Hierarchy of Evidence

Central serous chorioretinopathy

- Fourth most common 'wet maculopathy' (after AMD, DME, RVO)
- Irreversible vision loss and decreased vision-related QoL in chronic CSC
- Highly variable preferred practice treatment patterns around the world
  (Mehta et al Brit J Ophthalmol 2017)

CONTROVERSY

- Breukink...Boon, Clin Ophthalmol 2016
- Mrejen et al, Ophthalmology 2019
- Salehi M et al. Cochrane Database Syst Rev 2015
- Daruich A et al. Prog Retin Eye Res 2015

VICI TRIAL

studying treatment of chronic CSC

Supplementary Table 14 Complete or partial resolution of subretinal fluid at each time-point by randomised allocation

Outcome	Visit	Classification	Randomised to placebo (n=57)	Randomised to eplerenone (n=57)
Resolution of SRF in study eye	4 weeks	Complete resolution	2/54 (4%)	4/56 (7%)
		Partial resolution	4/54 (7%)	8/56 (14%)
		Non-responder	48/54 (89%)	44/56 (79%)
	3 months	Complete resolution	6/54 (11%)	5/52 (10%)
		Partial resolution	12/54 (22%)	15/52 (29%)
		Non-responder	36/54 (67%)	32/52 (62%)
	6 months	Complete resolution	11/54 (20%)	8/52 (15%)
		Partial resolution	10/54 (19%)	16/52 (31%)
		Non-responder	33/54 (61%)	28/52 (54%)
	9 months	Complete resolution	13/52 (25%)	9/51 (18%)
		Partial resolution	10/52 (19%)	14/51 (27%)
		Non-responder	29/52 (56%)	28/51 (55%)
	12 months	Complete resolution	16/54 (30%)	8/51 (16%)
		Partial resolution	13/54 (24%)	14/51 (27%)
		Non-responder	25/54 (46%)	29/51 (57%)

Data are presented as n/N (%)
SRF=subretinal fluid
Partial resolution of SRF is defined as a decrease of >25 % of central macular thickness from baseline.
A non-responder is defined as having an increase in SRF or decrease in SRF ≤25% from baseline.

Lotery et al. Lancet 2020

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Lotery et al. Lancet 2020

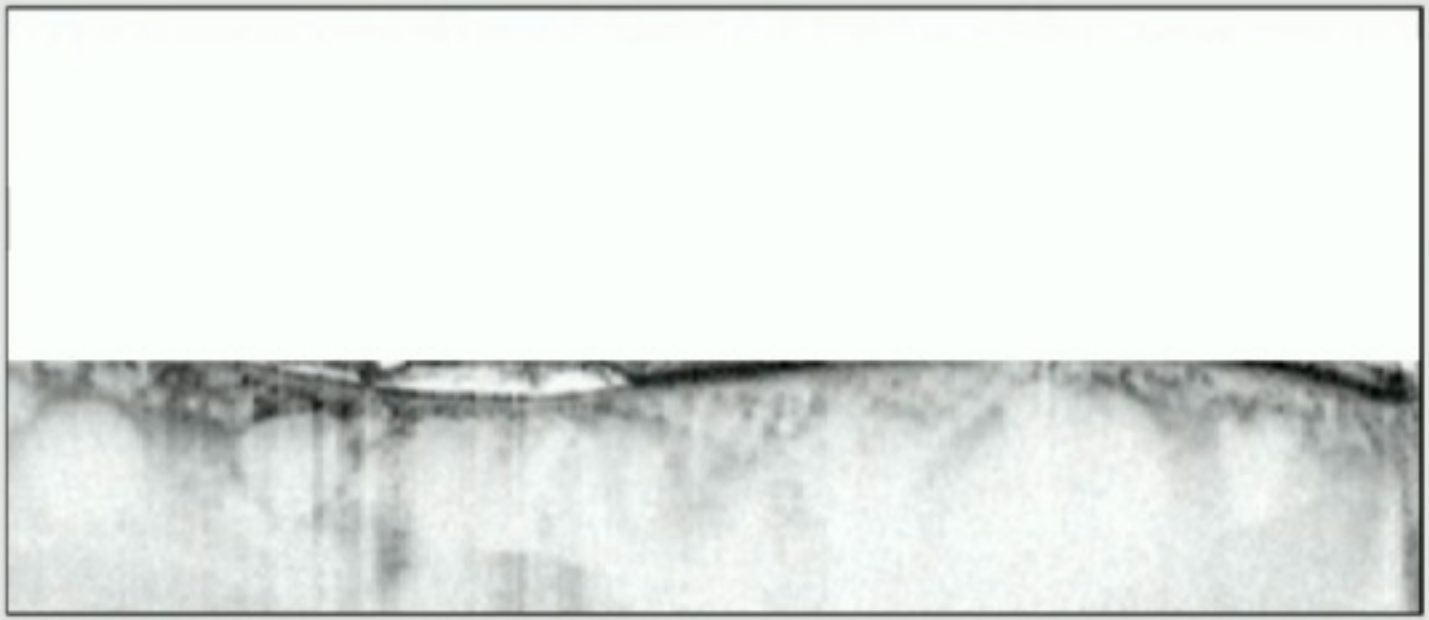

EVIDENCE

The retino-choroidal interface: maintaining the equilibrium

Philippe Petit, Twin Towers, 197

RPE / choroid / both: pachychoroid

disequilibrium



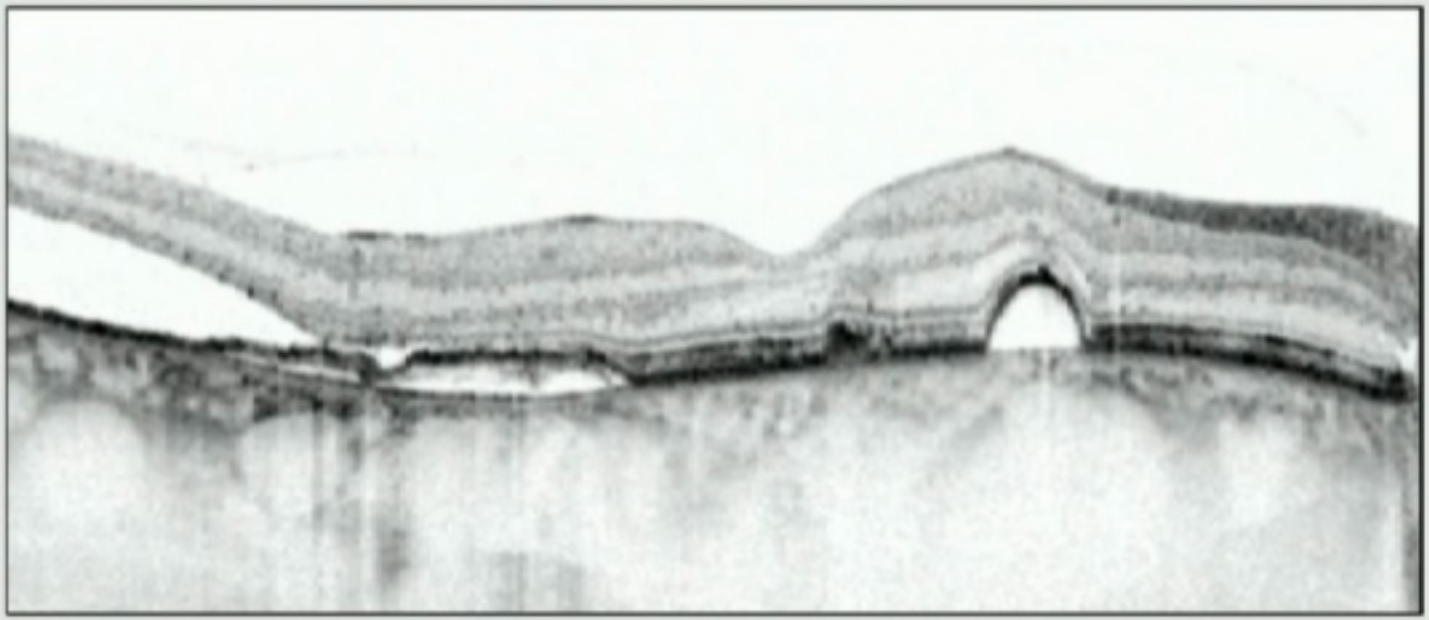
RPE pump

choroidal flow & permeability

Cheung,…, Freund. Eye 2018

RPE / choroid / both: pachychoroid

disequilibrium



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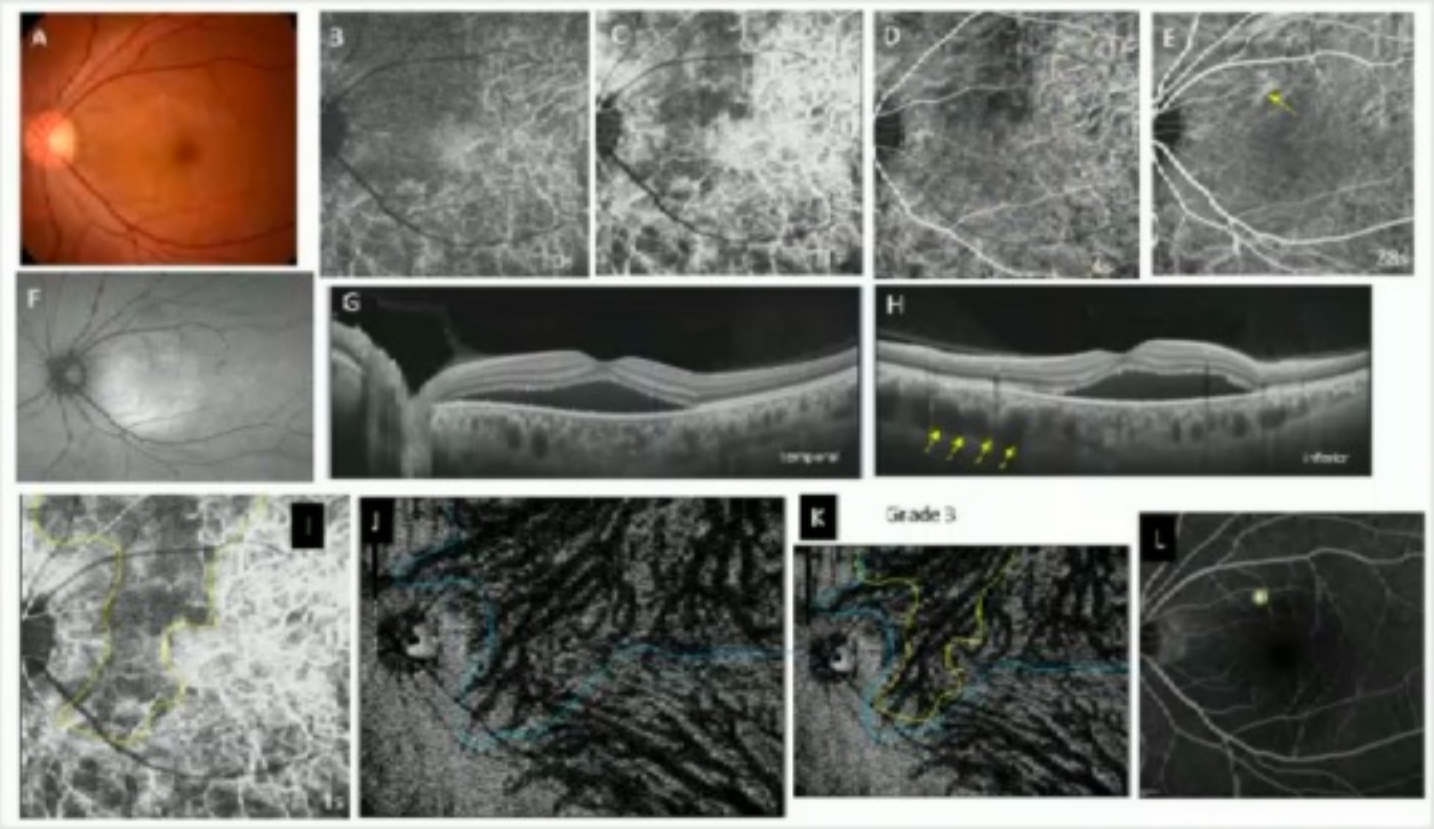
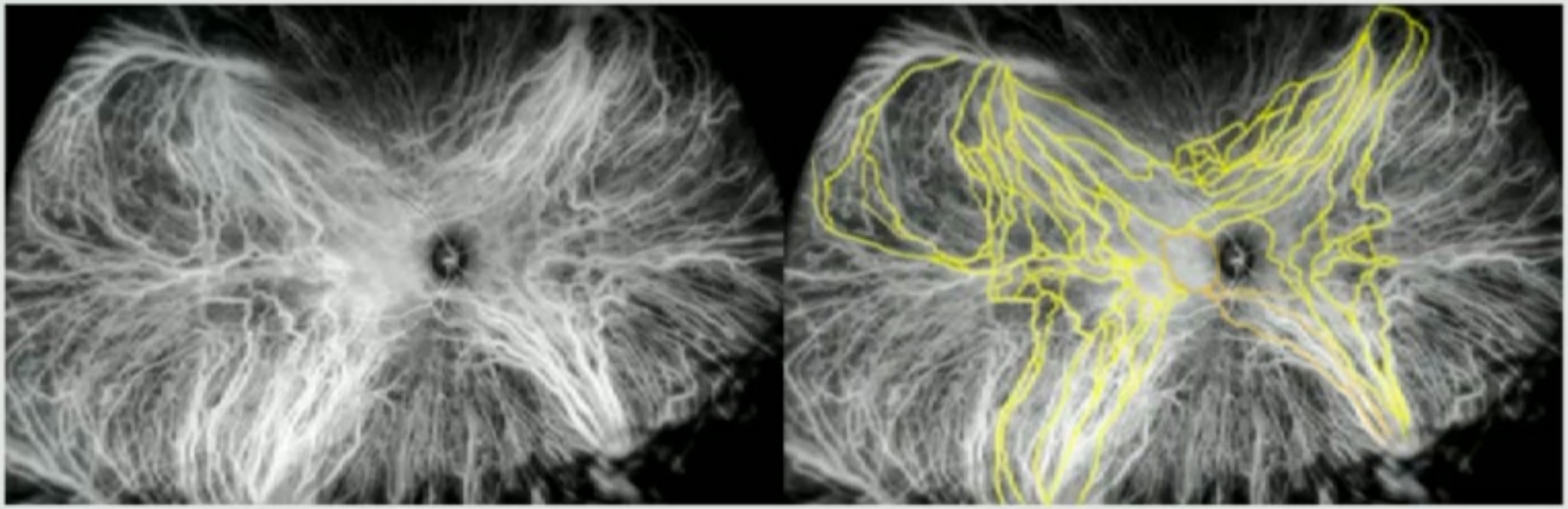
Venous congestion
Asymmetric venous drainage
No clear watershed zones
Delayed filling and ischemia of choriocapillaris



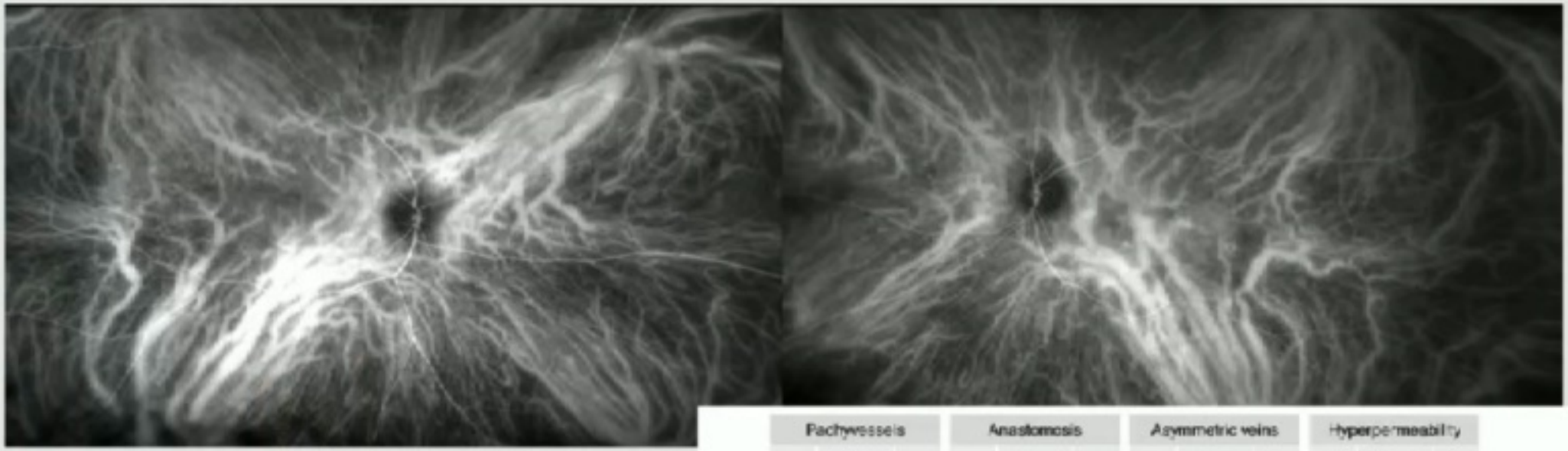
Hiroe & Kishi, Ophthalmology Retina 2018
Kishi et al. PlosONE 2018

Venous overload choroidopathy

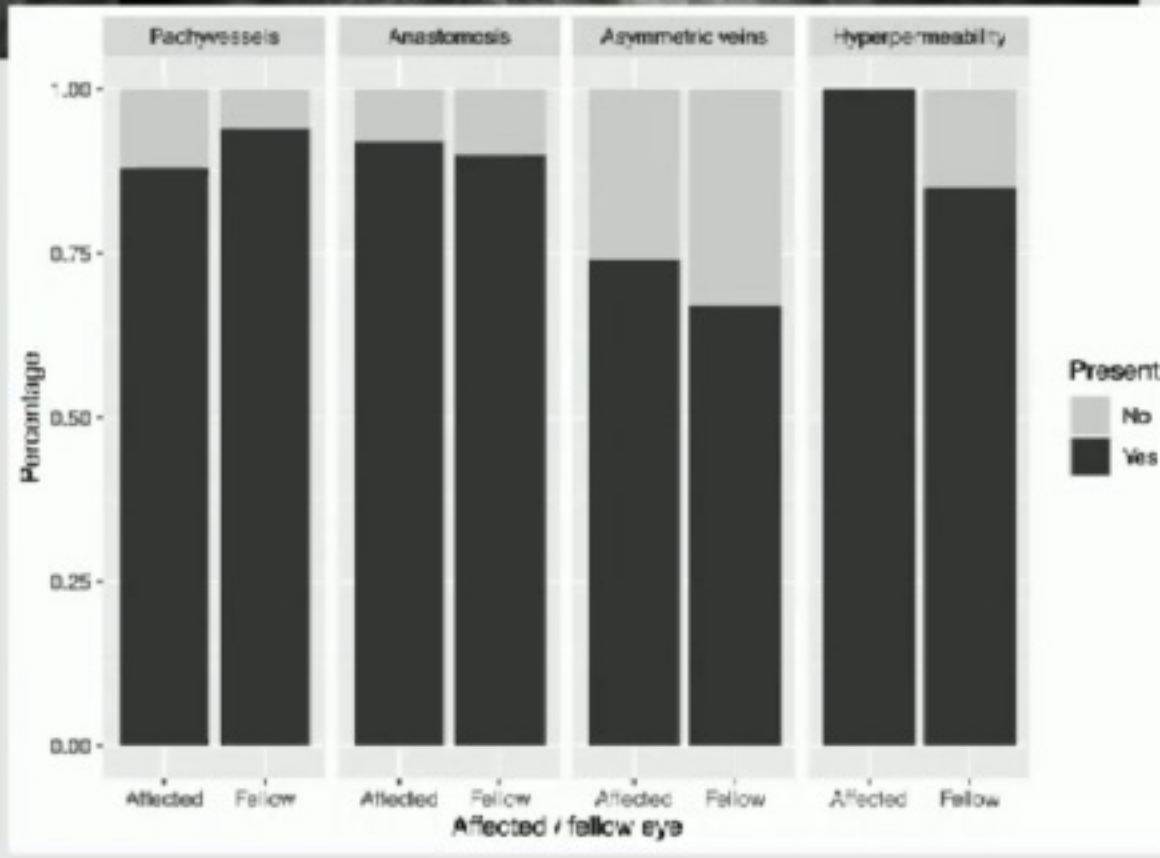


Spaide et al. Prog Ret Eye Res 2022

Venous overload choroidopathy



Pauleikhoff L,…Boon.
Ophthalmology Retina (in press)
n=91 patients



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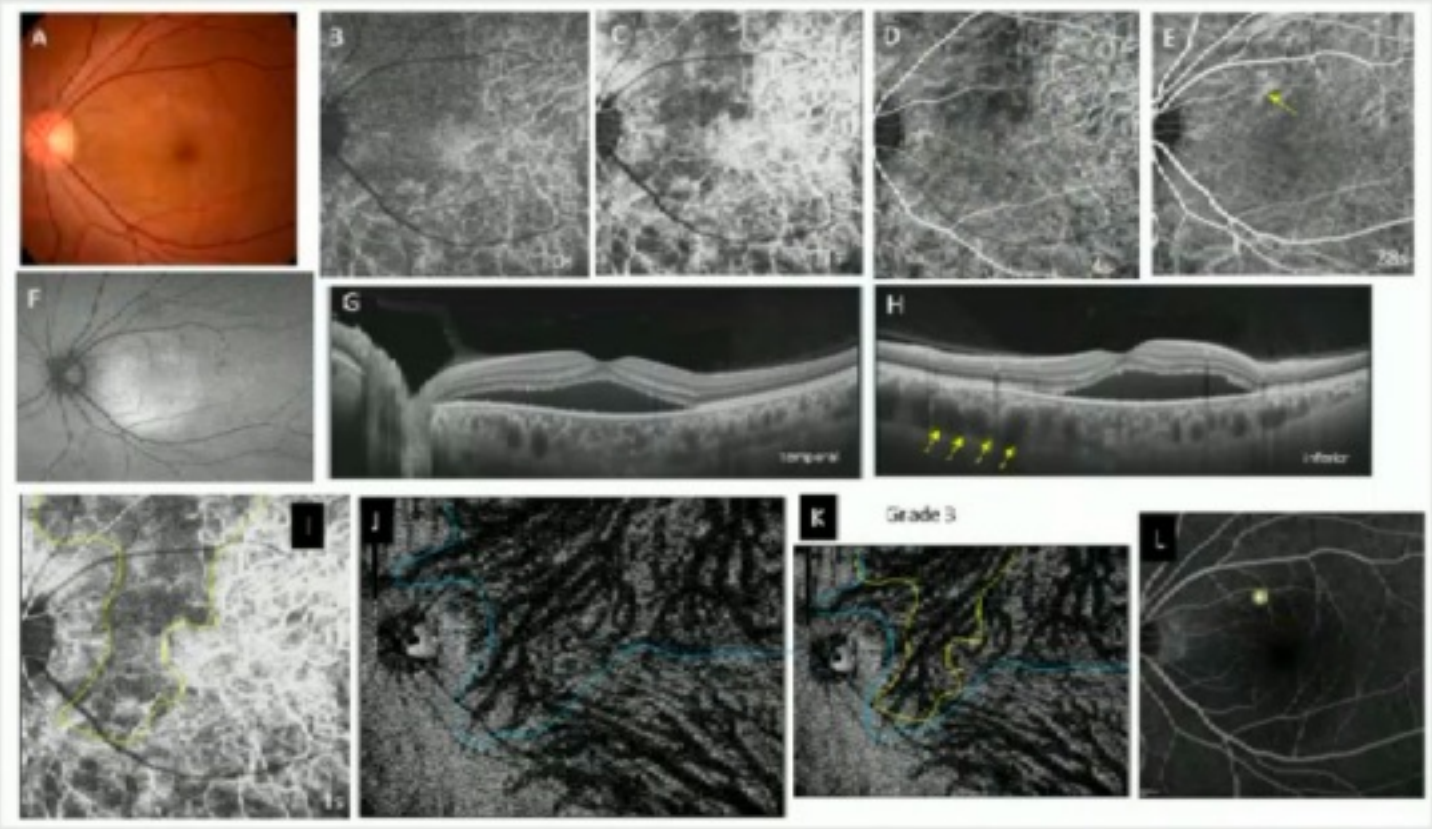

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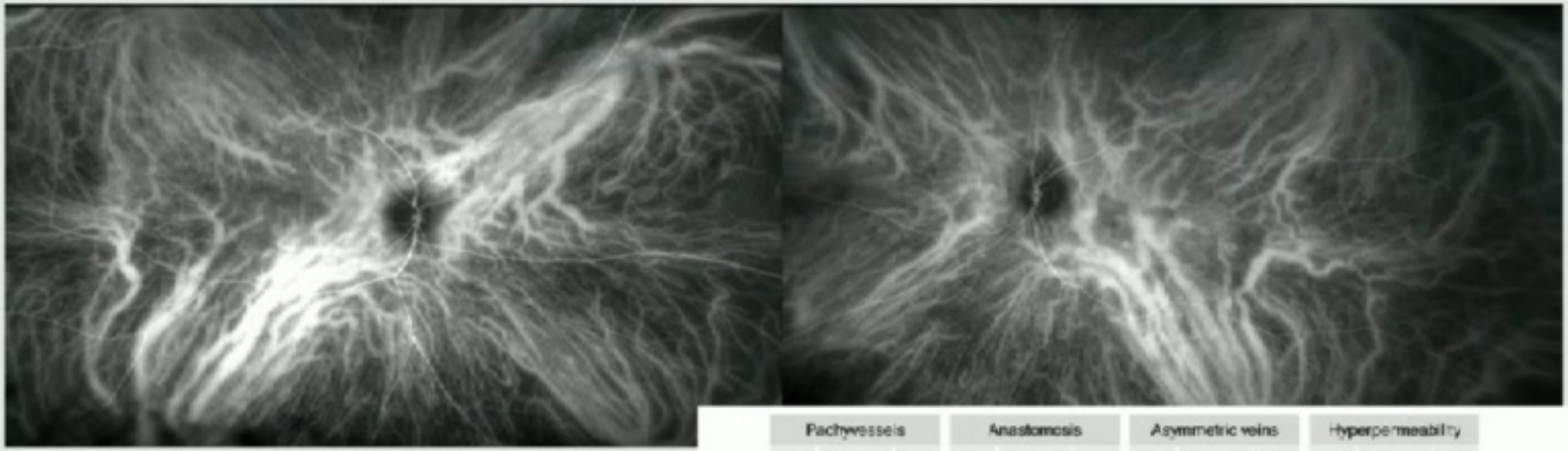

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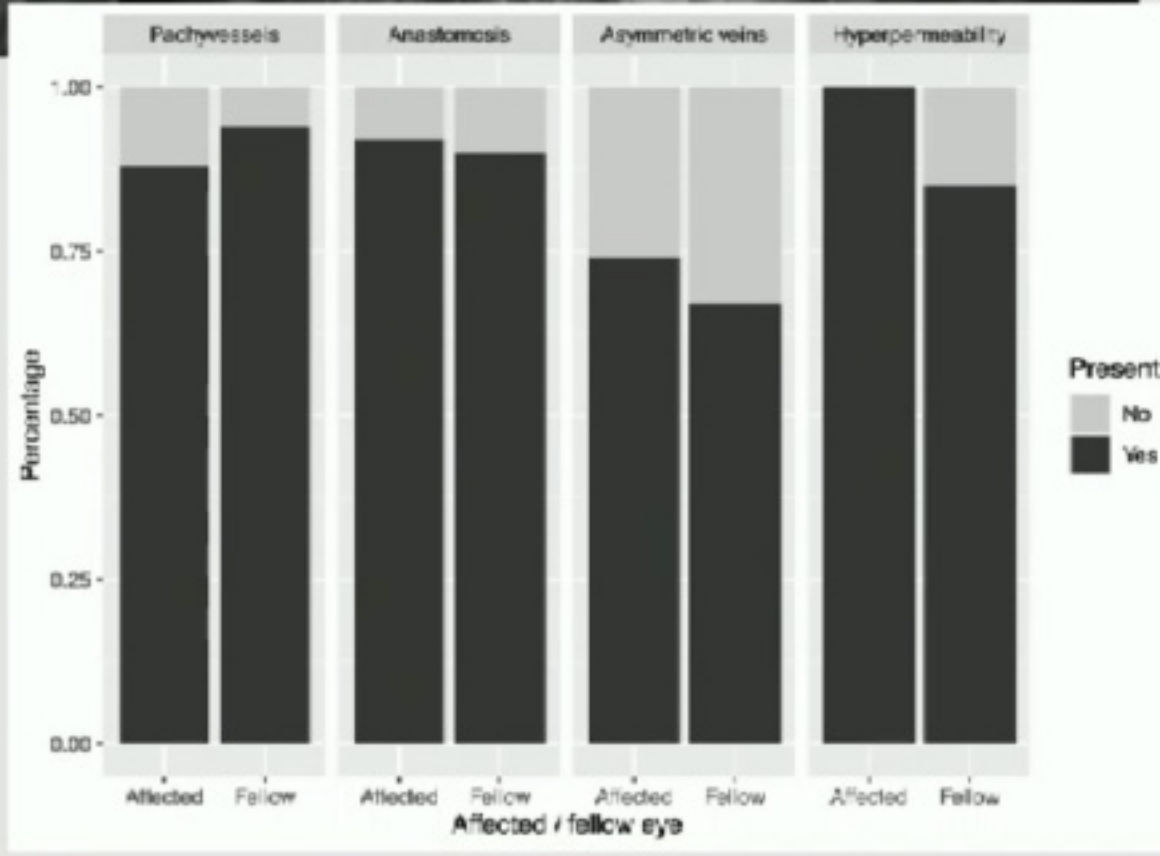
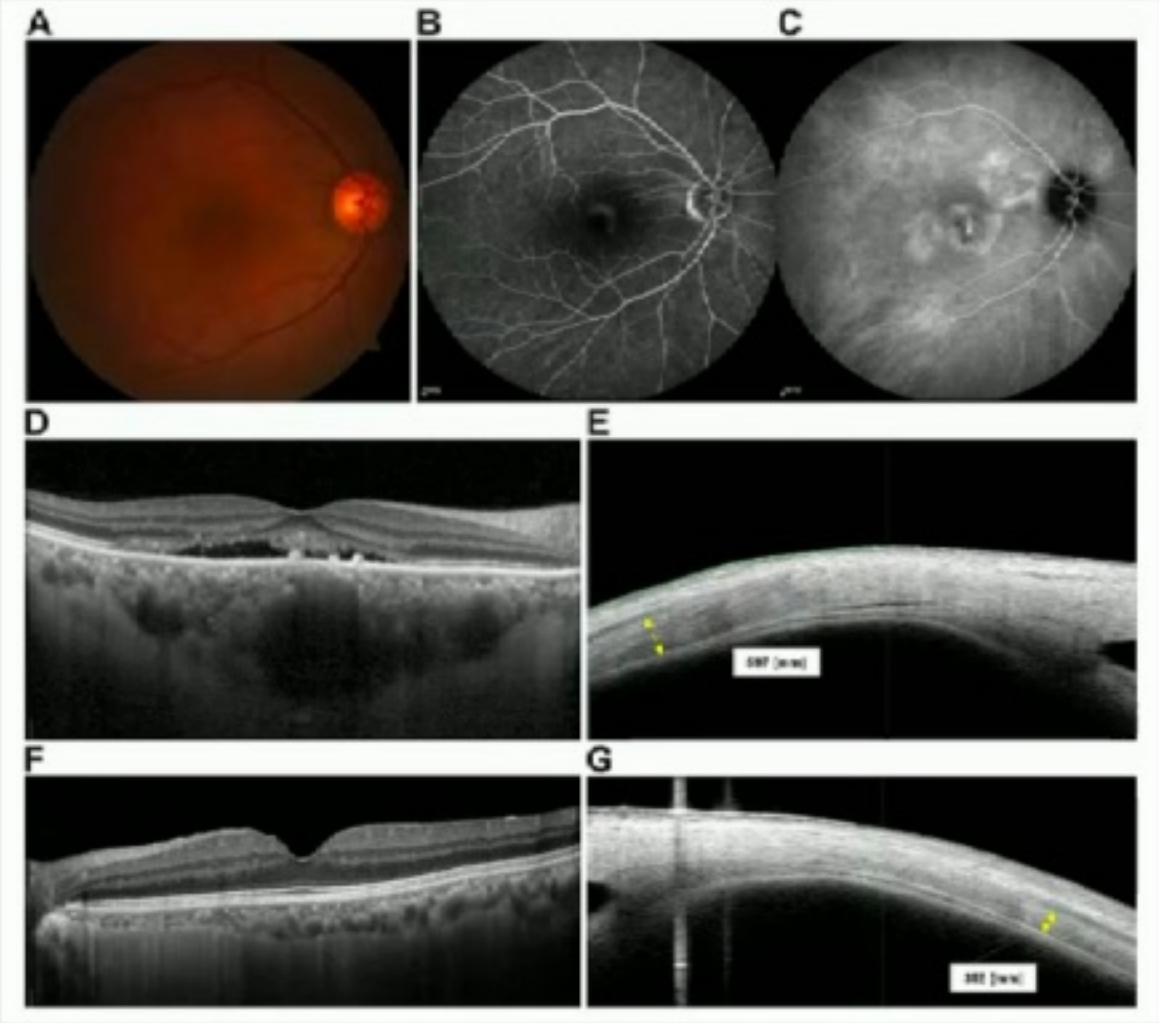


Increased scleral & choroidal thickness in CSC

Choroidal folds



Lee et al. Sci Rep 2021
Imanaga et al. IOVS 2023
Cohen,…,Mrejen. Retin Cases Brief Rep 2022

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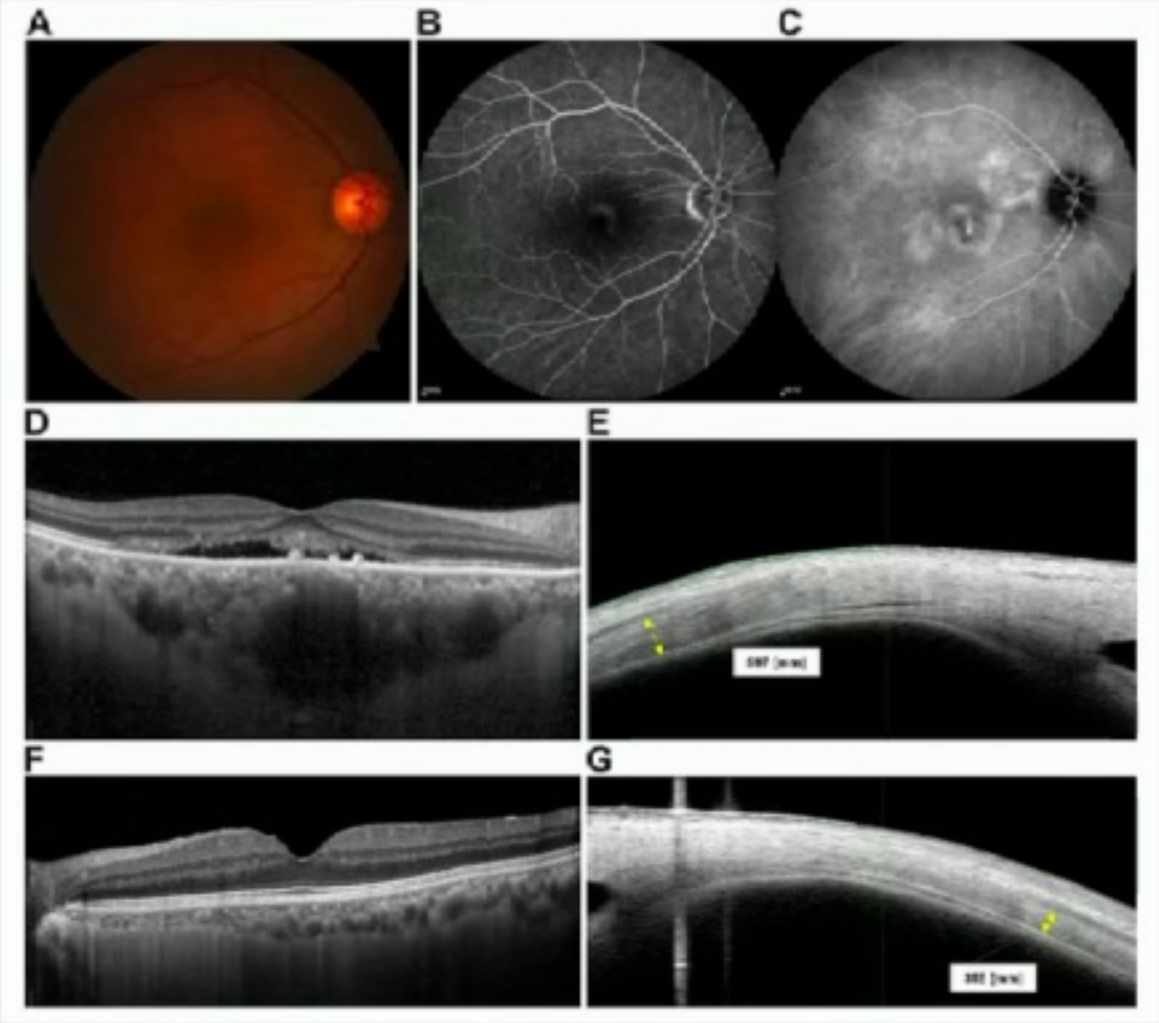
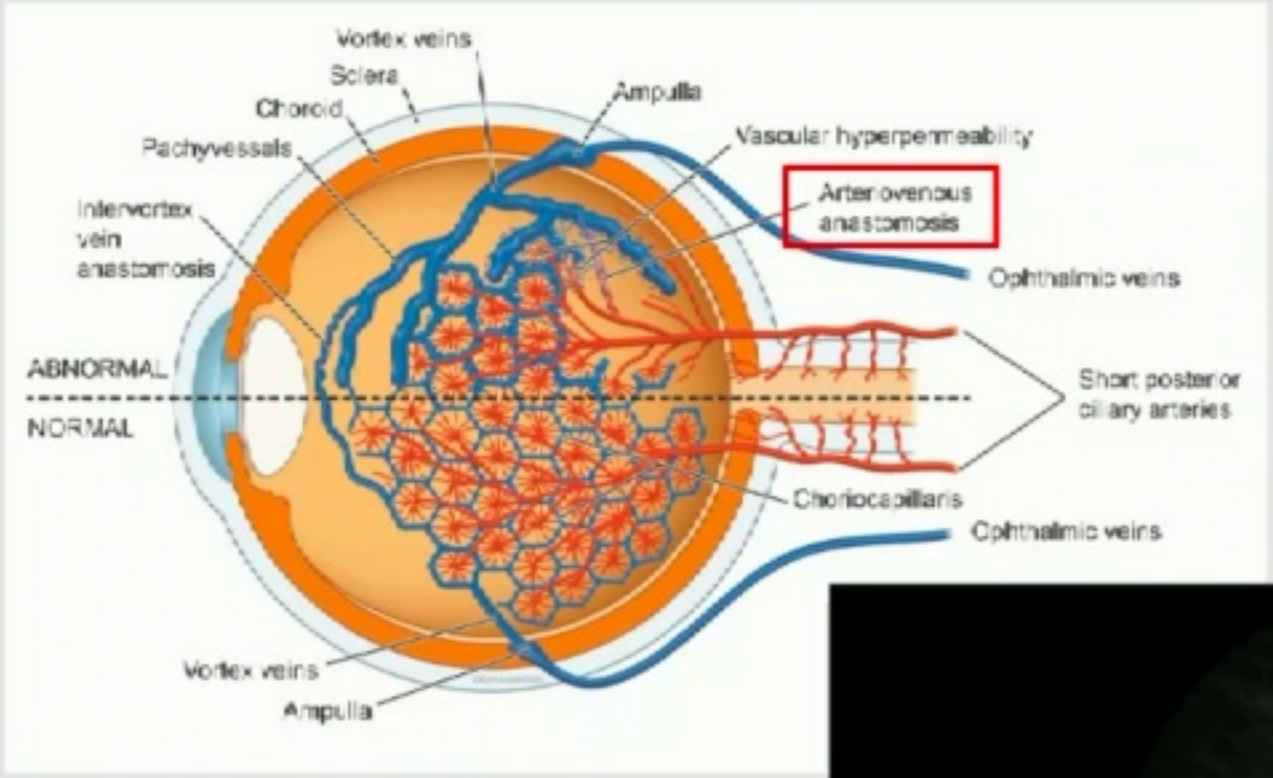


Lee et al. Sci Rep 2021
Imanaga et al. IOVS 2023
Cohen,…,Mrejen. Retin Cases Brief Rep 2022

Arteriovenous anastomosis



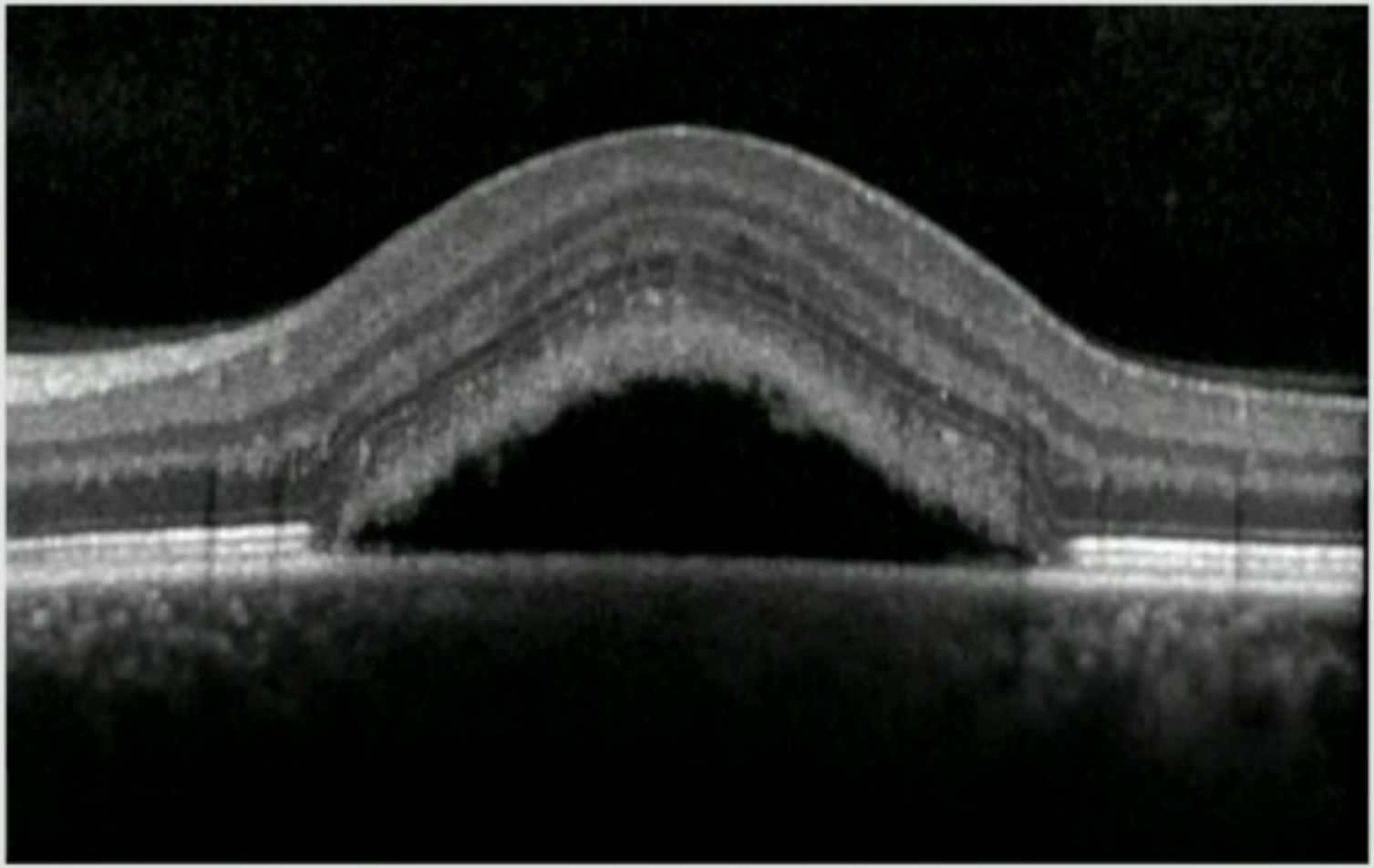
Brinks, …, Boon. Acta Ophthalmologica 2022

Choroidal vascular congestion and leakage are pivotal features of CSC pathogenesis

important target for treatment

Aims of treatment & evaluation of efficacy

- Get rid of the subretinal fluid / leakage to improve vision



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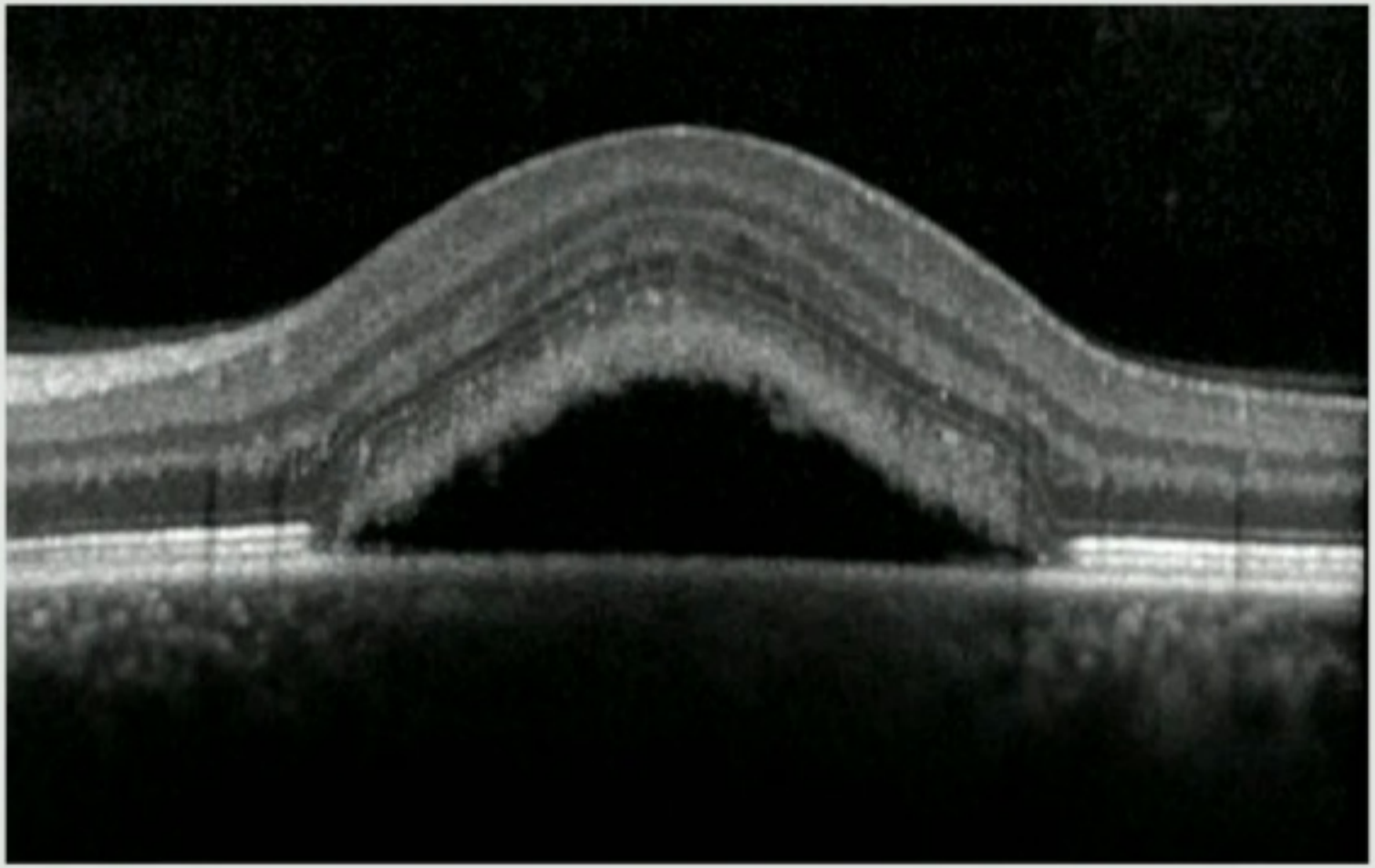

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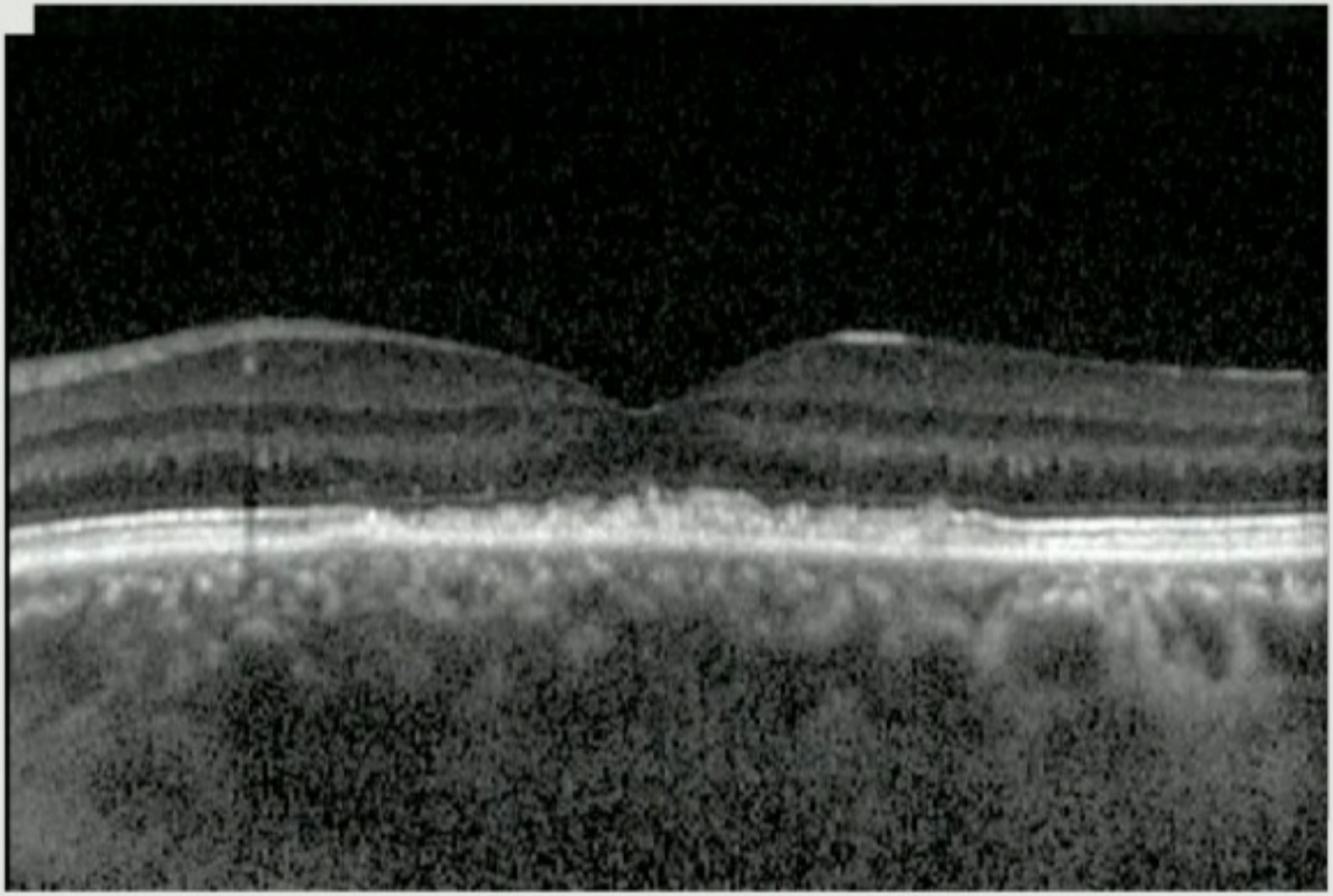

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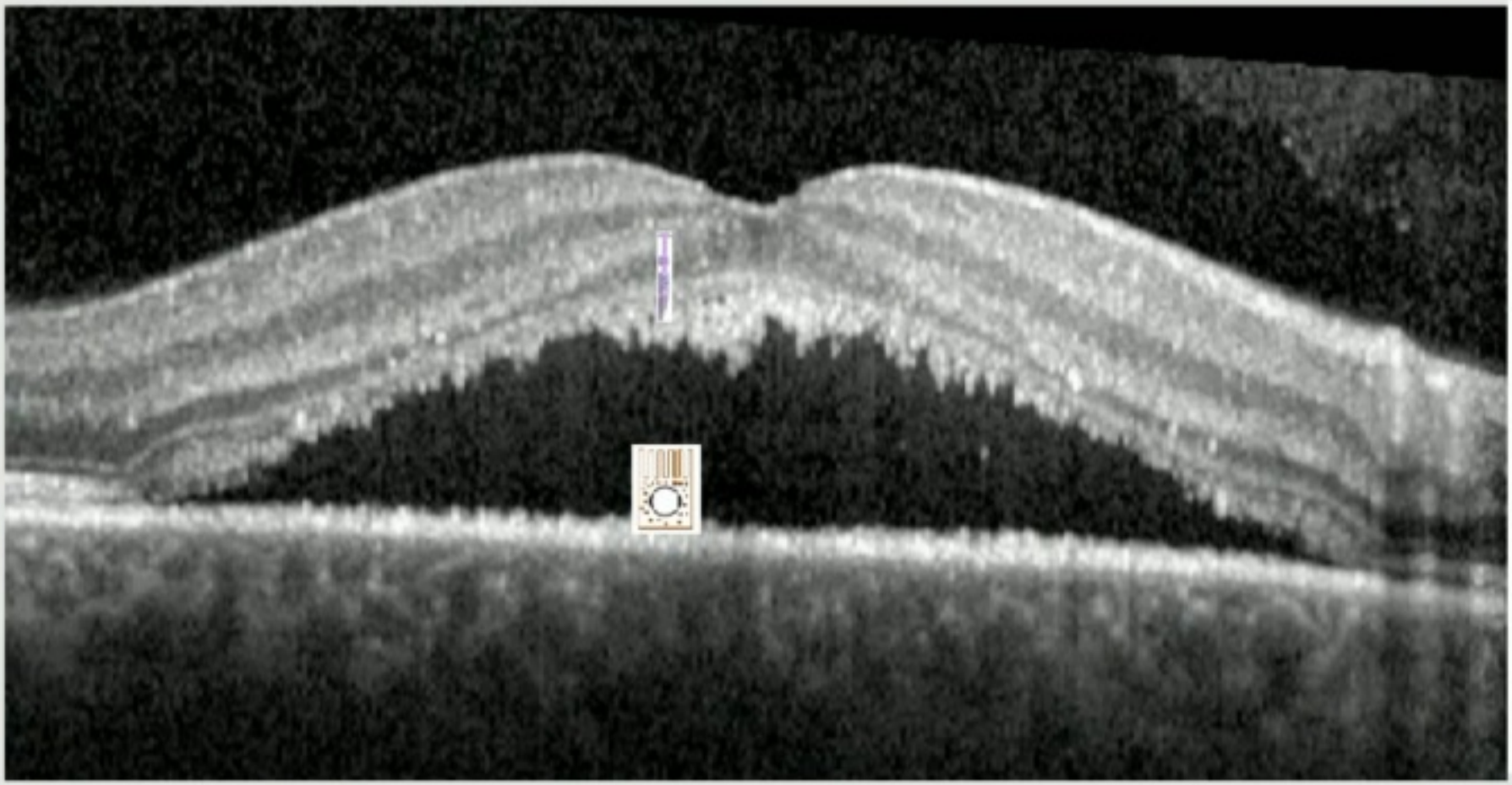
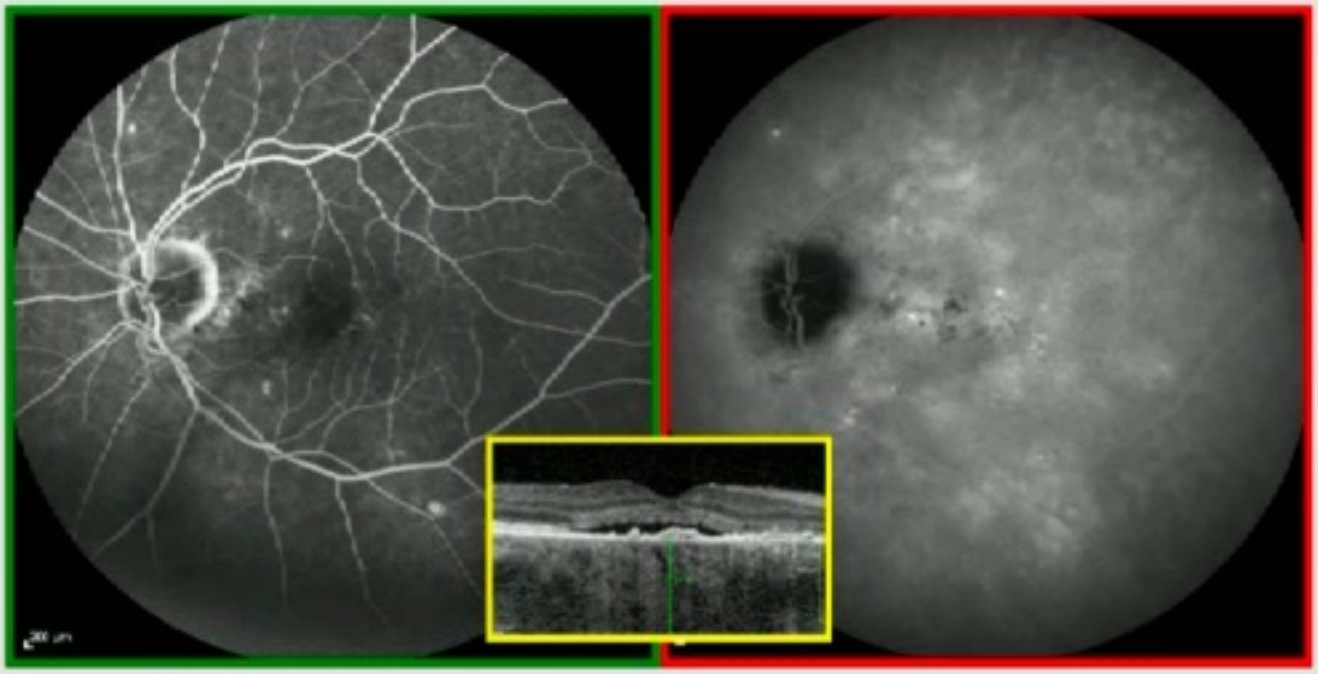


Aims of treatment & evaluation of efficacy

- Get rid of the subretinal fluid / leakage to improve vision

- Reduce / prevent recurrences by addressing the underlying primary problem: the choroid



Aims of treatment & evaluation of efficacy

- Problematic in many studies:

  retrospective

  small

  highly variable inclusion criteria

  highly variable efficacy outcome measures

- Classification controversy

- OCT parameters

- Visual acuity

Treatment options in chronic CSC

1) Photodynamic therapy (PDT)
2) Micropulse laser treatment
3) Conventional laser treatment
4) Anti-VEGF
5) Other: MR-antagonists, β-blockers, …

Photodynamic therapy (PDT)

- Rationale
- Full settings
- Half-dose / Half-fluence / Half-time

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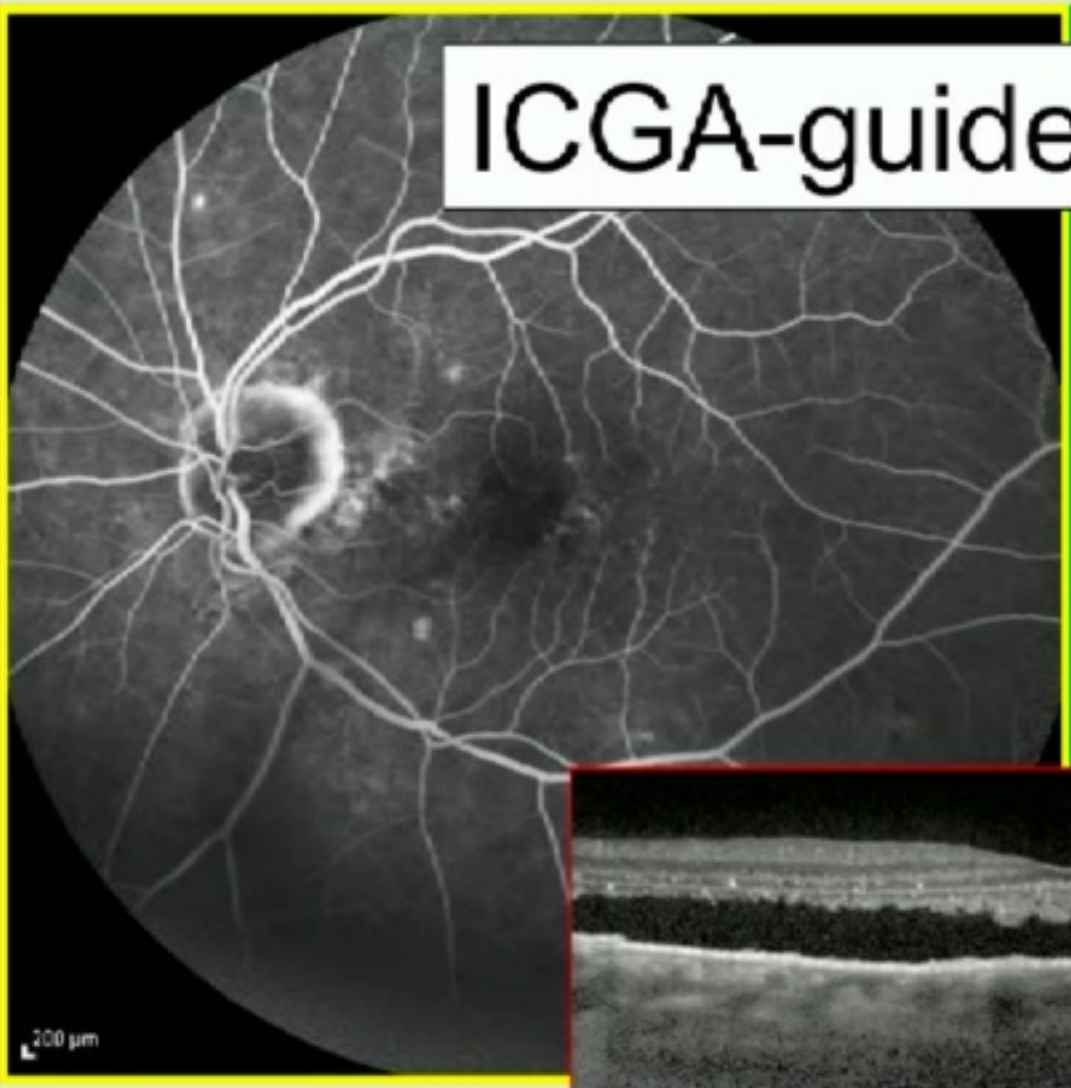
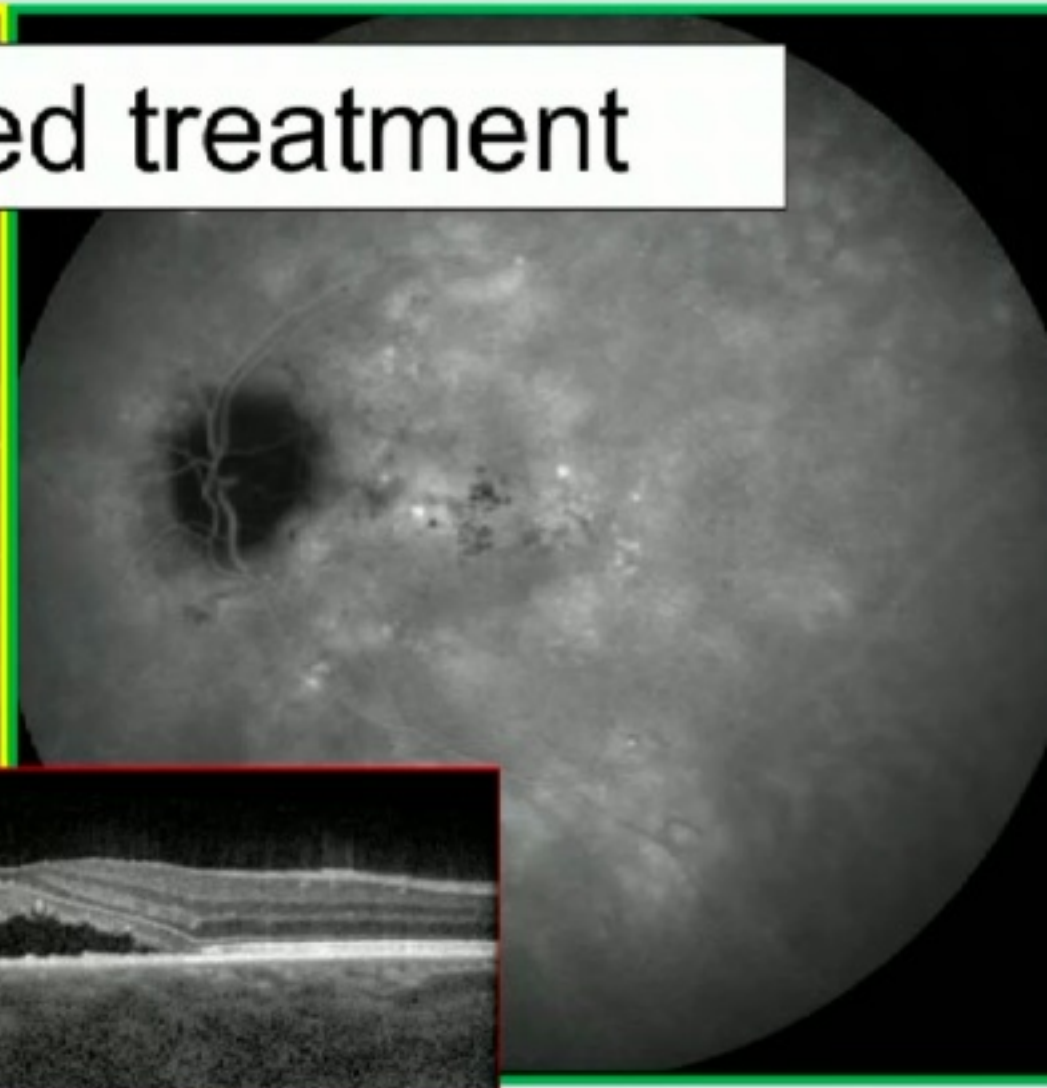
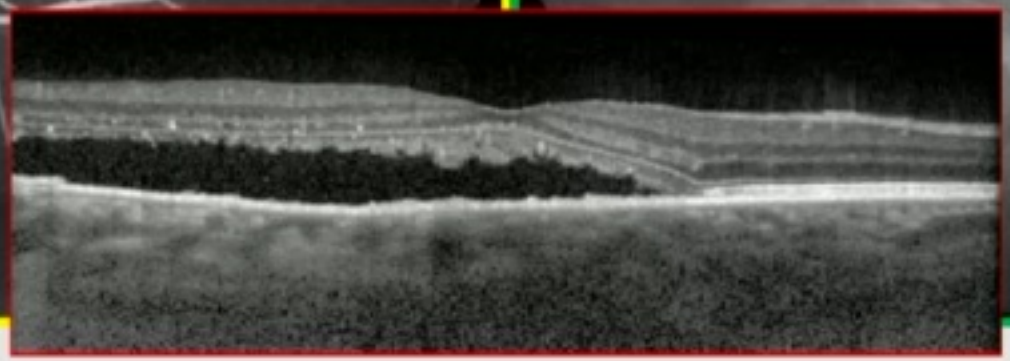
Daruich et al. Prog Ret Eye Res 2015
Van Rijssen et al. Prog Ret Eye Res 2019
Bousquet et al. Exp Eye Res 2019
Lotery et al. Lancet 2020

PLACE

ICGA-guided treatment







PLACE Results - SRF on OCT

Complete resolution of SRF on OCT	PDT-treated patients	HSML-treated patients	P-value
At Evaluation Visit 1	41/80 (51.2%)	11/80 (13.8%)	<0.001
At Final Evaluation Visit	45/67 (67.2%)	19/66 (28.8%)	<0.001

PLACE Results - microperimetry

Increase in retinal sensitivity (dB)	PDT-treated patients	HSML-treated patients	P-value
At Evaluation Visit 1	+ 2.01	+ 0.92	0.046
At Final Evaluation Visit	+ 3.24	+ 1.38	0.008

Photodynamic therapy is more effective than HSML in the treatment of chronic CSC

with regard to anatomical success

– a complete resolution of SRF –

as well as functional parameters

Van Dijk,…, Boon. Ophthalmology 2018

Photodynamic therapy is more effective than HSML in the treatment of chronic CSC

This is the case for chronic CSC regardless of a more focal or diffuse leakage pattern

(Van Rijssen,…,Boon. Am J Ophthalmol 2019, PLACE Trial Report No. 3)

Half-dose PDT after previous unsuccessful HSML treatment for cCSC is still effective, not vice versa

(Van Rijssen,…,Boon. Am J Ophthalmol 2020: the REPLACE Trial)

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Daruich et al. Prog Ret Eye Res 2015
Van Rijssen et al. Prog Ret Eye Res 2019
Bousquet et al. Exp Eye Res 2019
Lotery et al. Lancet 2020

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SPECTRA

first large prospective randomized controlled RCT
comparing
half-dose PDT versus eplerenone treatment

SPECTRA

Results

- 107 patients were included in the trial
- 3 months post-treatment
- Intention to treat analysis

Complete resolution of SRF on OCT	PDT group (n = 53)	Eplerenone group (n = 54)	P-value
At Evaluation Visit 1	39/50 (78%)	8/46 (17%)	<0.001

Secondary outcomes (mean)	PDT group	Eplerenone group	P-value
BCVA (ETDRS letters) At evaluation visit 1	84.0 (increase of 5.9)	82.9 (increase of 3.0)	0.583
Retinal sensitivity microperimetry (dB) At evaluation visit 1	25.4 (increase of 2.7)	24.0 (increase of 1.4)	0.041
VFQ-25 questionnaire (increase in score) At evaluation visit 1	87.2 (increase of 5.5)	83.6 (increase of 4.2)	0.094

Van Rijssen, Van Dijk,…, Boon. Am J Ophth 2022

Treatment of chronic CSC: the evidence

- Prospective RCTs are essential

- PLACE trial: half-dose PDT superior over micropulse laser

  Van Dijk,…, Boon. Ophthalmology 2018

- VICI trial: eplerenone not better then placebo

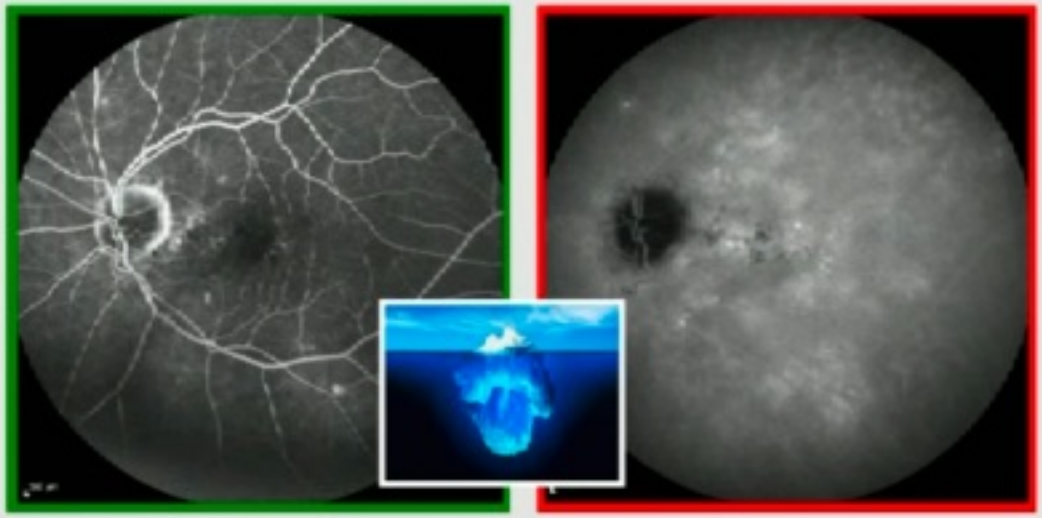
  Lotery et al. Lancet 2020

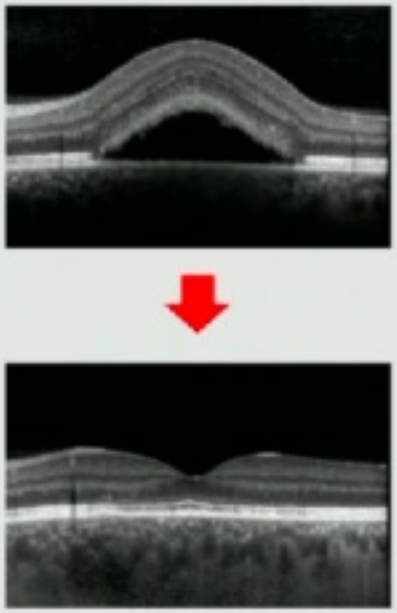
- SPECTRA trial: half-dose PDT superior over eplerenone

  Van Rijssen,…, Boon. Am J Ophthalmol 2022

Why does PDT work best at present?

- More direct and rapid treatment of choroidal / RPE problem (Van Rijssen,…, Boon. Retina 2021; Feenstra,…, Boon. Retina 2022)
- Most effective in relatively rapid and complete SRF resolution (PLACE trial, SPECTRA trial, etc)
- Less recurrences (Van Rijssen,…, Boon. Acta Ophthalmol 2021)

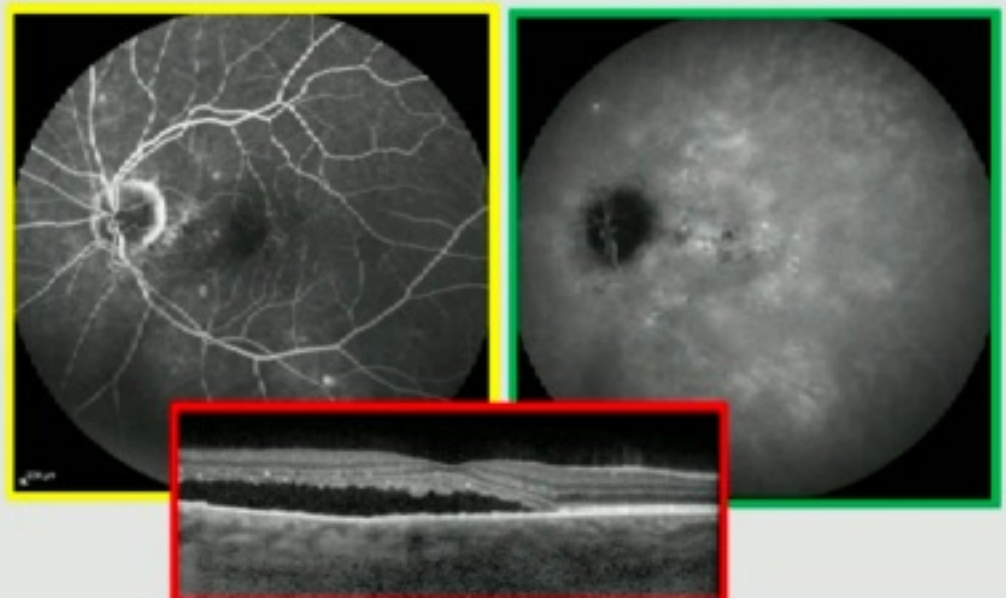




Fovea-involving half-dose PDT

- 57 patients from PLACE and SPECTRA trial
- Chronic CSC
- Single treatment of half-dose PDT with the treatment spot covering the fovea (at least partially) and achieving complete SRF resolution at first visit
- 2 year follow-up

- 3 mg/m^2
- 50 J/cm^2, 83 seconds, 689 nm
- Treatment from 15 min after start of verteporfin infusion



Fovea-involving half-dose PDT

- Marked improvement of outer retinal structures (EZ, ELM)
- Likewise for functional parameters

- NONE of the patients developed any atrophy of EZ, ELM, RPE on SD-OCT and FAF

PDT in chronic CSC is effective and safe

Evidence-based treatment of CSC: key messages

- Current evidence strongly suggests that half-dose (or half-fluence) PDT is the treatment of choice in chronic CSC: it is the **most effective**, and it is **safe**
- Observation may be the preferred approach in first-episode acute CSC, but consider treatment in selected cases
- PDT primarily treats the choroidal abnormalities in CSC, which lie at the basis of this disease
- Beware of the broad differential diagnosis of CSC
- More treatment options are needed