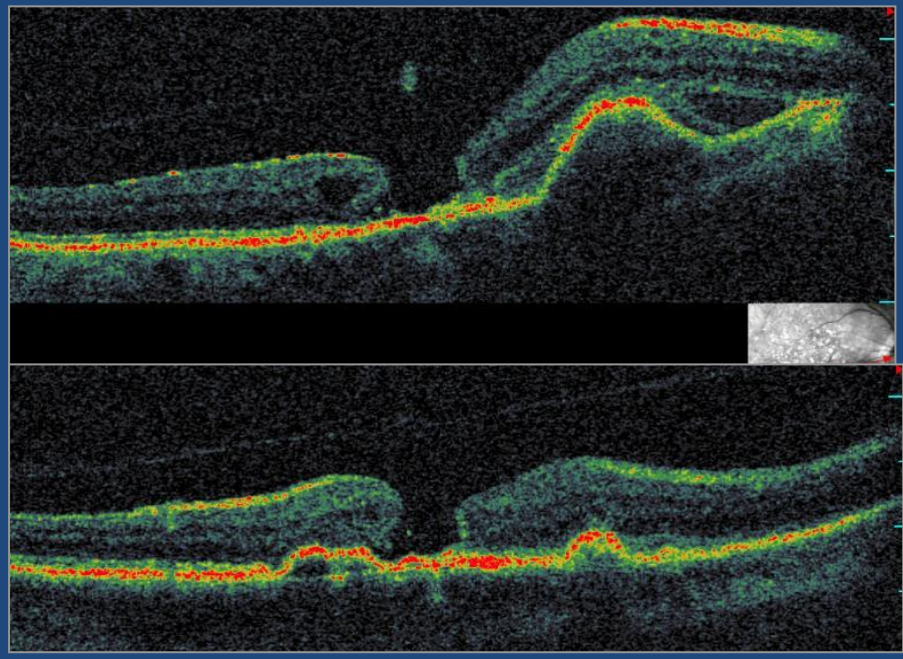





Diagnosis-3

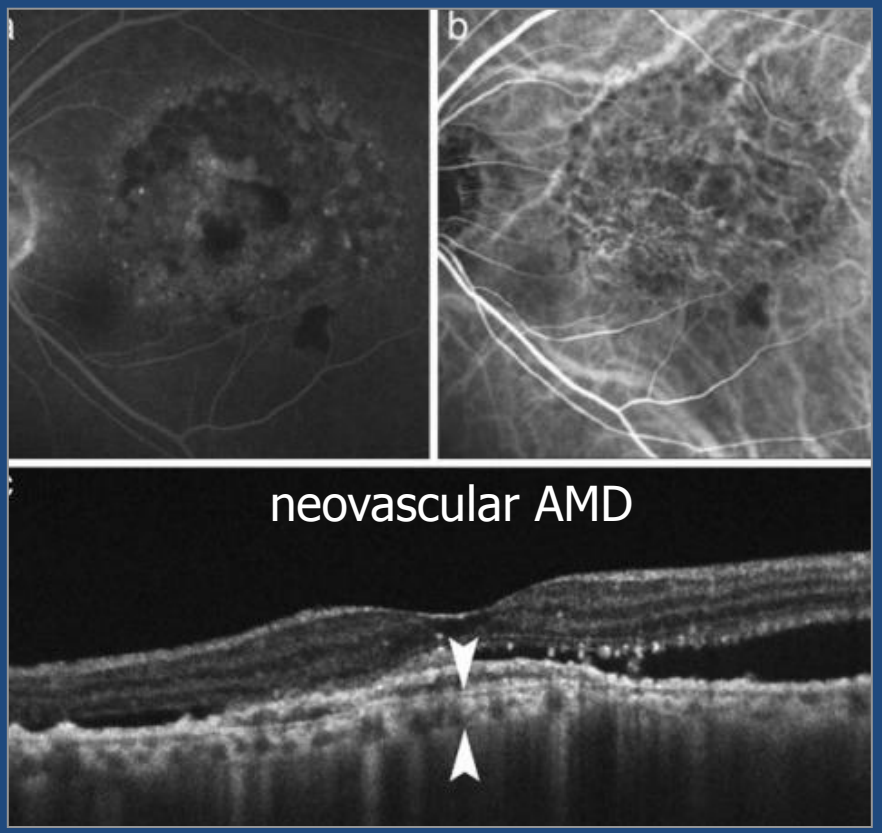
Optical Coherence Tomography

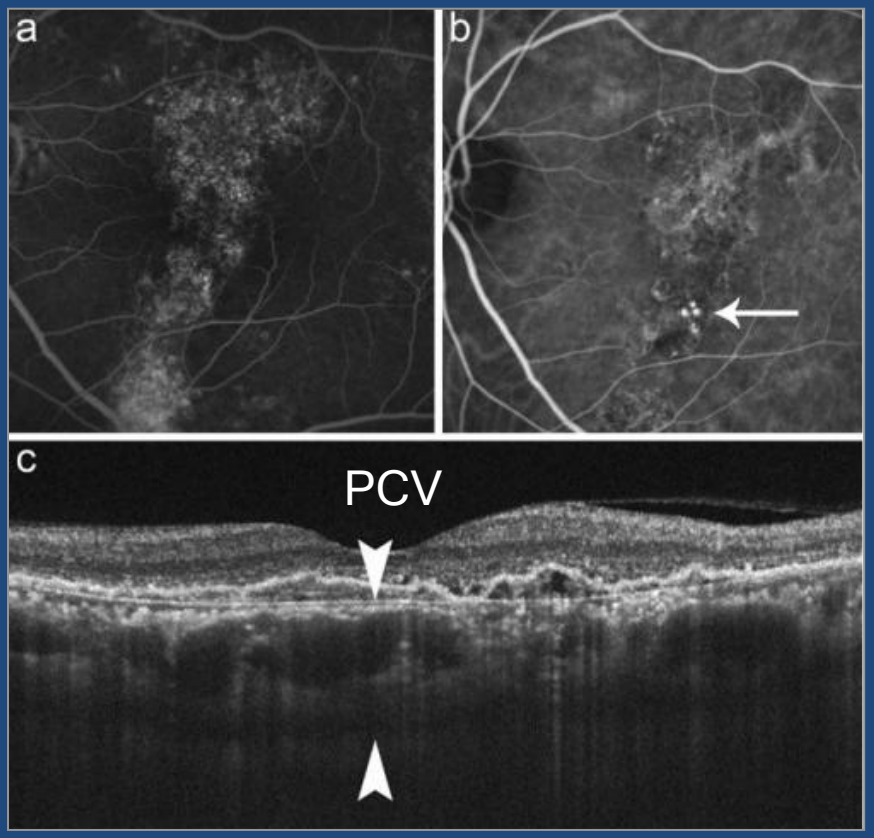
- Inverted V shaped solid RPE elevation
- Moderate reflectivity within the dome
- Irregular ondulation of RPE (branching vascular network)





PCV – Choroidal thickness / EDI OCT





- Subfoveal choroidal thickness is significantly greater in PCV group
- The risk of PCV development is 5.6 times greater in eyes with a choroidal thickness of >300 microns

Koizumi H et al. Graefes Arch Clin Exp Ophthalmol. 2011 Aug;249(8):1123-8

Retinal Angiomatous Proliferation (Type 3 CNV)

Accounts for 12%-15% of newly diagnosed exudative AMD

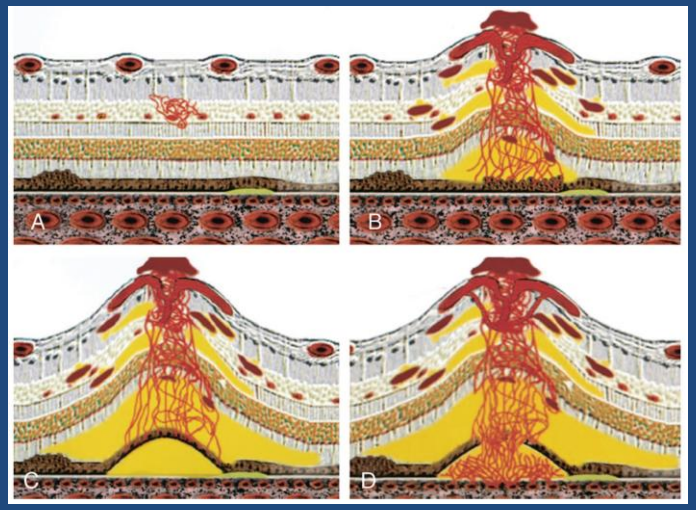
- The clinical hallmark is the presence of an intraretinal vascular lesion

  Retinal angiomatous lesion

  Angiomatous proliferation of capillaries from deep capillary plexus in the paramacular area
  Retinal - choroidal anastomosis

- 2008 Freund, Yannuzzi:

  Type 3 neovascularization (dual origin, retinal and/or choroidal)



Retinal Angiomatous Proliferation

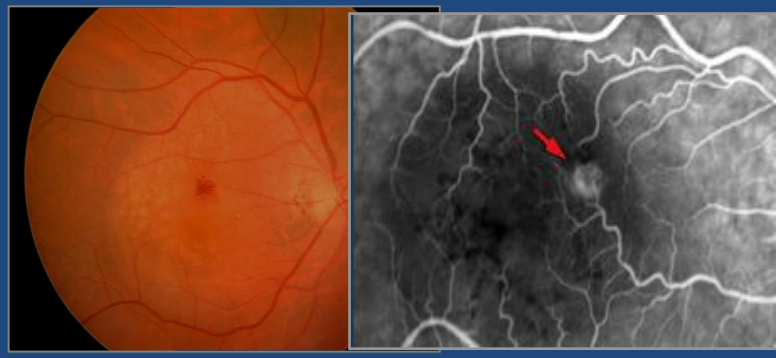
Yannuzzi LA et al. Retina 2001; 21:416-434

Stage 1 : Intraretinal neovascularization

Intraretinal edema

Pre / intraretinal hemorrhage, exudate

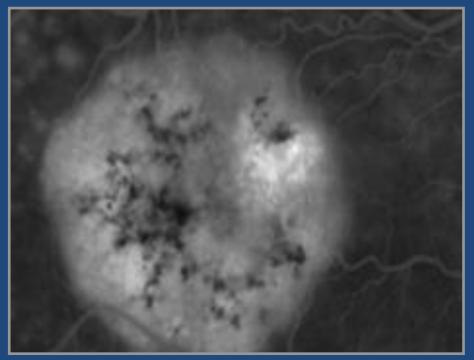
Retinal-retinal anastomosis



Stage 2 : Subretinal neovascularization ± PED

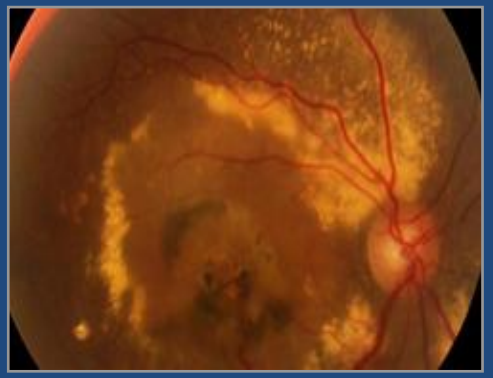
Neurosensory retinal detachment ± serous PED

Intraretinal / subretinal fluid, retinal hemorrhages

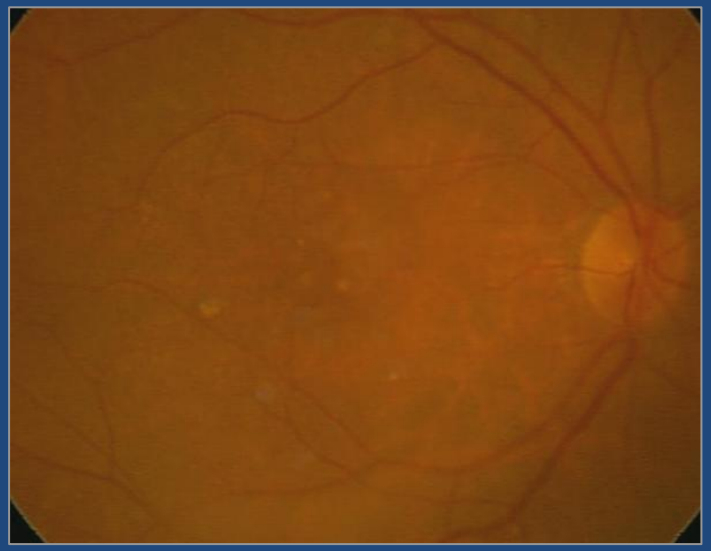


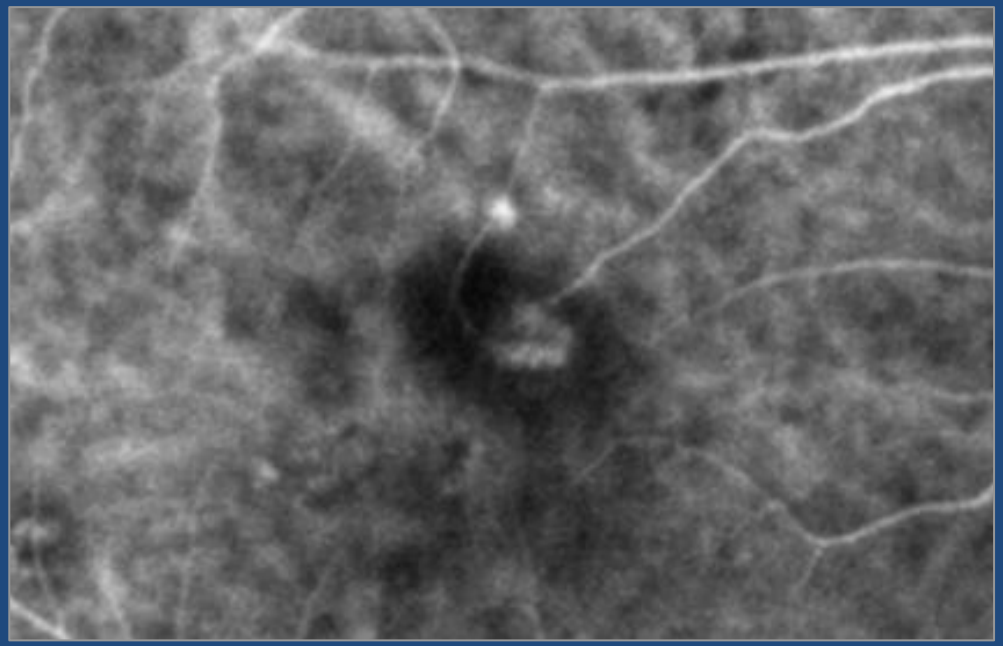
Stage 3 : Choroidal neovascularization with RCA

CNV, retinal-choroidal anastomosis

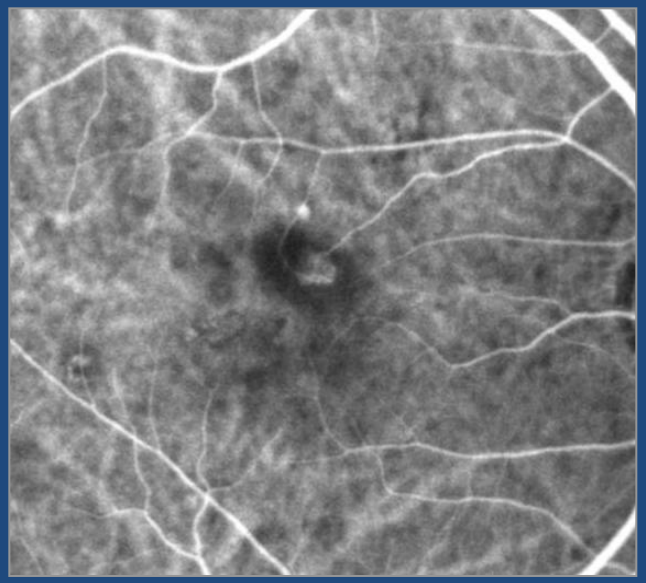


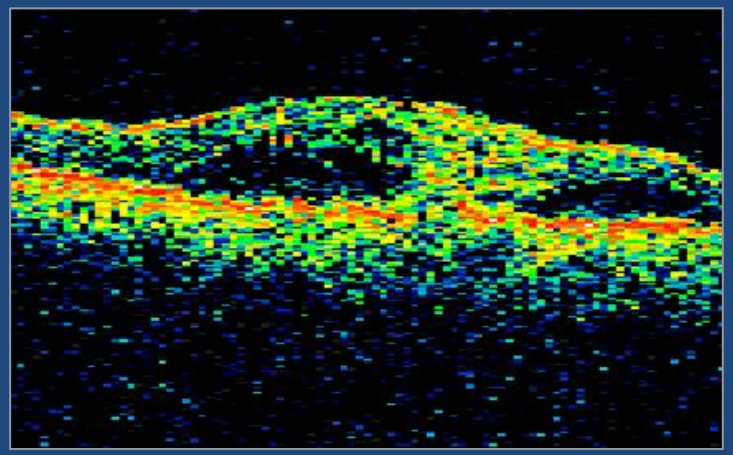
Stage 1: Intraretinal angiomatous proliferation + retinal-retinal anastomosis





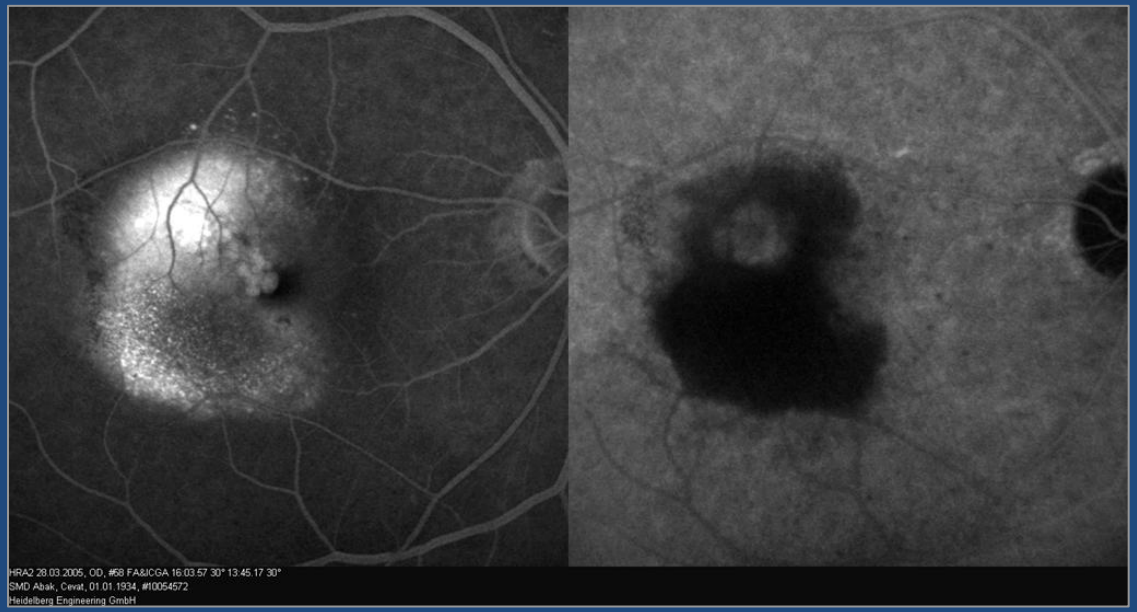
Stage 1 RAP: intraretinal nv + retinal edema



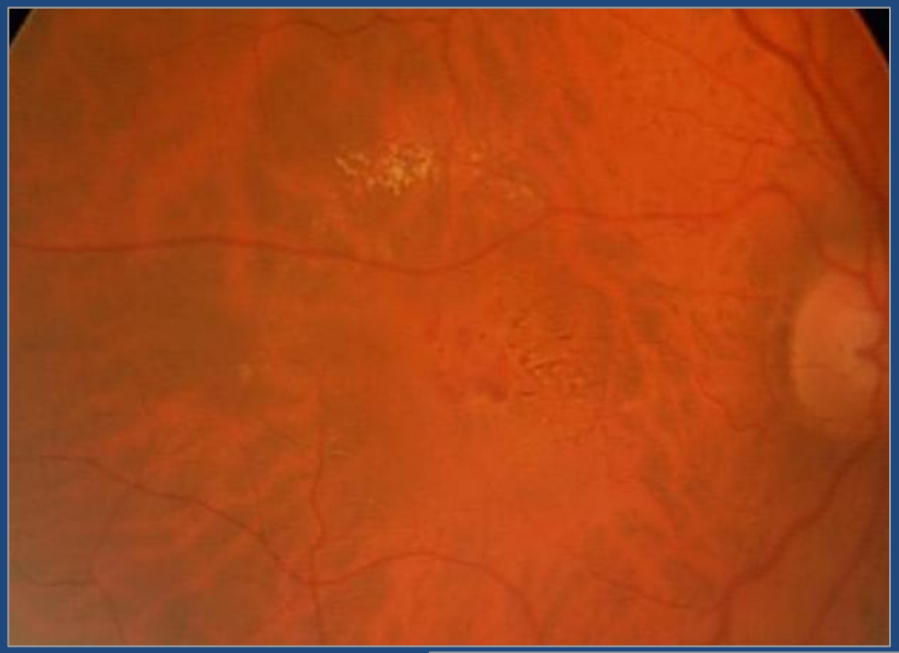


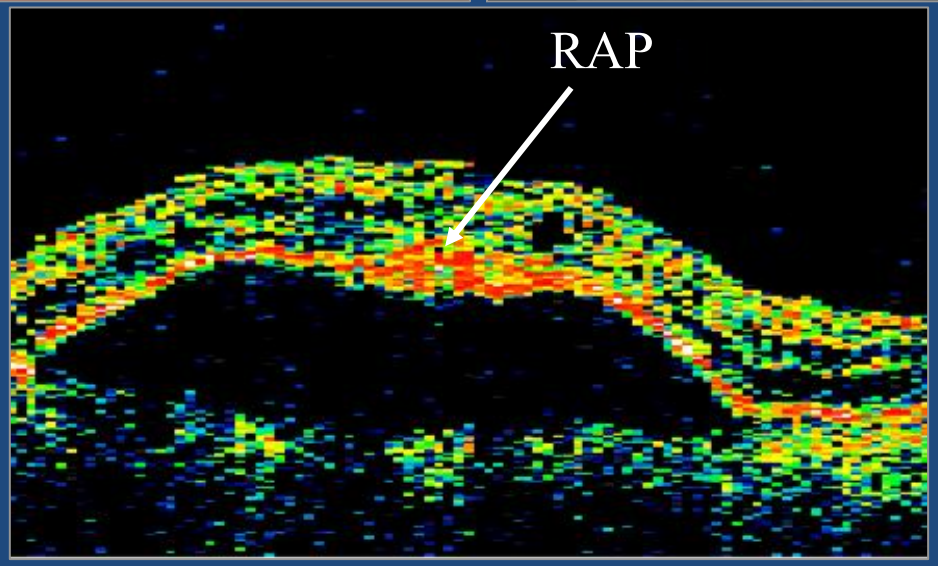
- The earliest sign is focal area of increased intraretinal reflectivity
- Retinal edema around the intraretinal nv

PED + hot spot ------- Stag 2 RAP



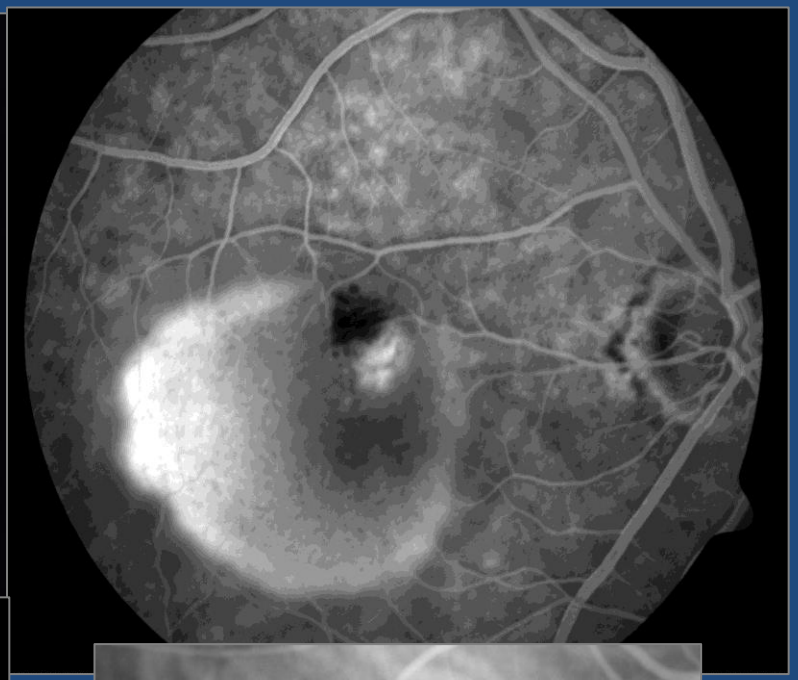
Stage 2 RAP: serous PED + focal intraretinal increased reflectivity

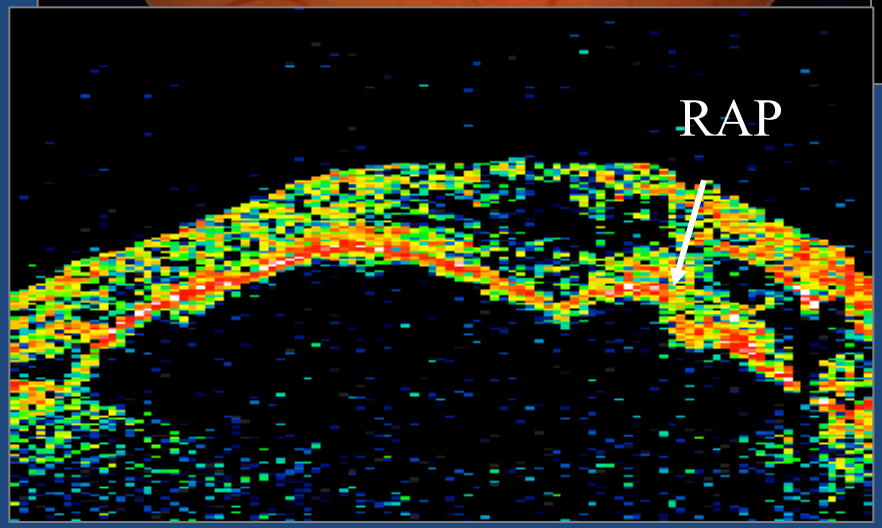


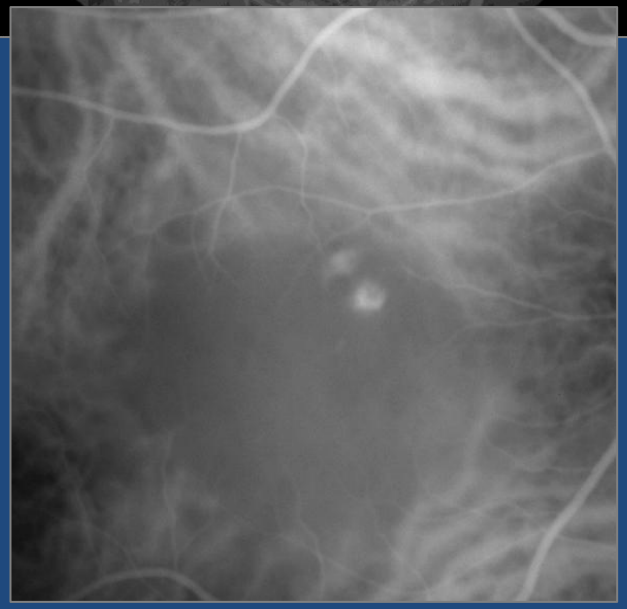


Dome-shaped elevation of RPE

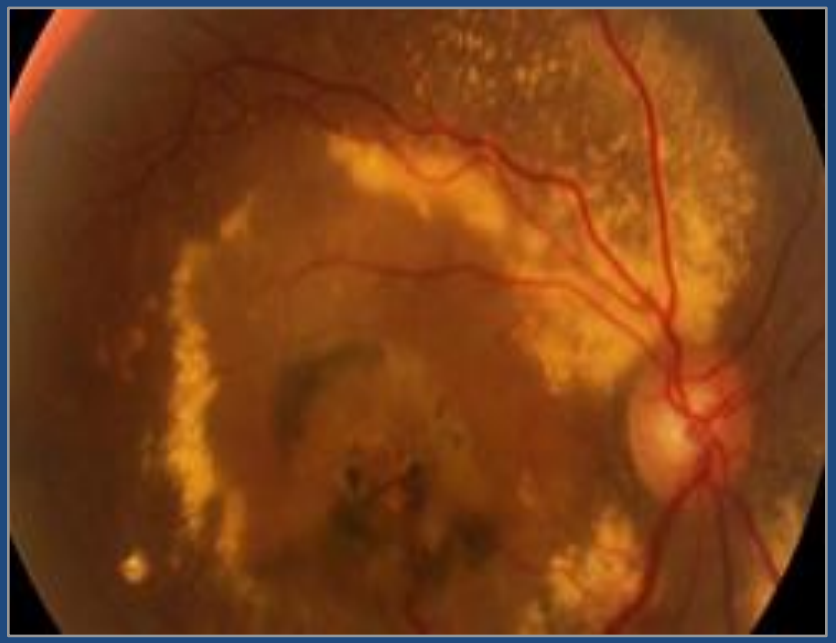
Stage 2 RAP

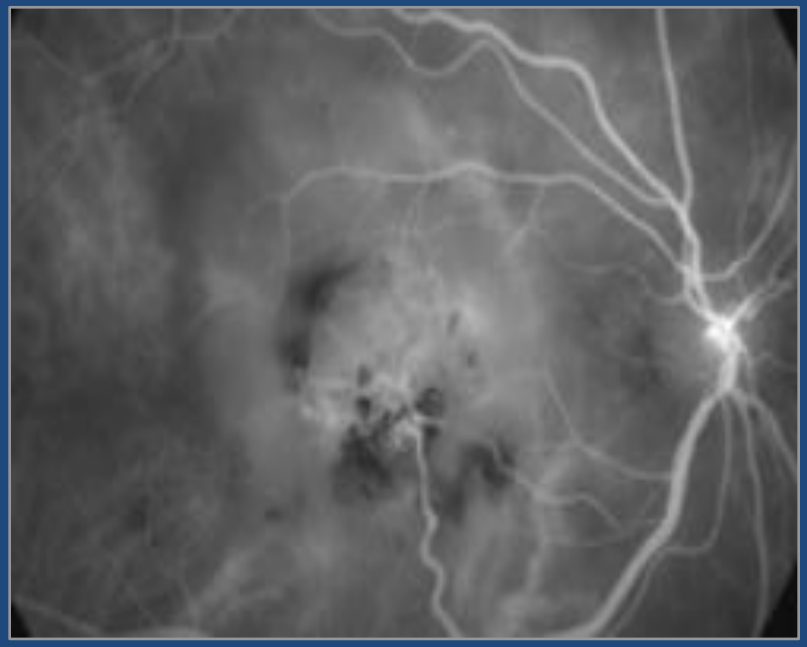


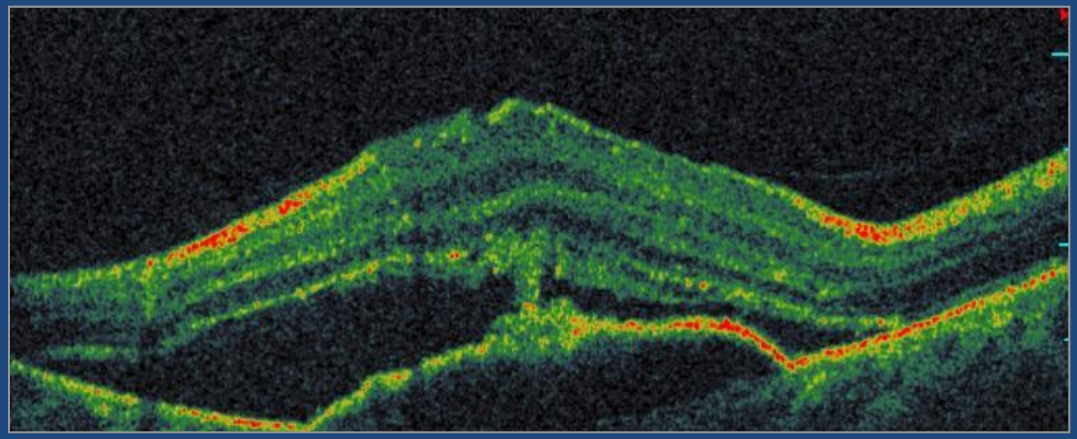




Stage 3 RAP: Choroidal CNV + retino-choroidal anastomosis







Retinal – choroidal anastomosis

It has been shown in SEVEN-UP study that,

50 % of neovascular AMD patients who received intravitreal ranibizumab injections, still required active treatment with another anti-VEGF agent at the 7th year of follow-up

Causes of poor response to anti-VEGF-1

- Inadequate treatment
  - Less than 6 months
  - Sub-optimal dosing
- Misdiagnosis
  - Polypoidal choroidal vasculopathy
  - Retinal angiomatous proliferation
  - Adult vitelliform dystrophy
  - Chronic CSCR
  - Macular telengiectasia-Type 2

Causes of poor response to anti-VEGF-2

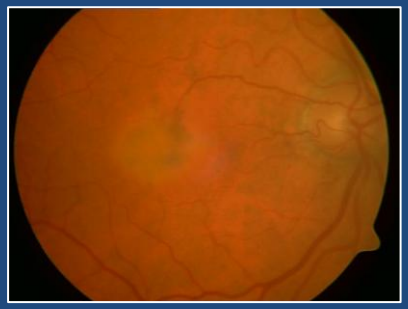
- Resistance to anti-VEGF treatment
  - * Tachyphylaxis, Tolerance
  - * Anti-VEGF antibodies
  - * Lesion alterations
- Genetic factors
- Unfavourable prognostic factors (initial lesion characteristics)
- Poor response to ranibizumab in eyes with fibrovascular PED

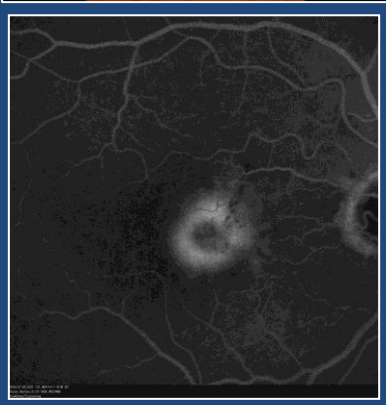
Inoque M et al. Retina 2013;33:990-997

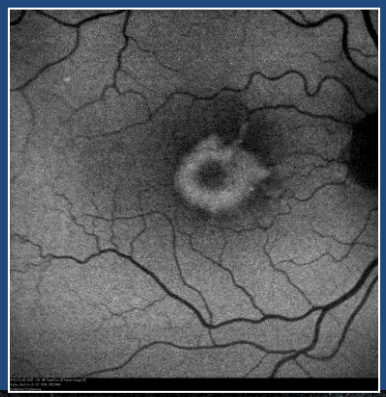
Misdiagnosis:

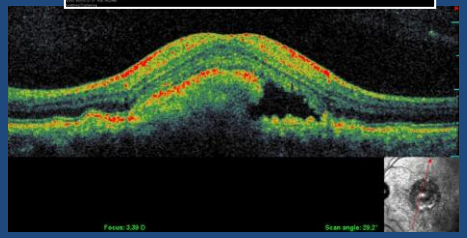
Lesions that resembling CNV on the biomicroscopic examination

Adult-onset vitelliform

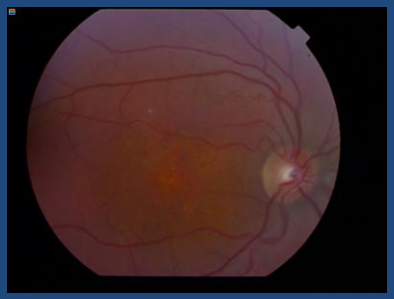


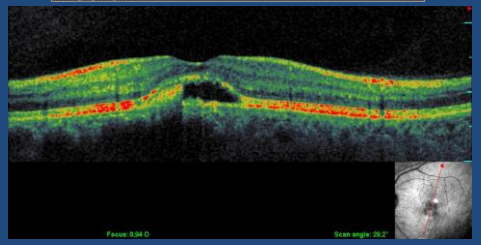




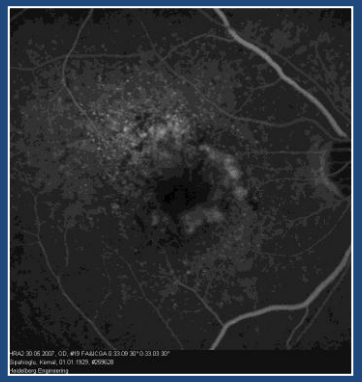


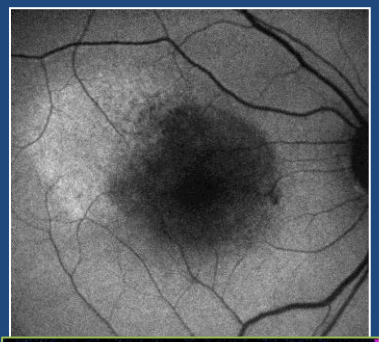
Chronic CSCR

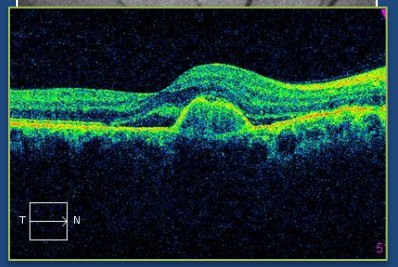




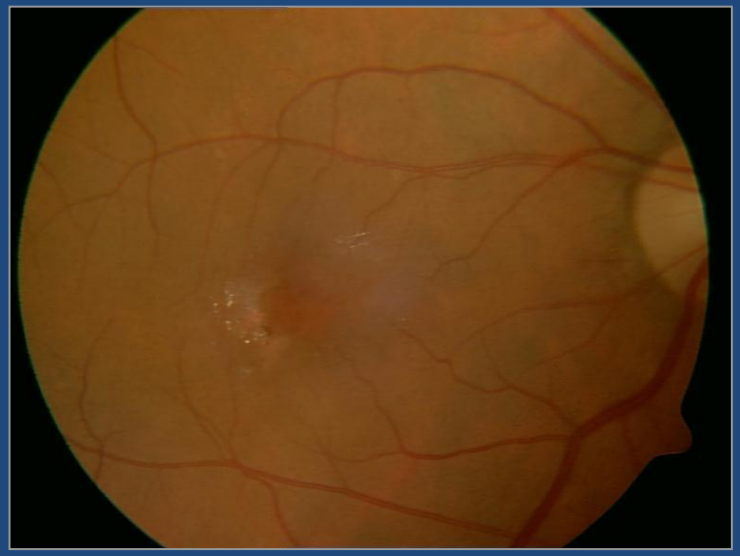
Classic / Wet-AMD

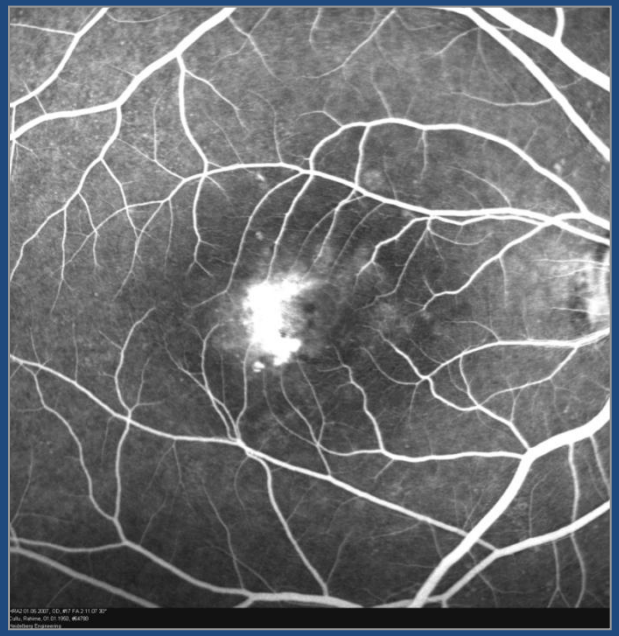


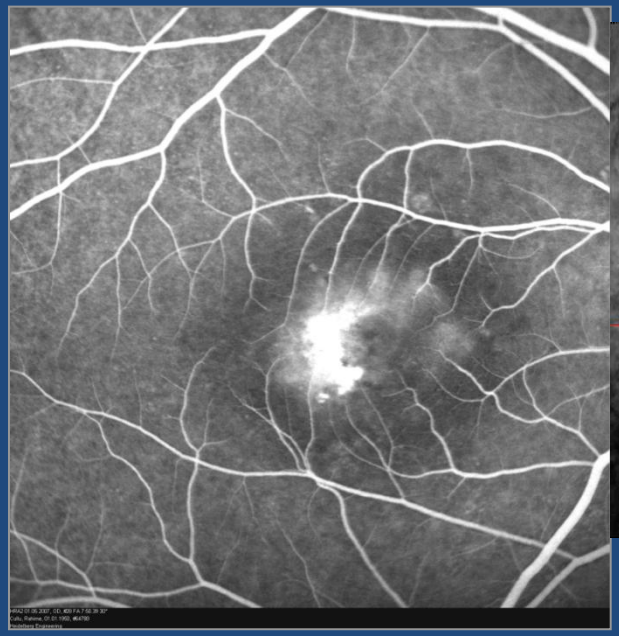


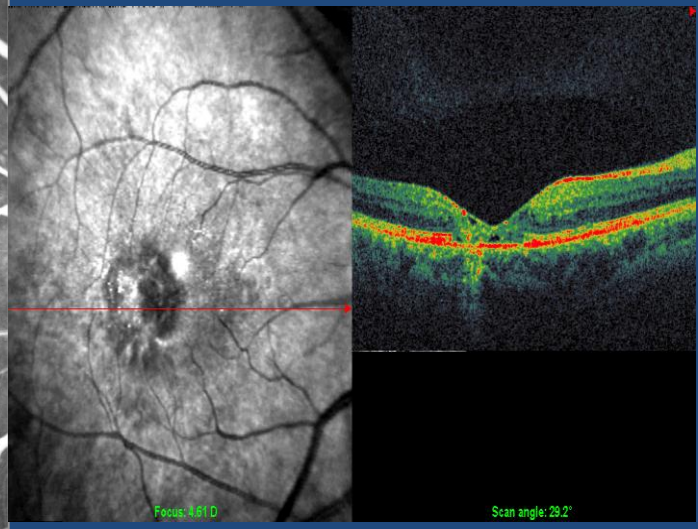


Macular Telengiectasia – Type 2









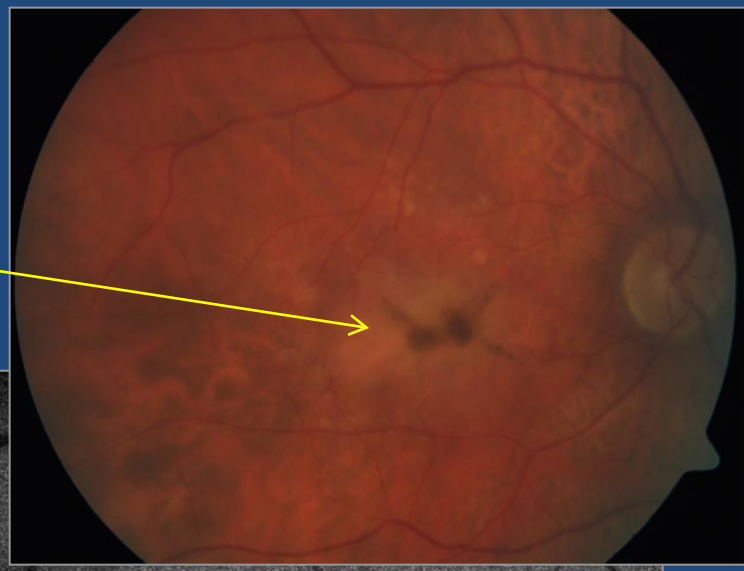
PIGMENTATIONS

Melanin, melanolipofuscin ---- black (colored fundus, FFA)

Melanin ---------- black (FAF)
Melanolipofuscin ---------- white (FAF)

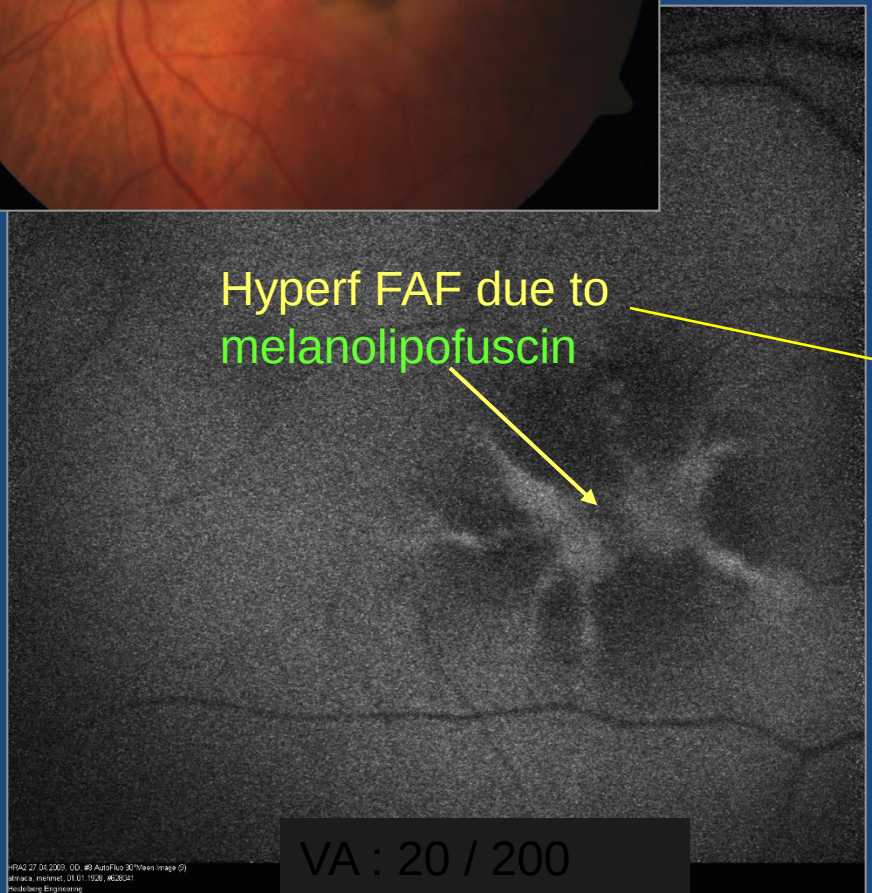
Butterfly-shaped pattern dystrophy

Aged 80, male

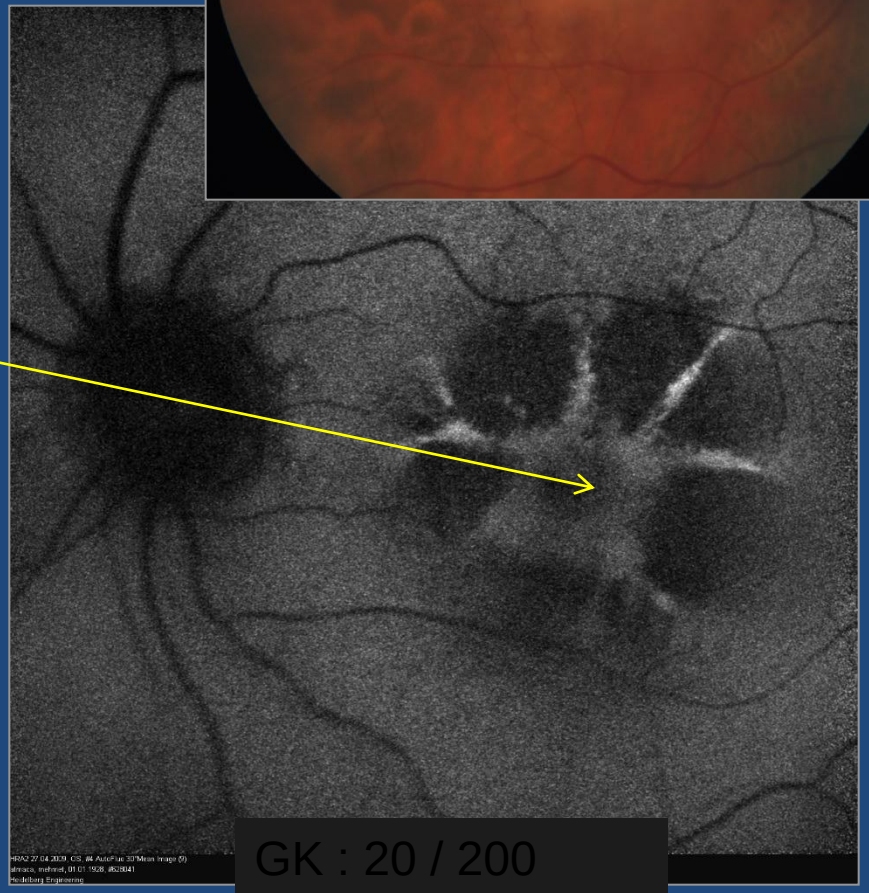


Black deposits

Hyperf FAF due to melanolipofuscin



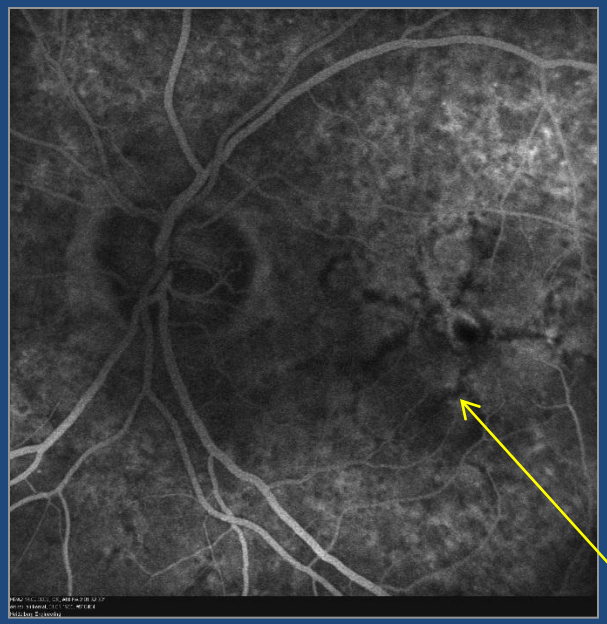
VA : 20 / 200



GK : 20 / 200

Pattern Dystrophy

FFA



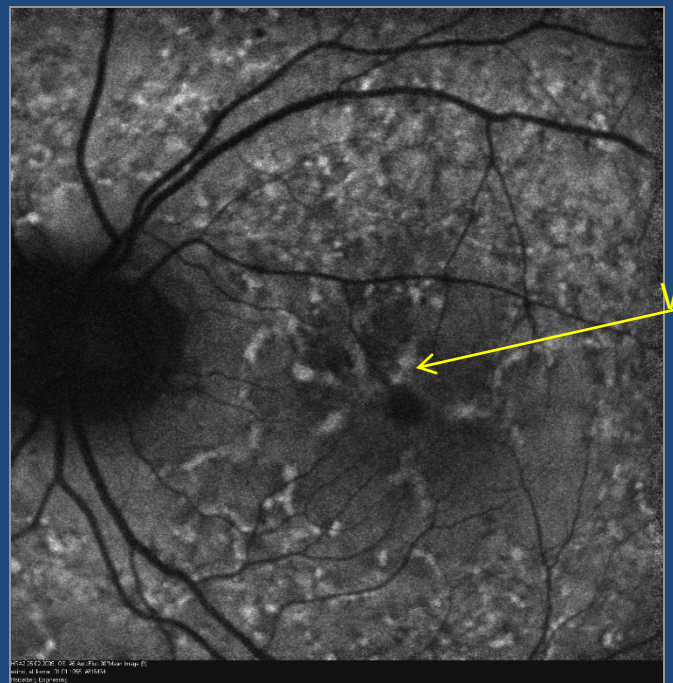
Black on FFA

Grayish subtle discoloration

Melanolipofuscin

White on FAF

SW-FAF

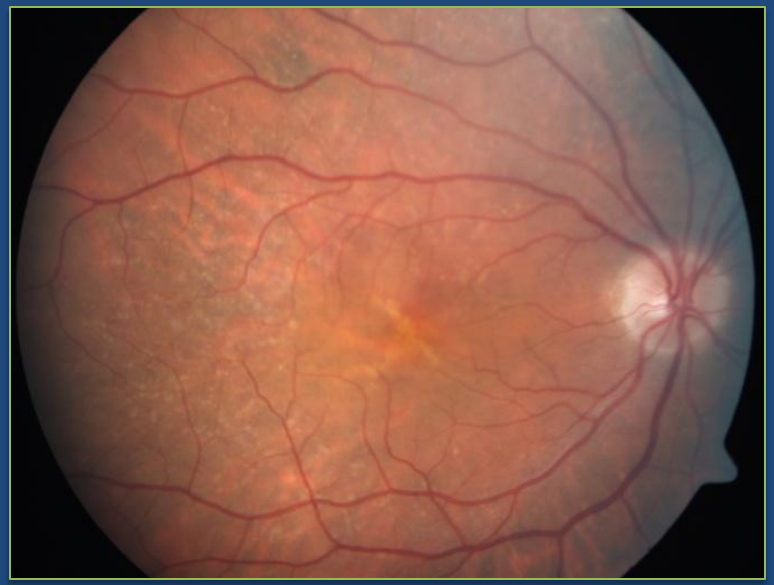


Only FAF discloses alterations and confirms the diagnosis

Multifocal pattern dystrophy:
Accumulation of melanolipofuscin

Aged 57, female

VA: 20 / 20



Faint pigmentation

Diagnosis ?

Widespread pattern shaped accumulations

Melanolipofuscin creates white lines in contrast to melanin

Conclusion

If anti-VEGF therapy fails from the beginning : Misdiagnosis

Use ICGA to identify PCV => combined therapy

RAP => more treatments required, combined therapy

If poor response to anti-VEGF develops after an initial successful treatment period :

- Tachyphylaxis

  Switch the drug from one type of anti-VEGF to another, combined treatment

- Tolerance

  Increase the dose or reduce the treatment intervals

No response to anti-VEGF : Genetic factors

Switch to another anti-VEGF ??

Intravitreal Aflibercept (VEGF Trap-Eye) injections in neovascular AMD refractory to Lucentis theraphy: Early results

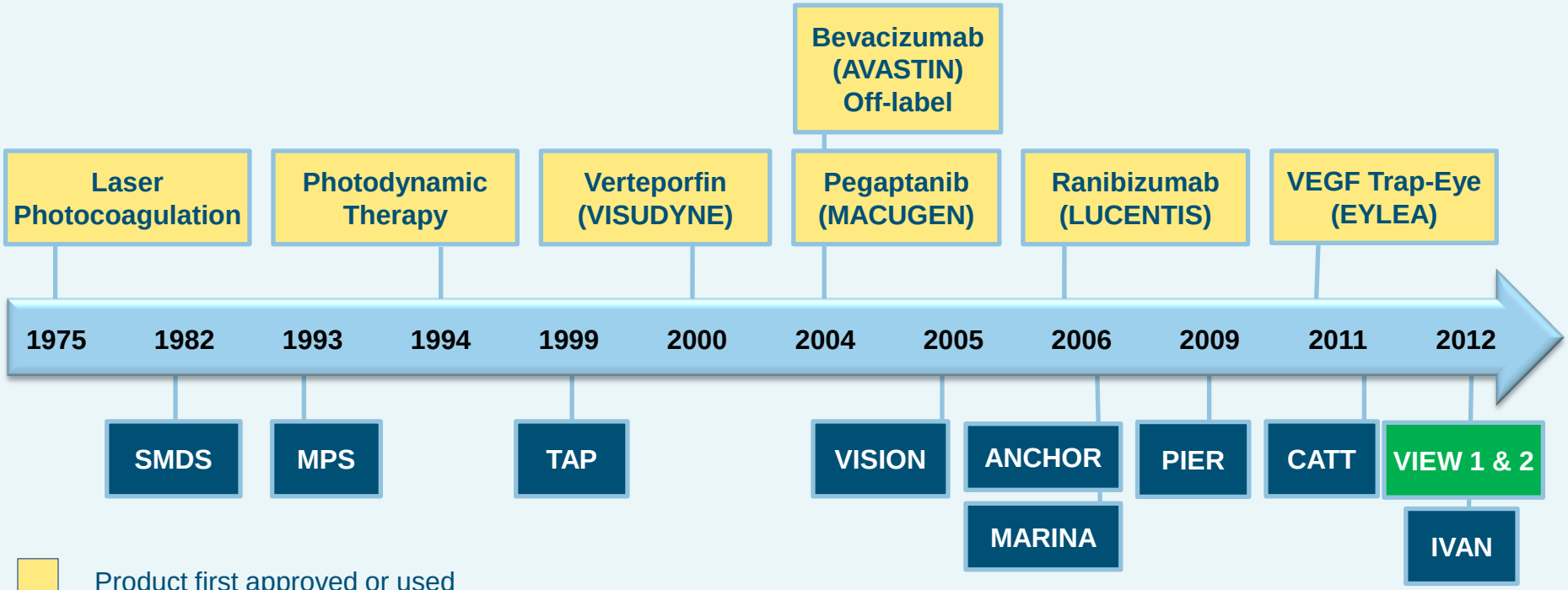
Prof.Dr.Emin Özmert
Prof.Dr.Figen Şermet
Dr.Sibel Demirel
Ankara University Faculty of Medicine Ophthalmology Department

There are strong evidences in the literature disclosing that:

Clinical outcomes improves after switching the treatment from intravitreal ranibizumab to aflibercept in refractory neovascular age-related macular degeneration.

- Yonekawa Y et al. Conversion to aflibercept for chronic refractory or recurrent neovascular age-related macular degeneration. Am J Ophthalmol. 2013;156(1):29-35.
- Hoerster R, Muether PS, Sitnilska V et al. Fibrovascular pigment epithelial detachment is a risk factor for long-term visual decay in neovascular age-related macular degeneretion. Retina. 2014 Jun 14.
- Heussen FM, Shao Q, Ouyang Y et al. Clinical outcomes after switching treatment from intravitreal ranibizumab to aflibercept in neovascular age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol DOI 10.1007/s00417-013-2553-7.

wAMD: Milestones in Treatment



ANCHOR = Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration; CATT = Comparisons of Age-Related Macular Degeneration Treatments Trials; IVAN = A Randomised Controlled Trial of Alternative Treatments to Inhibit VEGF in Age-Related Choroidal Neovascularisation; MARINA = Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration; MPS = Macular Photocoagulation Study Group; PIER = Phase IIIb, Multi-center, Randomized, Double-Masked, Sham Injection-Controlled Study of Efficacy and Safety of Ranibizumab in Subjects With Subfoveal CNV With or Without Classic CNV Secondary to AMD; SMDS = Senile Macular Degeneration Study; TAP = Treatment of AMD With Photodynamic Therapy; VIEW 1 & 2 = Vascular Endothelial Growth Factor Trap-Eye for Neovascular Age-Related Macular Degeneration; VISION = VEGF Inhibition Study in Ocular Neovascularization.

VEGF Trap-Eye (Aflibercept=Eylea)

- VEGF has been implicated in pathological angiogenesis and vascular permeability

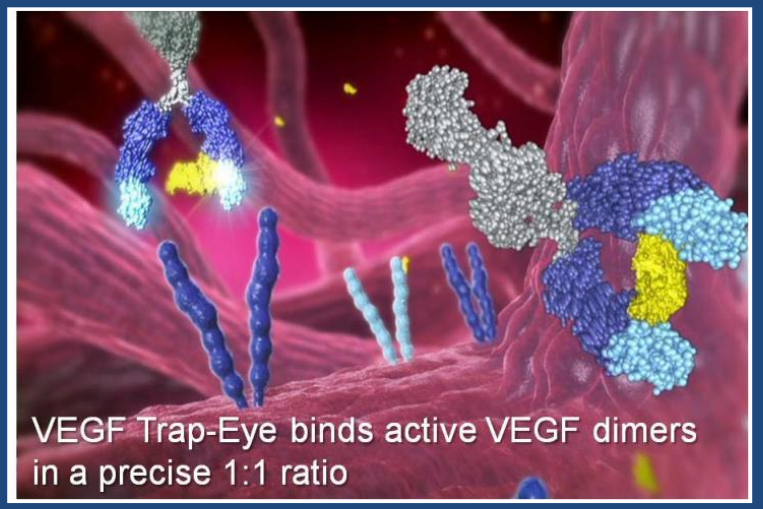
- Under pathological conditions, increased PlGF, as well as VEGF-A, recruits bone-marrow-derived monocytes/macrophages via VEGF-R1 to inflammatory lesions, and significantly enhances pathological angiogenesis

VEGF Trap-eye (Eylea)

- Binds active VEGF dimers in a precise 1:1 ratio
- Binds both all VEGF-A isoforms and PlGF with higher affinity than native receptors
- Estimated biological activity:

  0.5 mgr Ranibizumab: 30 days

  2 mgr VEGF Trap-Eye: 83 days



Materials & Methods -1

- Retrospective study
- Number of patients : 28 patients (29 eyes)
- Gender: 17 male, 11 female
- Mean age: 73.89±7,49 (62-92 years)
- Mean follow-up: 4,55 ± 2,14 (3-11 mos)
- During the monthly follow-up examinations:
  - Complete ophthalmic exam.
  - Best corrected visual acuity (BCVA) – ETDRS chart
  - SD- OCT (Spectralis, Heidelberg Engineering, Heidelberg, Germany): intraretinal / subretinal fluid - PED
  - Central macular thickness (CMT)

Inclusion critaria

- Consecutive 6 injections of ranibizumab before aflibercept injection
- Persistence of intraretinal and / or subretinal fluid despite ranibizumab injections

  - Fibrovascular PED (24/29)
  - Polypoidal choroidal vasculopathy (3/29)
  - RAP (2/29)

Exclusion criteria

- Intraocular surgery
- Subfoveal laser photocoagulation
- Glaucoma
- Uveit

Materials & Methods-2

- 2mg / 0,05 mL aflibercept
- Initial 3 monthly injections (loading dose)
- Followed by one injection
- every two months

- Retreatment decision (as needed= PRN):
  - Loss of min 5 letters associated with fluid on OCT
  - Persistent or recurrent subretinal / intraretinal fluid on OCT
  - New macular hemorrhage due to CNV

Results-1

Mean number of injections before Aflibercept : 11.75 ± 5.73 (6-25)

Mean number of Aflibercept injections: 3,44 ± 0,73 (3- 5)

Central Macular Thickness μm)		**Visual Acuity (LogMAR)**	
Before Aflibercept	After Aflibercept	Before Aflibercept	After Aflibercept
471,3 (97-1365)	345,1 (97-585) **(P<0,001)**	1,08 (47,4 letter)	0,80 (50 letter) **(P>0,05)**

Results-2

	Before aflibercept	After aflibercept
Dry macula	0 %	58.6 %
PED existence	82.76 %	75.86 %

After aflibercept treatment:

Retinal fluid: Partially diminished 34.4%, unchanged 7%

PED: partially diminished 66.6%, unchanged 16.6%, increase in height 8.3%

Results-3

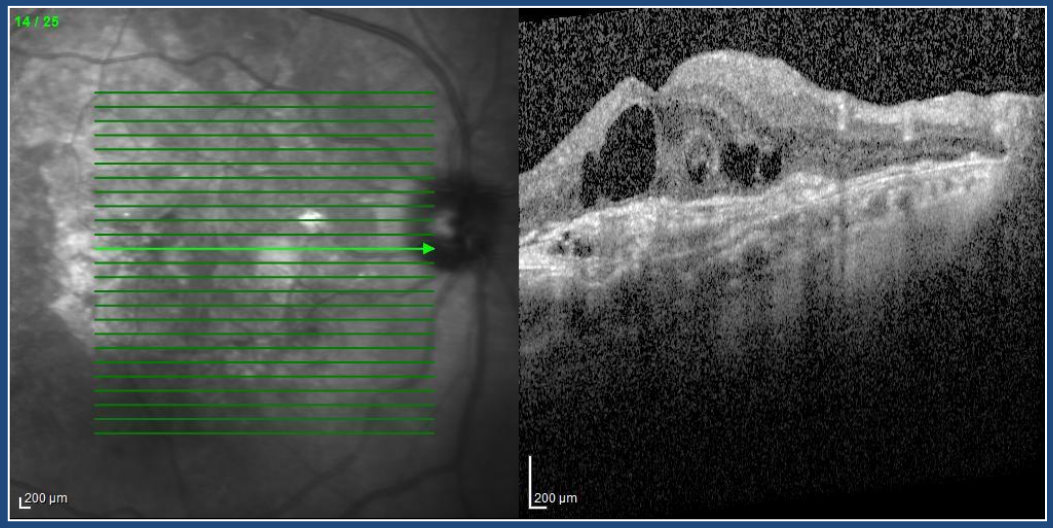
- There was no significant change in visual acuity (P>0,05)
  Most likely due to tissue damage before aflibercept

- CMT was decreased significantly after aflibercept treatment (P<0,001)
  471,3 µm → 345,1 µm

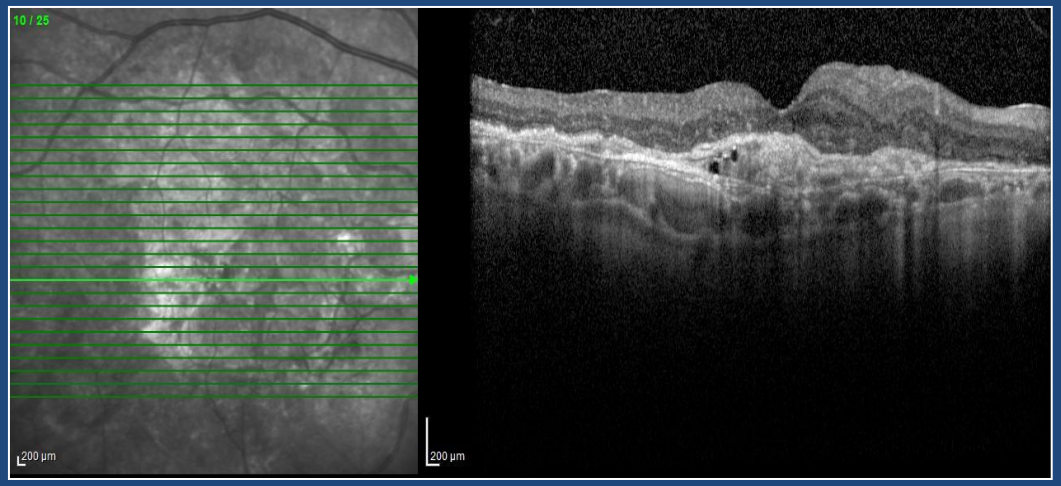
- The height of PED was diminished significantly (p<0.05)
  350,4 µm → 255,5 µm (%27,05)

81 Y, E

14 x ranibizumab injection



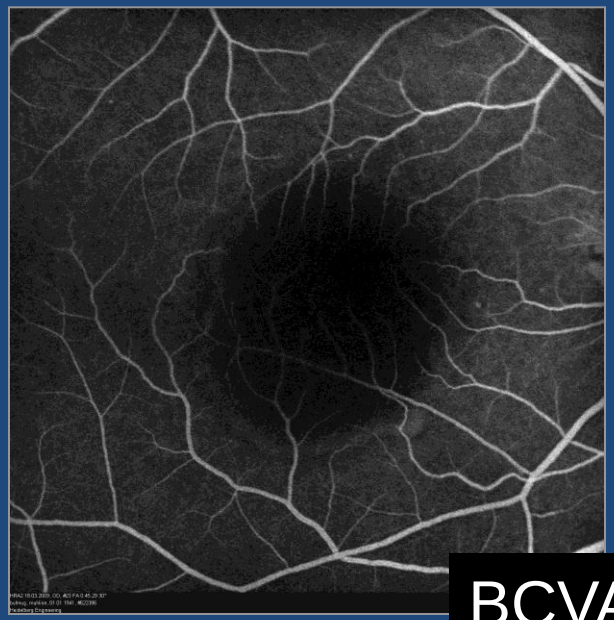
Before Aflibercept BCVA 1.00 LogMAR (35 letters)
CMT 547 micron

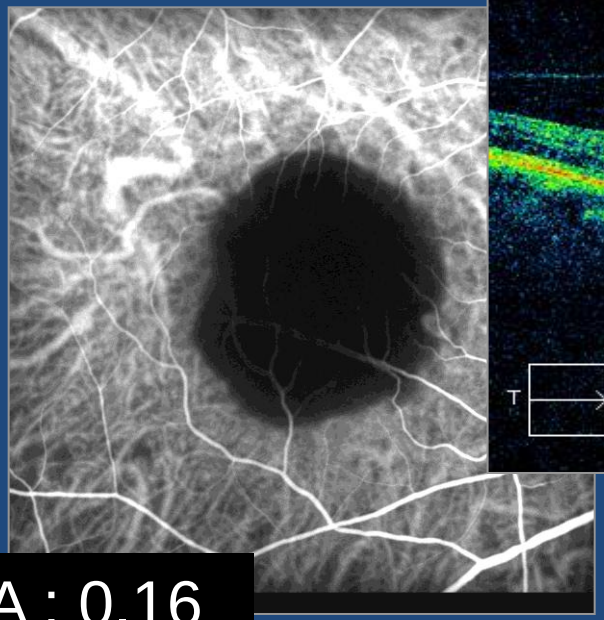


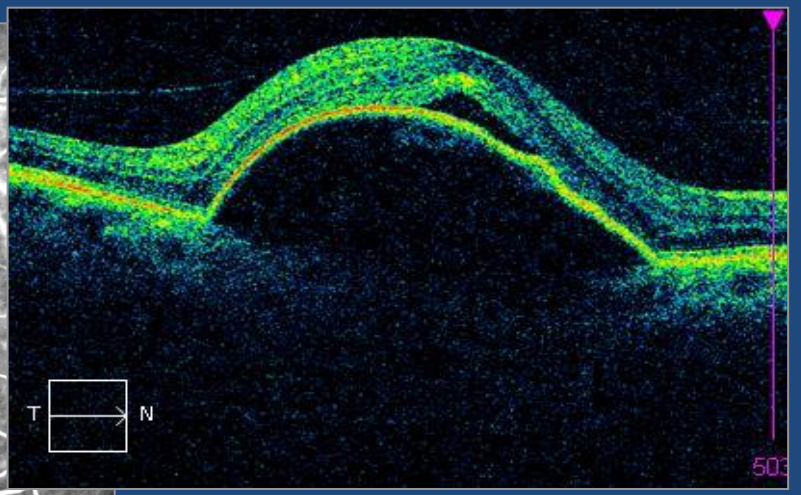
3 x Aflibercept
BCVA 0,9 LogMAR (39 letters)
CMT 388 micron

69 yo, female

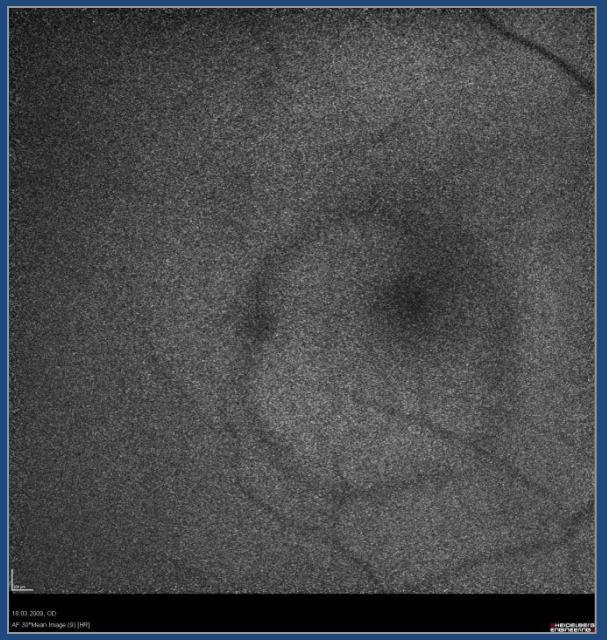
RAP Stage 2



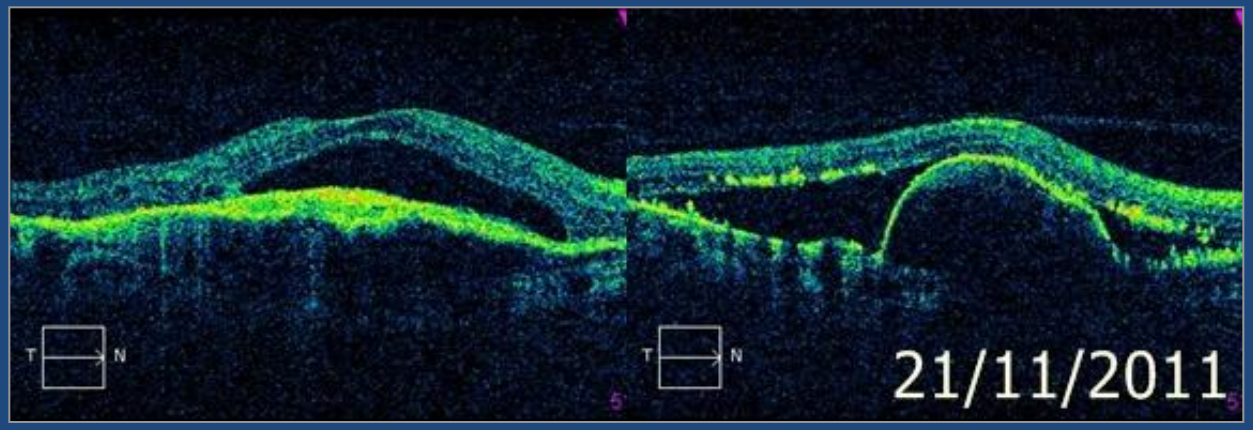


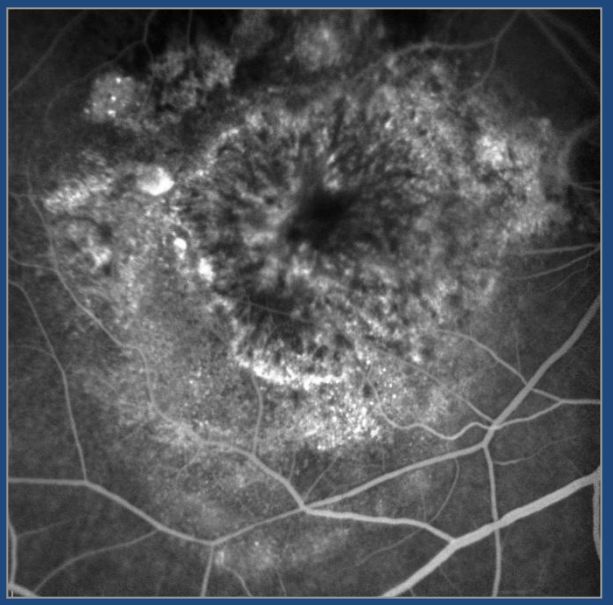


BCVA : 0.16

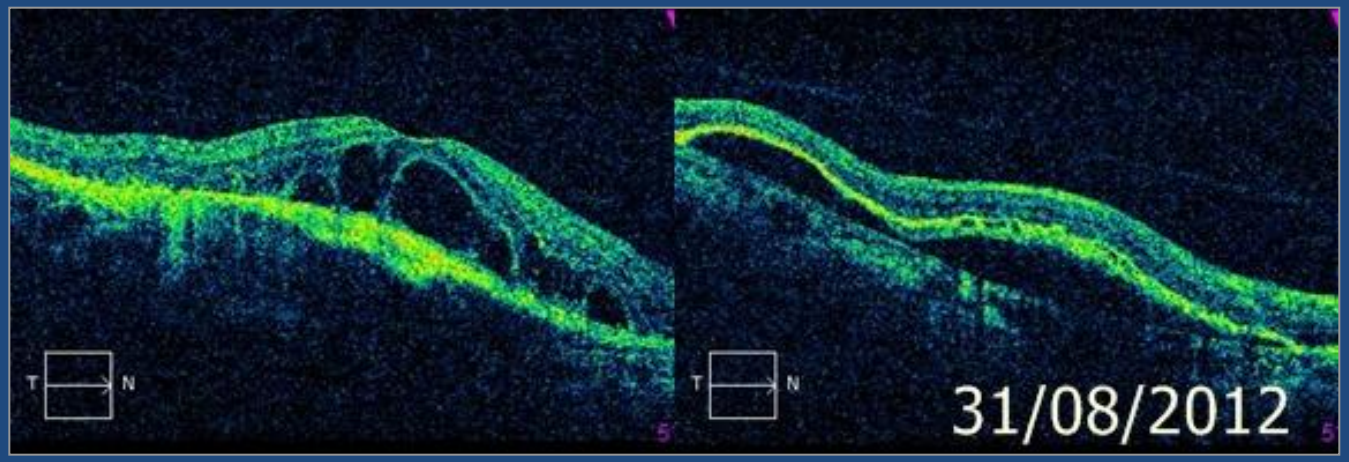


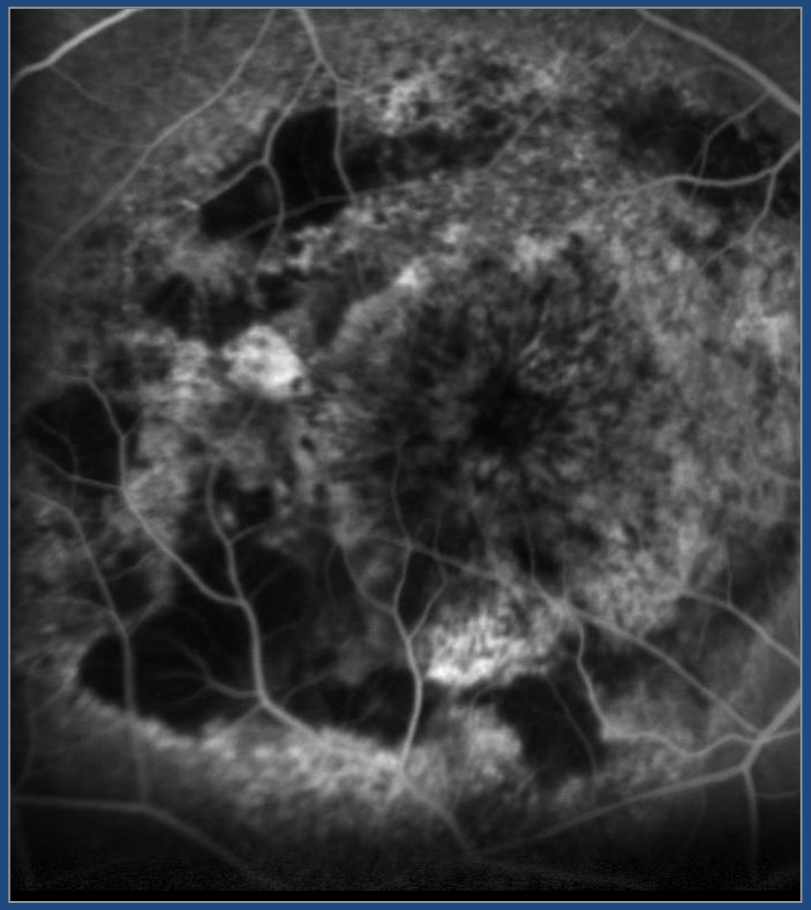
14 x ranibizumab, BCVA: 0.2

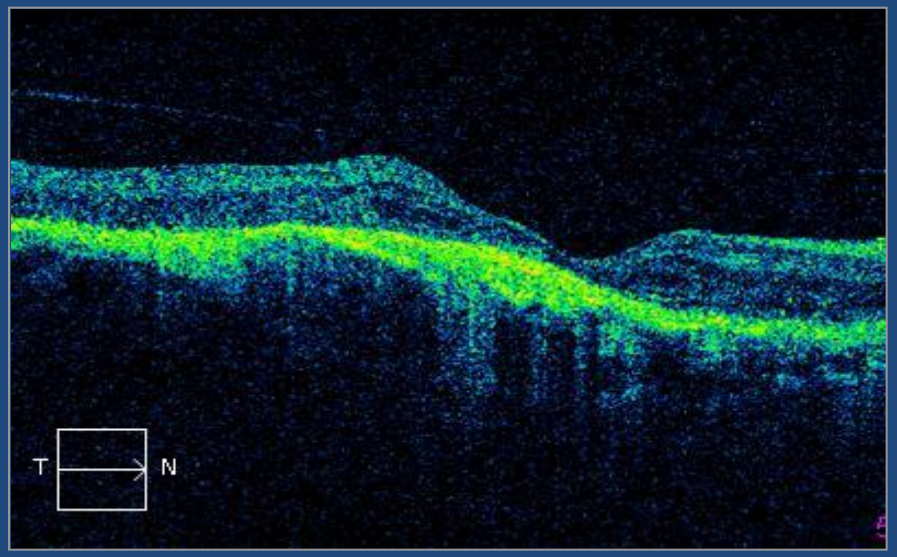




19 x ranibizumab, 2 x bevacizumab, BCVA:0.05

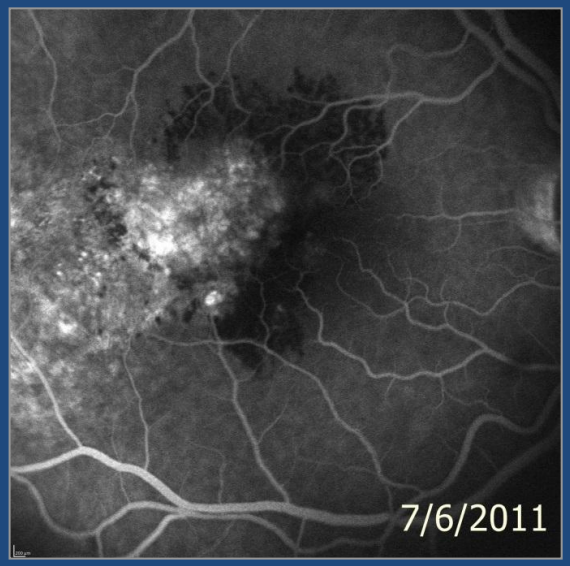


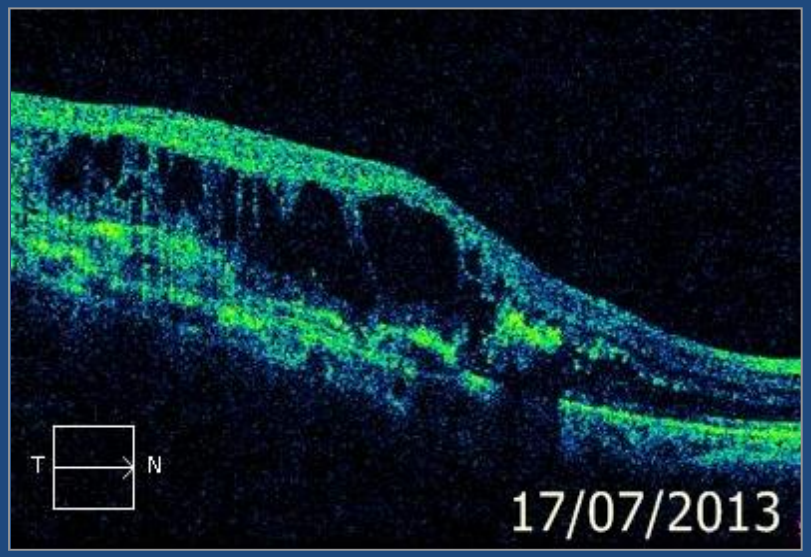




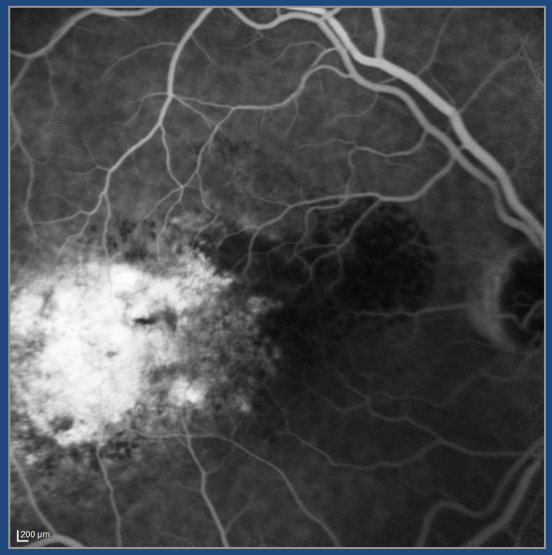
3 x aflibercept, BCVA: cf1m

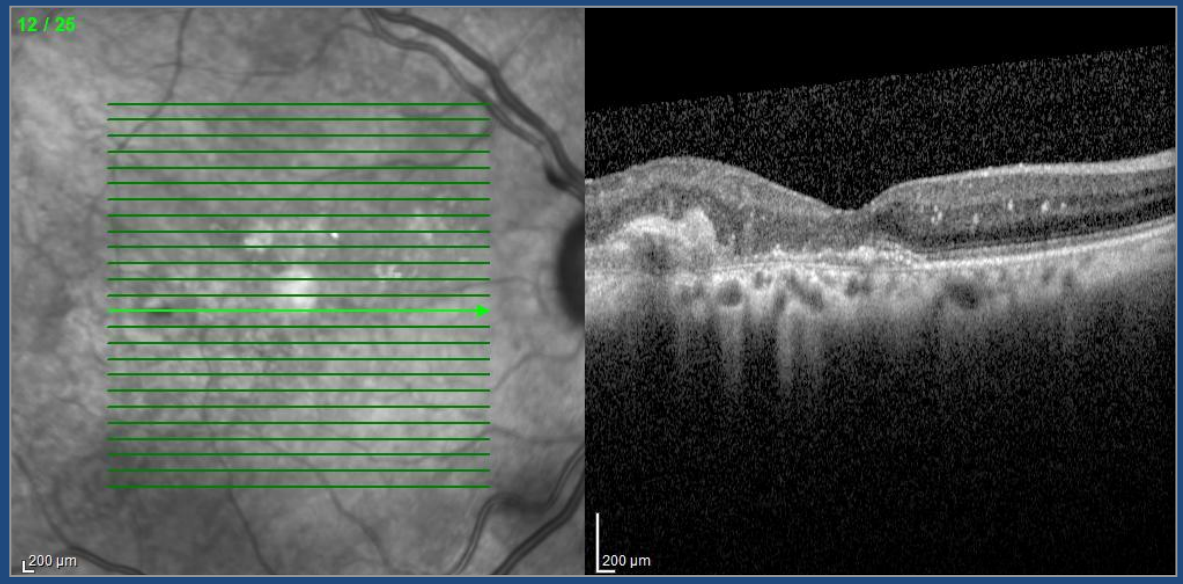
66 yo, female





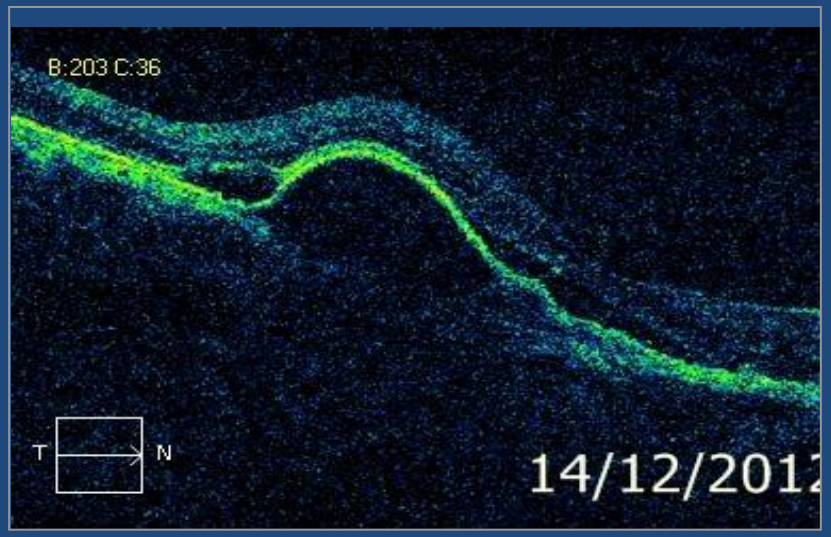
1xPDT, 3xPegaptanib, 11x ranibizumab; BCVA: 0,2



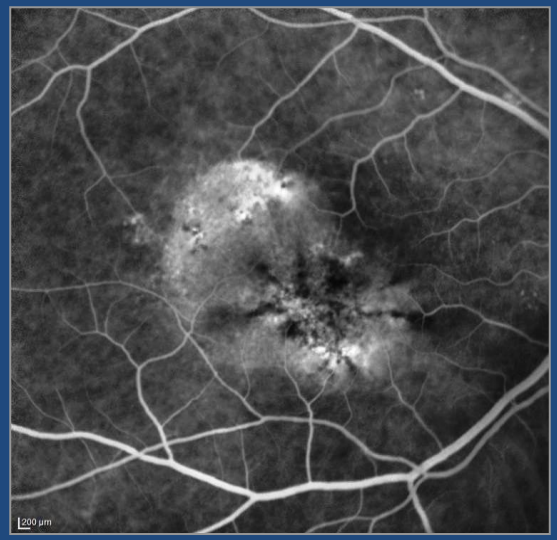


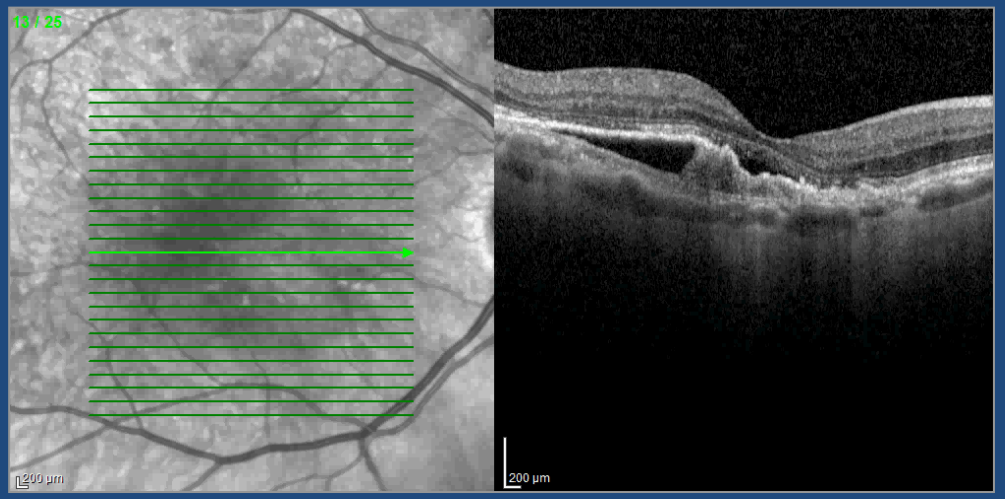
3 x aflibercept, BCVA: 0.4

71 yo, male



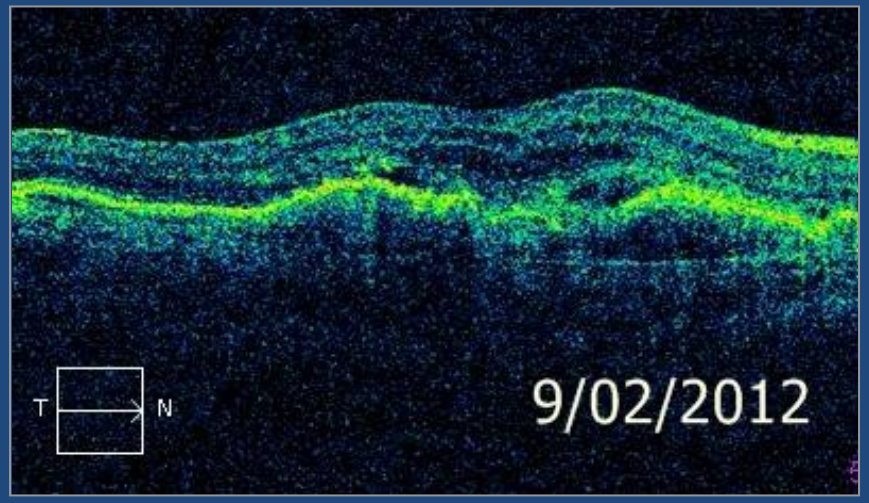
After 11 months, 8 x ranibizumab, BCVA:0.3



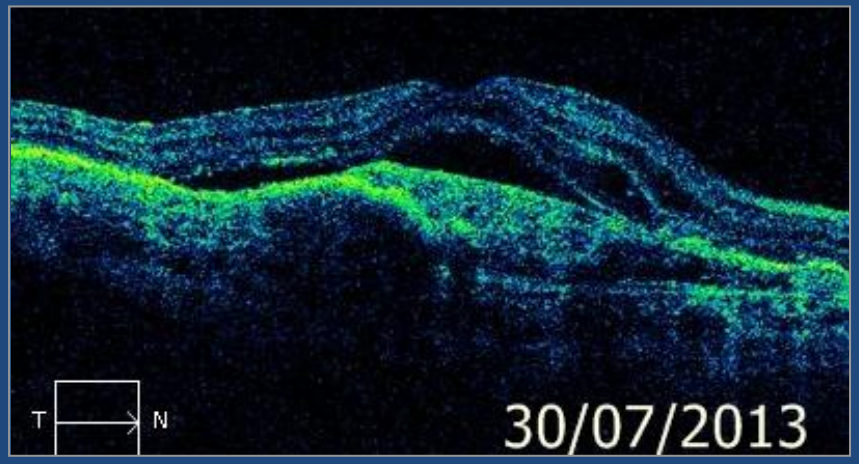


3 x aflibercept, BCVA:0.4

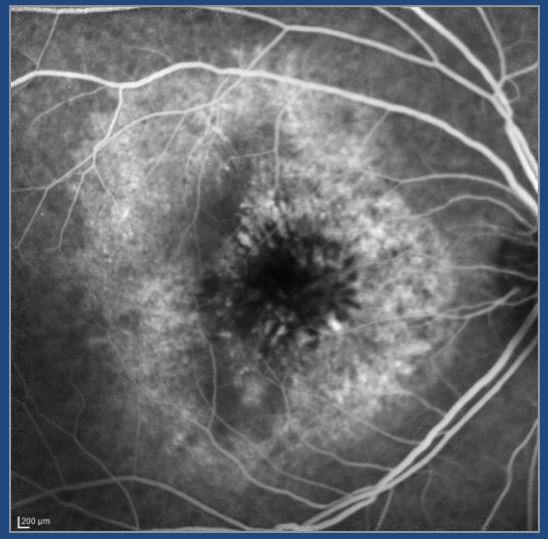
62 yo, female

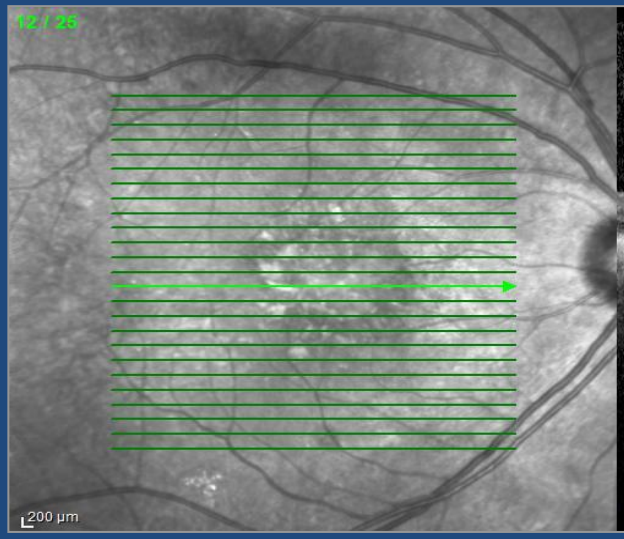


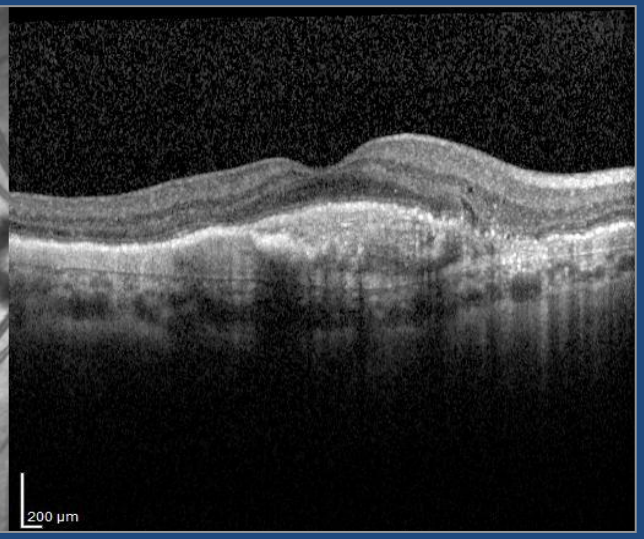
VA 0.2



VA 0.2: 12 x Ranibizumab



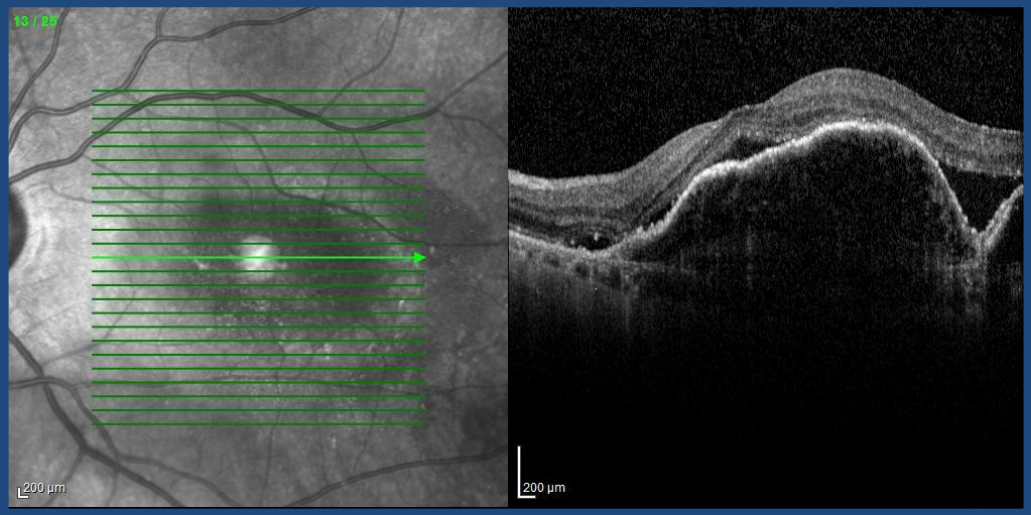




VA 0.3: 3 x Aflibercept

65 Y, F

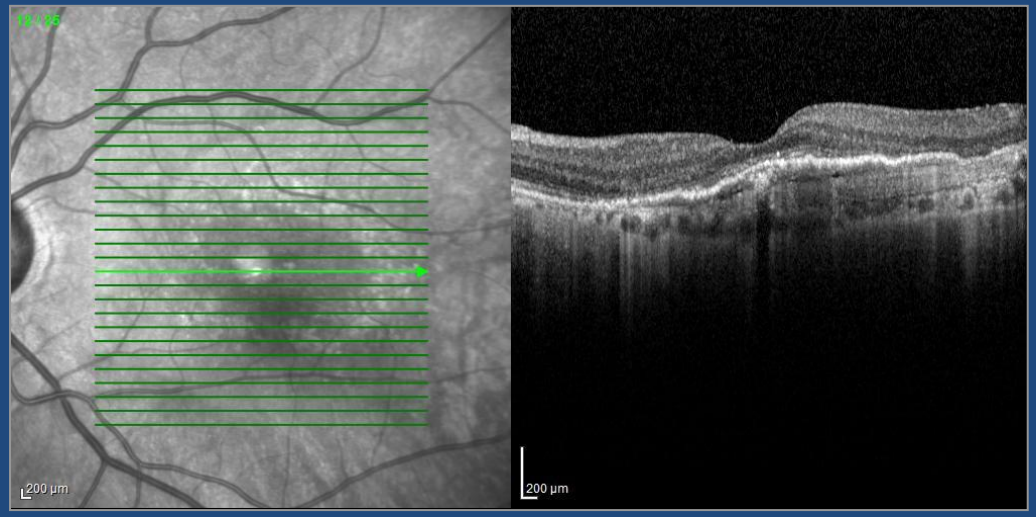
16 x ranibizumab injections



Before aflibercept:

VA 0,5 LogMAR (56 letters)

CMT 596 micron



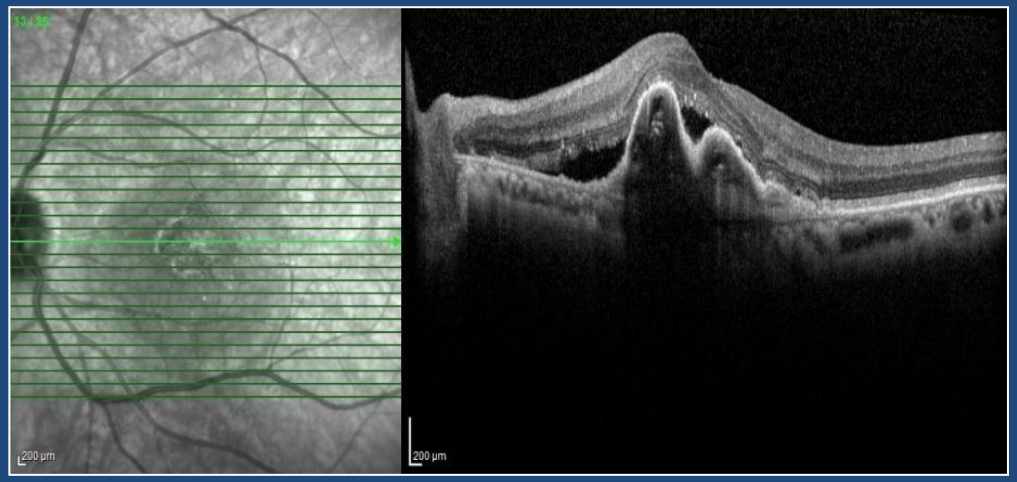
Last exam: 3 x Aflibercept

VA 0,5 LogMAR (56 letters)

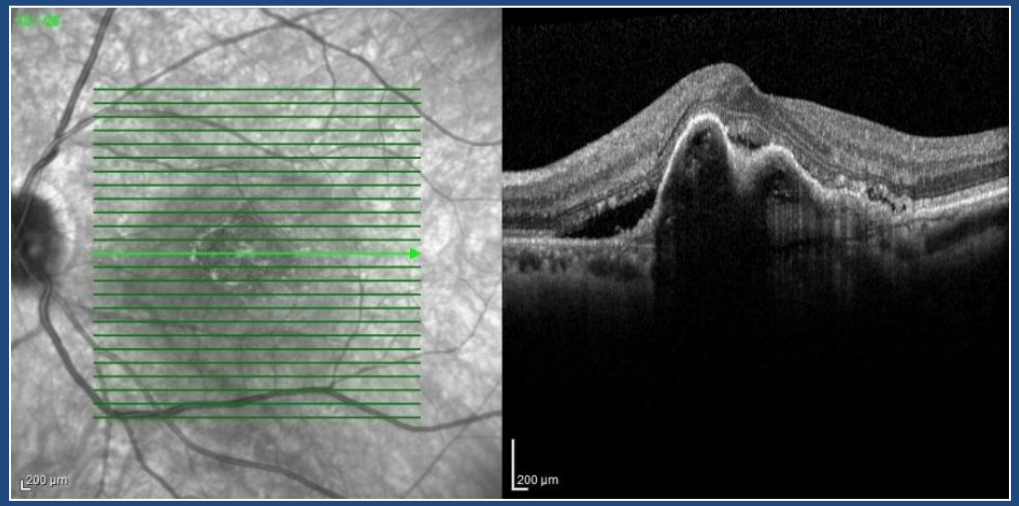
CMT 296 micron

70 Y, E

9 x ranibizumab injection



Before Aflibercept BCVA 0,2 LogMAR (75 letters)
CMT 658 micron



3 x Aflibercept injctions
BCVA 0,1 LogMAR (78 letters)
CMT 630 micron

Conclusion

- Intravitreal aflibercept treatment is a powerful alternative option in neovascular-AMD patients refractory to ranibizumab treatment

- More prospective, randomized, multicenter head-to-head studies are necessary in terms of first line treatment in neovascular AMD, particularly in cases with RAP, PCV, and fibrovascular PED