

# THE ROLE OF FLUIDS IN nAMD

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Maura Mancini, MD , PhD

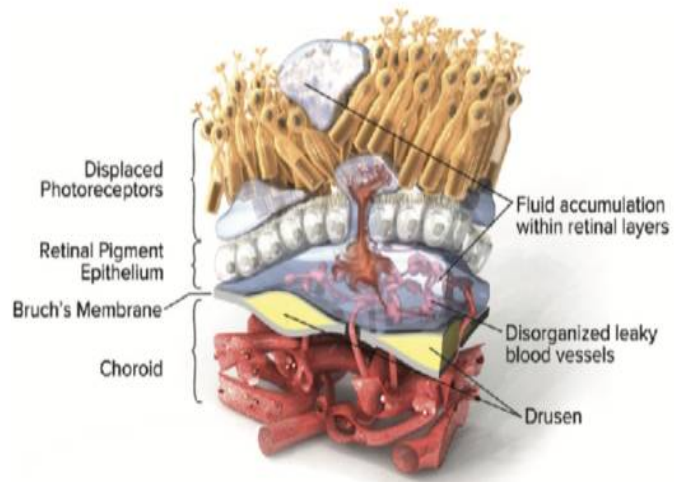
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Ophthalmology Clinic

Prof. Pasquale Aragona



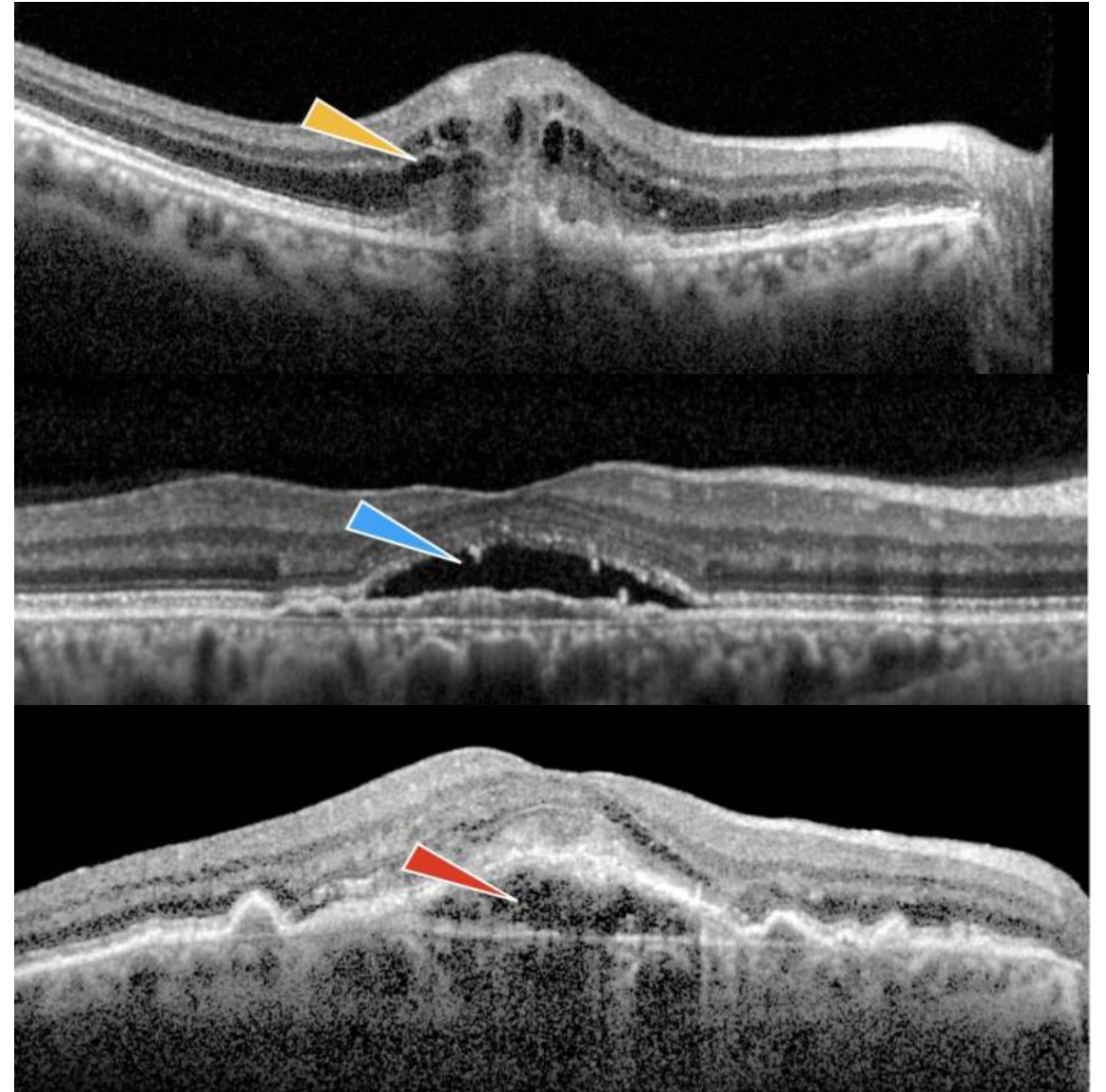
# TYPES OF FLUID IN NEOVASCULAR AMD



- **Intra- Retinal (IRF)**

- **Sub – Retinal (SRF)**

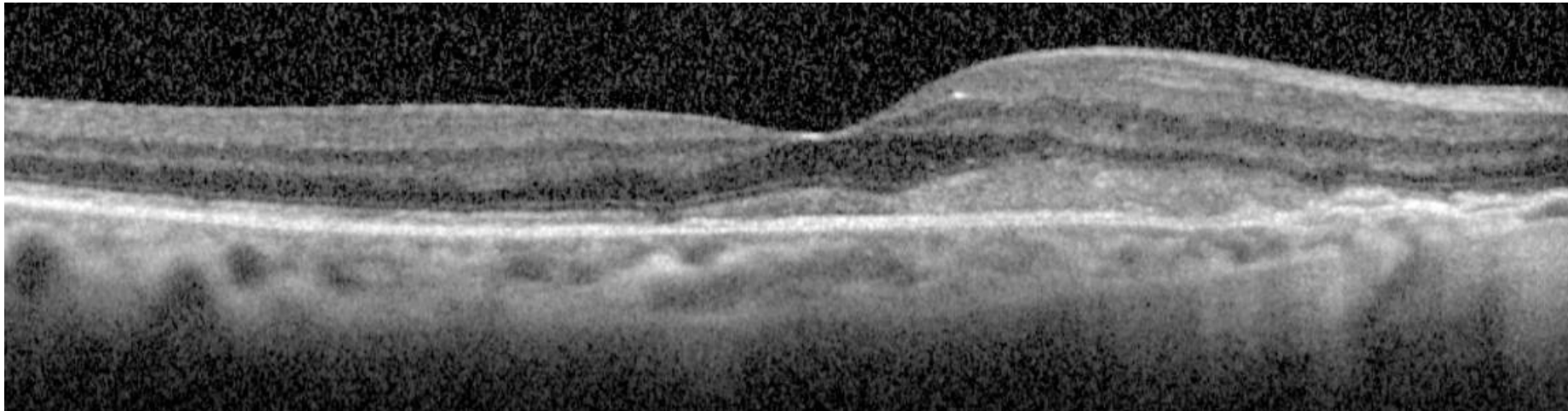
- **Sub - RPE**



# TYPES OF FLUID IN NEOVASCULAR AMD

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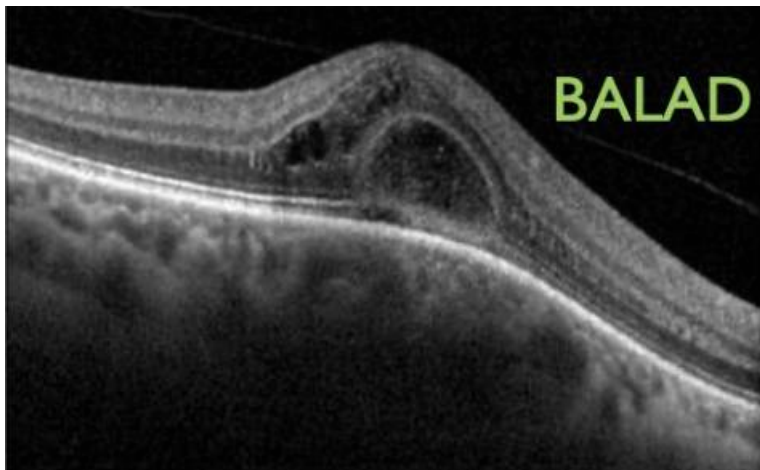
- **SUBRETINAL HYPERREFLECTIVE EXUDATION ( SHE):** The material appears as regions of featureless accumulations of relatively uniform increased reflectivity. The material may include a mixture of serum, fibrin, inflammatory cells.
- SHE represents a subtype of subretinal hyperreflective material (SHRM), a heterogeneous category that includes type 2 macular neovascularization (MNV), fibrosis, fibrin, vitelliform material, hemorrhage, and subretinal drusenoid accumulation. <sup>1</sup>



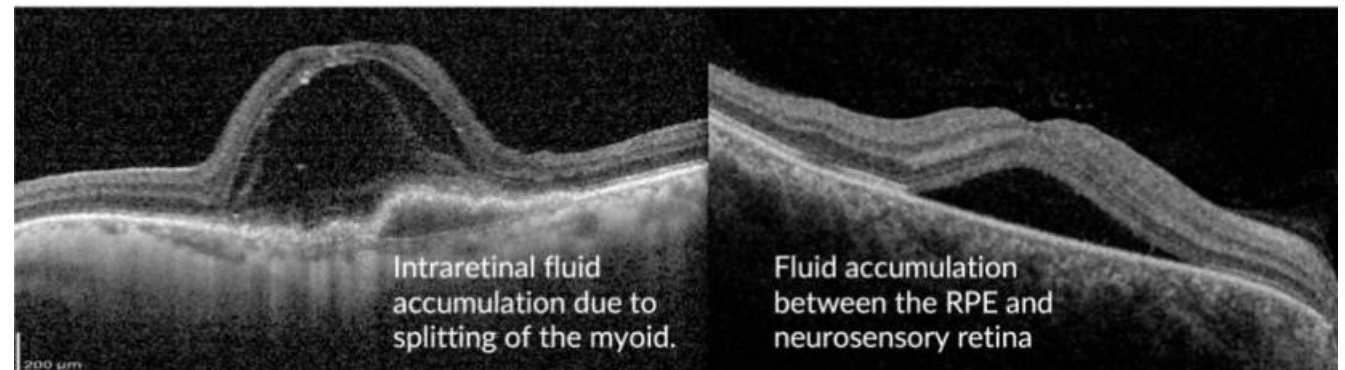


# TYPES OF FLUID IN NEOVASCULAR AMD

- **BACILLARY LAYER DETACHMENT ( BALAD):** It refers to an OCT finding of a schisis at the level of the myoid zone of the inner segment of the photoreceptors, leading to the development of intraretinal fluid-filled cavities. The outer segment of the photoreceptors remains attached to the retinal pigment epithelium (RPE). Fluid accumulates between the innermost hyperreflective band, the external limiting membrane (ELM), and the second innermost hyperreflective band, the ellipsoid zone (EZ).

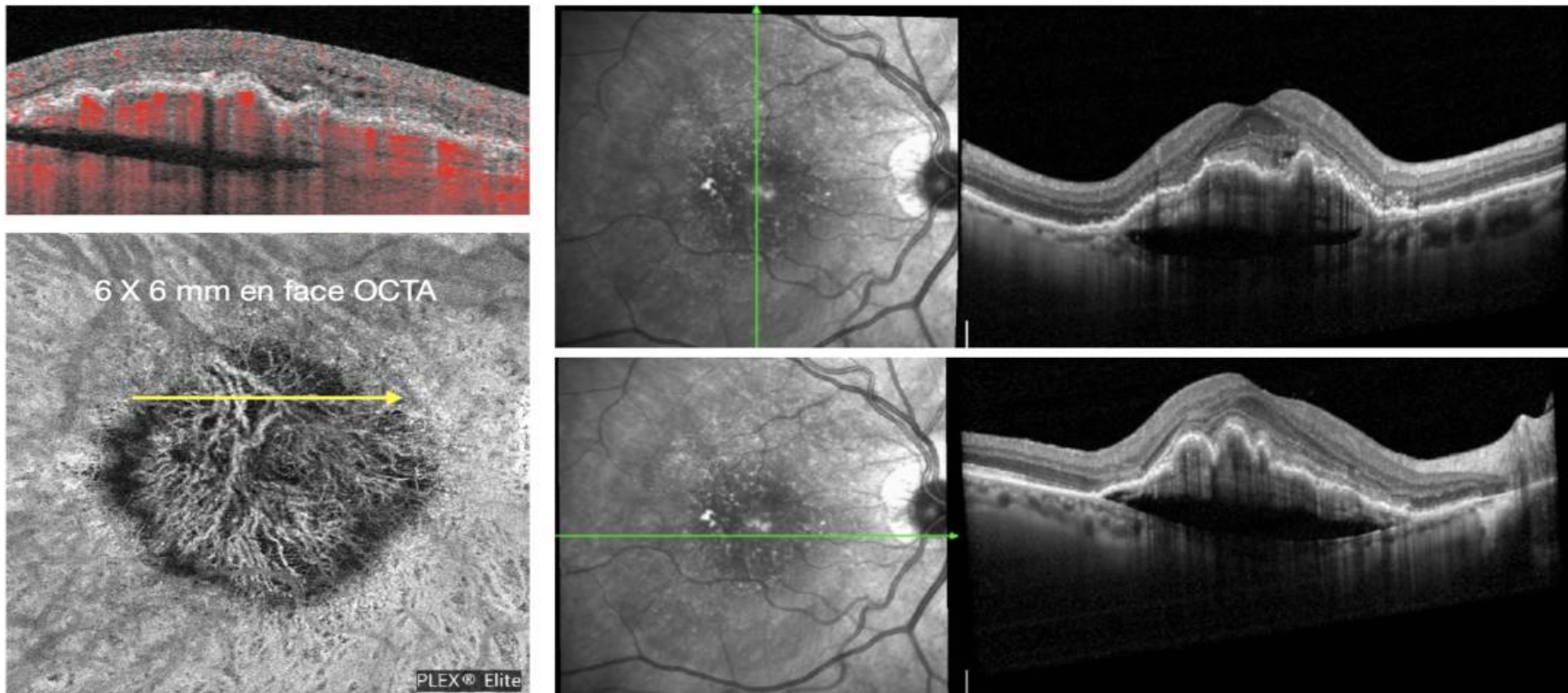


## BALAD VS SRF



# TYPES OF FLUID IN NEOVASCULAR AMD

- **PRECHOROIDAL CLEFTS** : are defined as hyporeflective spaces sandwiched between two hyperreflective lines on OCT, the RPE, and Bruch membrane and are characterized by posterior bowing of Bruch membrane. <sup>1</sup>



# TYPES OF FLUID IN NEOVASCULAR AMD

- **PRECHOROIDAL CLEFTS**

“Prechoroidal cleft increased in association with MNV reactivation and decreased after treatment. Our results suggest that prechoroidal cleft could represent an accumulation of fluid actively exudating from the MNV and **should be considered a sign of nAMD activity.**”

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<https://doi.org/10.1007/s00417-021-05384-w>

## RETINAL DISORDERS



### Prechoroidal cleft thickness correlates with disease activity in neovascular age-related macular degeneration

Mariano Cozzi<sup>1</sup> · Davide Monteduro<sup>1</sup> · Salvatore Parrulli<sup>1</sup> · Federica Ristoldo<sup>1</sup> · Federico Corvi<sup>1</sup> · Federico Zicarelli<sup>1</sup> · Giovanni Staurenghi<sup>1</sup> · Alessandro Invernizzi<sup>1,2</sup>

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#### Abstract

**Purpose** The purpose of this study was to investigate the structural variations of the hyporeflective pocket of fluid (prechoroidal cleft) located between Bruch's membrane and the hyperreflective material within the pigment epithelial detachment (PED) in patients with neovascular age-related macular degeneration (nAMD).

**Methods** In this retrospective, observational case series study, patients diagnosed with nAMD and prechoroidal cleft associated with other activity signs of the macular neovascularization (MNV) were included. Structural optical coherence tomography (OCT) scans were evaluated to obtain anatomical measurements of prechoroidal cleft and PED at three different visits (T0, inactive MNV; T1, active MNV; T2, treated inactive MNV). The variations in size of the cleft and the PED were correlated with nAMD activity.

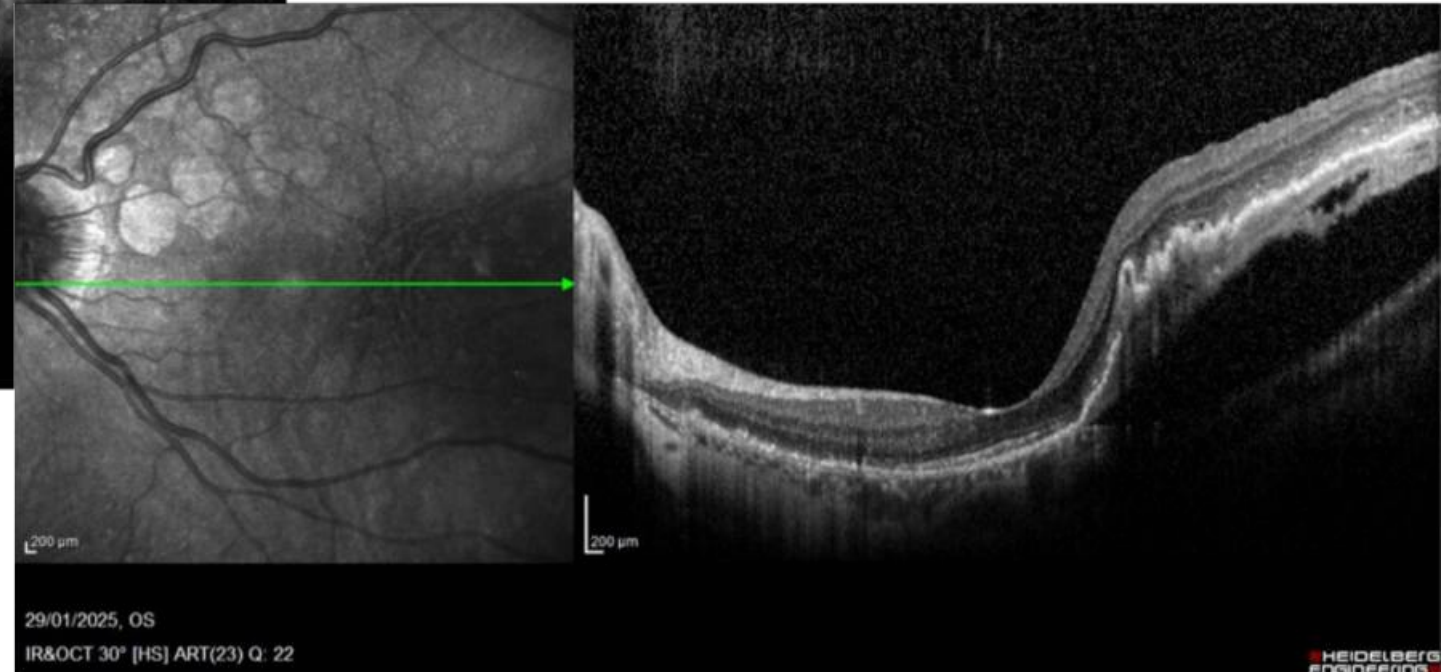
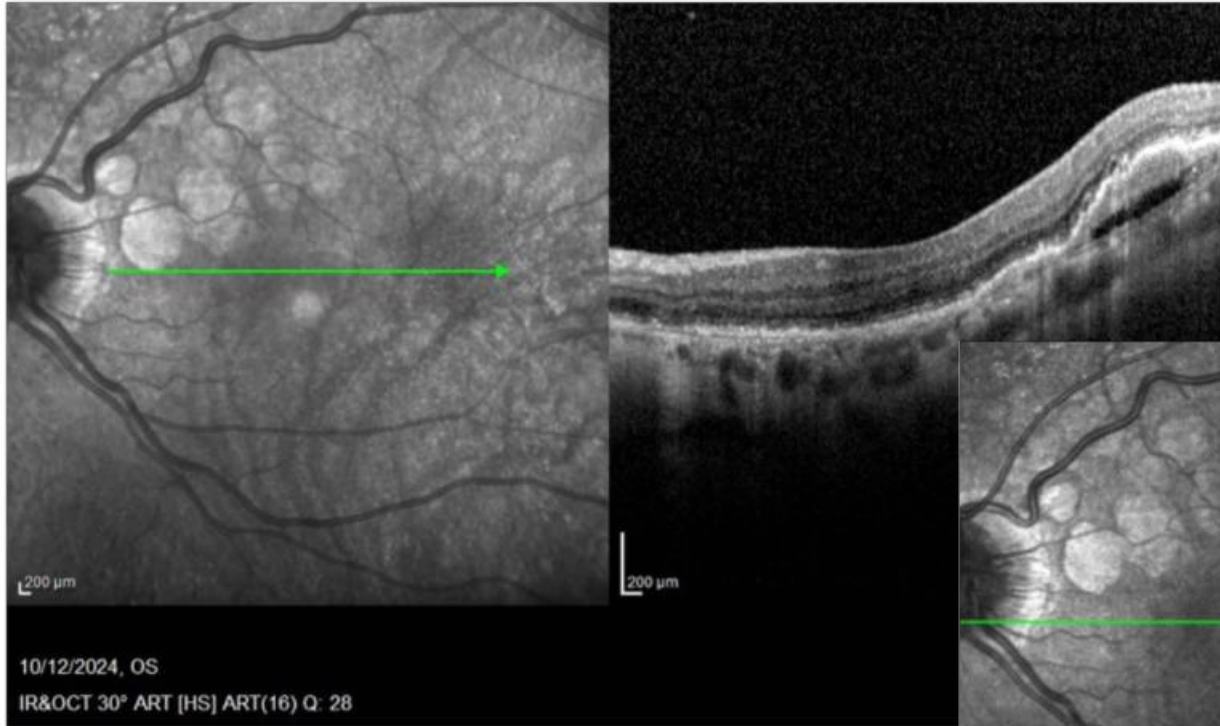
**Results** Twenty-nine eyes from 27 patients were included. The subfoveal measurements showed a significant increase of prechoroidal cleft height and width from T0 to T1 ( $P < 0.05$ ) and a subsequent decrease of the cleft height after treatment with anti-VEGF agents ( $P = 0.004$ ). A similar significant trend was observed for the greatest prechoroidal cleft height and width, obtained assessing the whole OCT raster. In the multivariate analysis, the cleft height was significantly affected by both time ( $P = 0.001$ ) and PED height ( $P < 0.0001$ ). By contrast, the effect of fibrovascular tissue size within the PED was not significant. Visual acuity did not correlate with prechoroidal cleft size.

**Conclusion** Prechoroidal cleft increased in association with MNV reactivation and decreased after treatment. Our results suggest that prechoroidal cleft could represent an accumulation of fluid actively exudating from the MNV and should be considered a sign of nAMD activity.



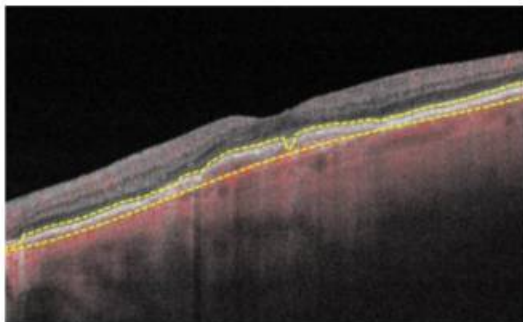
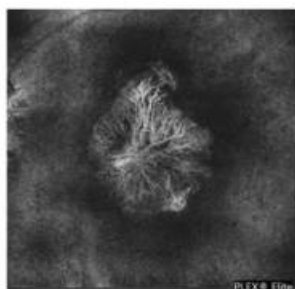
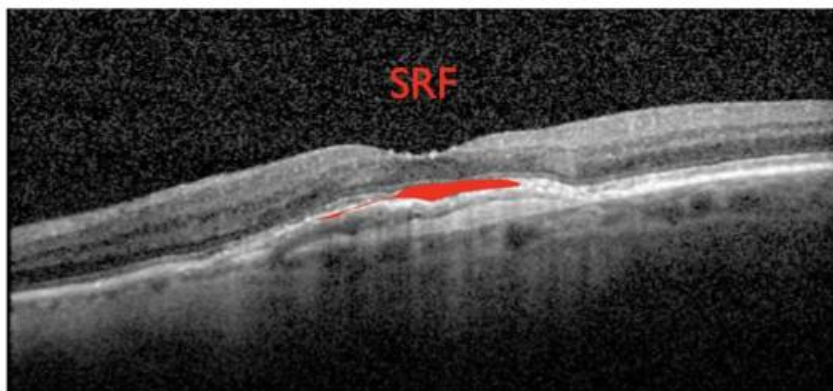
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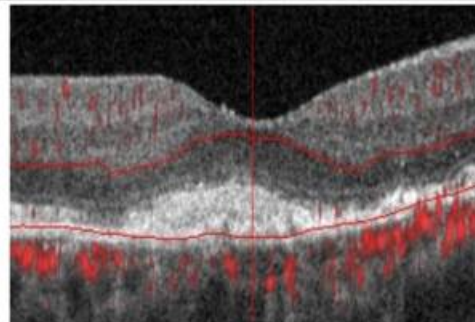
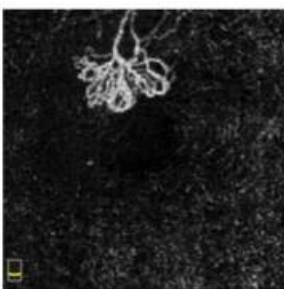
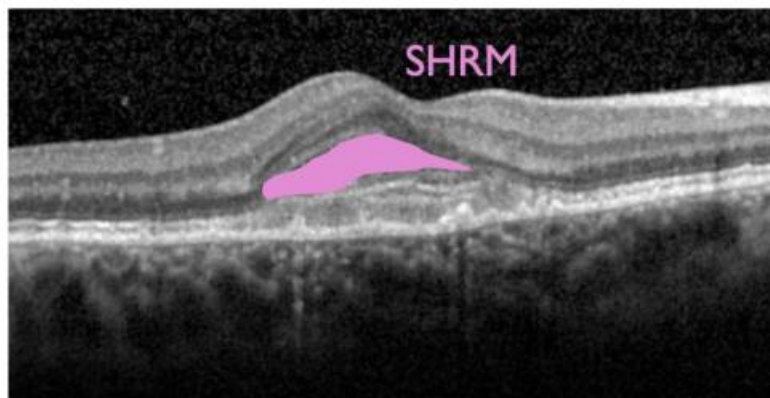


# TYPES OF FLUID IN NEOVASCULAR AMD

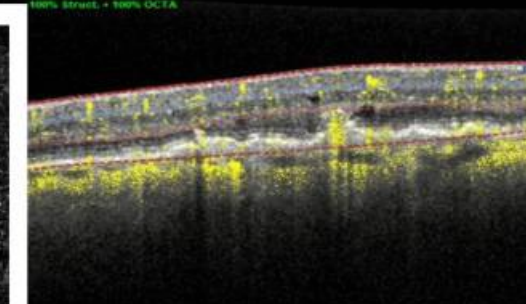
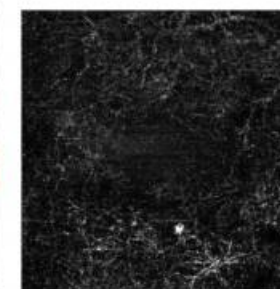
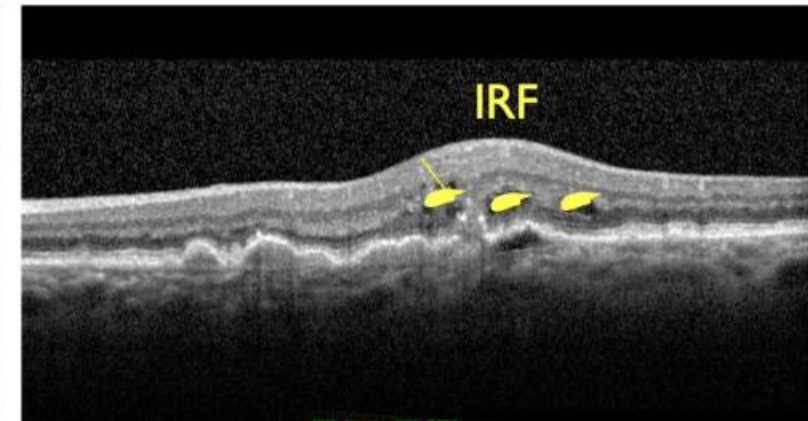
**Type I MNV, PCV**



**Type 2 MNV , Myopic**



**Type 3 MNV**





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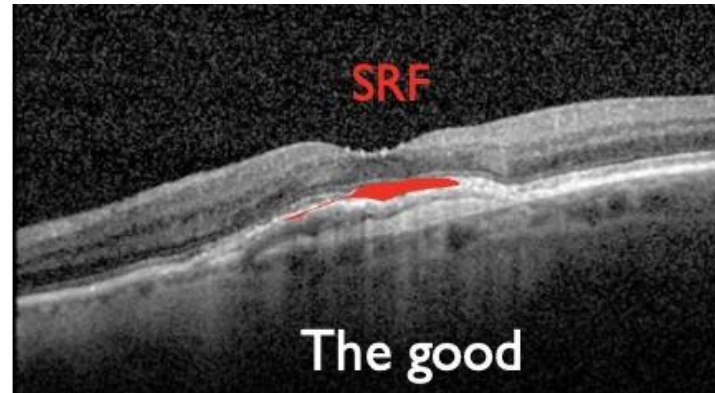
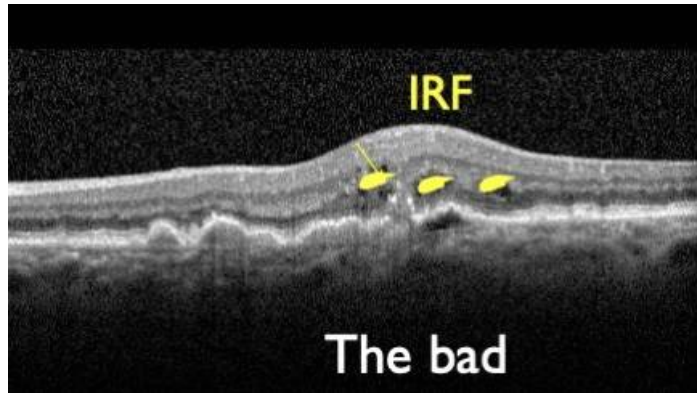


**1. Is the type of fluid related to the prognosis?**

**2. What is the impact of persistent fluid on the patient's VA?**

**3. Are there fluids that should not be treated?**

# FLUID AT PRESENTATION



- The presence of **IRF** is associated with worse VA and poorer outcomes.
- The presence of **SRF** has been identified as a predictive factor for greater visual gains. The 5- year results of the CATT study revealed that eyes without SRF had worse visual outcomes compared to eyes with SRF.
- **EXCITE study**: Patients with baseline SRF achieved comparable visual gains regardless of whether they received monthly or quarterly anti-VEGF therapy injections.

# PERSISTENT FLUID: RANDOMIZED STUDIES



## Predominantly Persistent Intraretinal Fluid in the Comparison of Age-related Macular Degeneration Treatments Trials

Jason Q. Core, BS,<sup>1</sup> Maxwell Pistilli, PhD,<sup>2</sup> Peiyang Hua, MS,<sup>2</sup> Ebenezer Daniel, MBBS, PhD,<sup>2</sup> Juan E. Grunwald, MD,<sup>2</sup> Cynthia A. Toth, MD,<sup>3</sup> Glenn J. Jaffe, MD,<sup>3</sup> Daniel F. Martin, MD,<sup>4</sup> Maureen G. Maguire, PhD,<sup>2</sup> Gui-Shuang Ying, PhD,<sup>2</sup> for the Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group

**Purpose:** To describe predominantly persistent intraretinal fluid (PP-IRF) and its association with visual acuity (VA) and retinal anatomic findings at long-term follow-up in eyes treated with pro re nata (PRN) ranibizumab or bevacizumab for neovascular age-related macular degeneration.

**Design:** Cohort within a randomized clinical trial.

**Participants:** Participants in the Comparison of Age-related Macular Degeneration Treatments Trials (CATT) assigned to PRN treatment.

**Methods:** The presence of intraretinal fluid (IRF) on OCT scans was assessed at baseline and monthly follow-up visits by Duke OCT Reading Center. Predominantly persistent intraretinal fluid through week 12, year 1, and year 2 was defined as the presence of IRF at the baseline and in  $\geq 80\%$  of follow-up visits. Among eyes with baseline IRF, the mean VA scores (letters) and changes from the baseline were compared between eyes with and those without PP-IRF. Adjusted mean VA scores and changes from the baseline were also calculated using the linear regression analysis to account for baseline patient features identified as predictors of VA in previous CATT studies. Furthermore, outcomes were adjusted for concomitant predominantly persistent subretinal fluid.

**Main Outcome Measures:** Predominantly persistent intraretinal fluid through week 12, year 1, and year 2; VA score and VA change; and scar development at year 2.

**Results:** Among 363 eyes with baseline IRF, 108 (29.8%) had PP-IRF through year 1 and 95 (26.1%) had PP-IRF through year 2. When eyes with PP-IRF through year 1 were compared with those without PP-IRF, the mean 1-year VA score was 62.4 and 68.5, respectively ( $P = 0.002$ ), and was 65.0 and 67.4, respectively ( $P = 0.13$ ), after adjustment. Predominantly persistent intraretinal fluid through year 2 was associated with worse adjusted 1-year mean VA scores (64.8 vs. 69.2;  $P = 0.006$ ) and change (4.3 vs. 8.1;  $P = 0.01$ ) as well as worse adjusted 2-year mean VA scores (63.0 vs. 68.3;  $P = 0.004$ ) and changes (2.4 vs. 7.1;  $P = 0.009$ ). Predominantly persistent intraretinal fluid through year 2 was associated with a higher 2-year risk of scar development (adjusted hazard ratio = 1.49;  $P = 0.03$ ).

**Conclusions:** Approximately one quarter of eyes had PP-IRF through year 2. Predominantly persistent intraretinal fluid through year 1 was associated with worse long-term VA, but the relationship disappeared after adjustment for baseline predictors of VA. Predominantly persistent intraretinal fluid through year 2 was independently associated with worse long-term VA and scar development. *Ophthalmology Retina* 2022;6:771-785 © 2022 by the American Academy of Ophthalmology



Supplemental material is available at [www.opthalmologyretina.org](http://www.opthalmologyretina.org).

Randomized clinical trials have demonstrated that intravitreal injections of anti-VEGF agents improve visual acuity (VA) and control the growth and exudation of neovascular lesions. As such, these treatments have been established as the gold standard for the treatment of neovascular age-related macular degeneration (nAMD).<sup>1,2</sup> Intraretinal fluid (IRF), subretinal fluid (SRF), and subretinal pigment epithelium (sub-RPE) fluid are caused by leakage from immature blood vessels into the retinal tissue and indicate

ongoing neovascular activity.<sup>3</sup> The presence of retinal fluid detected using OCT is commonly considered an indication for additional anti-VEGF treatment in as-needed (pro re nata [PRN]) and treat-and-extend regimens.<sup>4</sup>

Among the types of retinal fluid, IRF has been most consistently associated with poor VA and morphologic outcomes.<sup>5-11</sup> Based on data from the Comparison of Age-related Macular Degeneration Treatments Trials (CATT), we previously reported that IRF was present cross-sectionally



## Predominantly Persistent Subretinal Fluid in the Comparison of Age-Related Macular Degeneration Treatments Trials

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**Objective:** To describe predominantly persistent subretinal fluid (SRF) in eyes receiving ranibizumab or bevacizumab for neovascular age-related macular degeneration and to compare visual acuity (VA) to eyes with nonpersistent SRF.

**Design:** Cohort within randomized clinical trial.

**Participants:** Comparison of Age-related Macular Degeneration Treatments Trials patients assigned to pro re nata treatment.

**Methods:** Graders evaluated monthly OCT scans for SRF. Predominantly persistent SRF through week 12 was defined as SRF at baseline and weeks 4, 8, and 12. Predominantly persistent SRF through 1 or 2 years was defined as SRF in 80% or more of visits by years 1 or 2, respectively. Linear regression models including baseline predictors of VA and predominantly persistent intraretinal fluid (IRF) were used to evaluate mean differences in vision outcomes.

**Primary Outcome Measures:** Predominantly persistent SRF through year 1, adjusted VA score and VA change, and foveal SRF thickness.

**Results:** Among 406 eyes with baseline SRF, SRF persisted in 108 eyes (26.6%) through week 12, in 94 eyes (23.2%) through year 1, and in 77 eyes (19.0%) through year 2. Adjusted VA means at year 1 were similar between eyes with predominantly persistent versus nonpersistent SRF by week 12 (68.1 vs. 70.2 letters;  $P = 0.18$ ), year 1 (67.6 vs. 70.2 letters;  $P = 0.11$ ), and year 2 (71.4 vs. 70.9 letters;  $P = 0.78$ ). Adjusted changes in mean VA at year 1 were similar between eyes with predominantly persistent versus nonpersistent SRF by week 12 (6.3 vs. 7.6 letters;  $P = 0.38$ ), year 1 (5.5 vs. 7.8 letters;  $P = 0.14$ ), and year 2 (8.1 vs. 7.7 letters;  $P = 0.78$ ). Among eyes with predominantly persistent SRF through year 1, foveal SRF was absent in 46 eyes (48.9%), thickness was 1 to 200  $\mu$ m in 48 eyes (50.0%) and more than 200  $\mu$ m in 1 eye (1.1%) at year 1.

**Conclusions:** Eyes with predominantly persistent and nonpersistent SRF through week 12, year 1, or year 2 showed similar VA outcomes after adjustment for baseline covariates and persistent IRF. At the foveal center, predominantly persistent SRF was most commonly absent or present in small quantities. *Ophthalmology Retina* 2021;5:962-974 © 2021 by the American Academy of Ophthalmology



Supplemental material available at [www.opthalmologyretina.org](http://www.opthalmologyretina.org).

Neovascular age-related macular degeneration (nAMD) involves the formation of immature, leakage-prone blood vessels with fluid accumulation within or below the retina, often resulting in reduced visual acuity (VA) through incompletely characterized mechanisms.<sup>1,2</sup> Intravitreal injections of anti-vascular endothelial growth factor (VEGF) agents are highly effective for improving and preserving VA and are the current standard of care.<sup>3-8</sup> Most treatment approaches are guided by the presence of fluid on OCT to identify ongoing neovascular activity.<sup>9,10</sup> Almost all large-scale clinical trials evaluating the efficacy of anti-VEGF therapies have used a zero-tolerance approach to fluid, with any amount of subretinal fluid (SRF) or intraretinal

fluid (IRF), and in some cases sub-retinal pigment epithelium (RPE) fluid, serving as an indication for re-treatment.<sup>5,11-13</sup>

Recent studies found SRF at both baseline and long-term follow-up visits to be predictors of better long-term VA outcomes,<sup>14-16</sup> challenging the assumption that any fluid in the context of nAMD is detrimental to vision. It is important to understand the functional consequences of fluid that persists despite aggressive anti-VEGF therapy to determine whether treatment modification should be sought to eliminate fluid and preserve vision. To accomplish this, SRF presence and its effect on VA must be examined not only cross-sectionally as previously described but also



## Impact of Intra- and Subretinal Fluid on Vision Based on Volume Quantification in the HARBOR Trial

Sophie Riedl, MD, Wolf-Dieter Vogl, PhD, Sebastian M. Waldstein, MD, PhD, Ursula Schmidt-Erfurth, MD, Hrvoje Bogunović, PhD

**Purpose:** To investigate the functional associations of intraretinal fluid (IRF) and subretinal fluid (SRF) volumes at baseline and after the loading dose as well as fluid change after the first injection with best-corrected visual acuity (BCVA) in patients with neovascular age-related macular degeneration (nAMD) who received an anti-VEGF treatment over 24 months.

**Design:** Post hoc analysis of a phase III, randomized, multicenter trial in which ranibizumab was administered monthly or in a pro re nata regimen (HARBOR).

**Participants:** Study eyes of 1094 treatment-naïve patients with nAMD.

**Methods:** IRF and SRF volumes were segmented automatically on monthly spectral domain OCT images. Fluid volumes and changes thereof were included as covariates into longitudinal mixed-effects models, which modeled BCVA trajectories.

**Main Outcome Measures:** BCVA estimates corresponding to baseline, follow-up, and persistent IRF/SRF volumes after the loading dose; BCVA estimates of change in fluid volumes after the first injection; and marginal and conditional  $R^2$ .

**Results:** Analysis of 22 494 volumetric scans revealed that foveal IRF consistently shows a negative correlation with BCVA at baseline and subsequent visits ( $-3.23$  and  $-4.32$  letters/100 nL, respectively). After the first injection, BCVA increased by  $+2.13$  letters/100 nL decrease in foveal IRF. Persistent IRF was associated with lower baseline BCVA and less improvement. Foveal SRF correlated with better BCVA at baseline and subsequent visits ( $+6.52$  and  $+1.42$  letters/100 nL, respectively). After the first injection, SRF decrease was associated with significant vision gain ( $+5.88$  letters/100 nL). Foveal fluid correlated more with BCVA than parafoveal IRF/SRF.

**Conclusions:** Although IRF consistently correlates with decreased function and recovery throughout therapy, SRF is associated with a more pronounced functional improvement. Moreover, SRF resolution provides increased benefit. Fluid-function correlation represents an essential base for the development of personalized treatment regimens, optimizing functional outcomes, and reducing treatment burden. *Ophthalmology Retina* 2022;6:291-297 © 2021 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).



Supplemental material available at [www.opthalmologyretina.org](http://www.opthalmologyretina.org).

Artificial intelligence (AI)-based analysis of OCT images has become a promising perspective in the field of retinal diseases, improving knowledge on disease activity, and therapeutic strategies.<sup>1</sup> In neovascular age-related macular degeneration (nAMD), exudative fluid, identifiable on OCT, represents the morphologic hallmark. After the introduction of AI-based methods in ophthalmic research, automated quantification of fluid volumes has accelerated scientific progress and is expected to replace manual evaluation in large-scale image-based analyses.<sup>2-4</sup> Once patients have received their loading dose, flexible treatment decisions, such as pro re nata and treat-and-extend protocols, are largely based on the identification of retinal fluid as the indicator of disease activity.<sup>5,6</sup>

Numerous investigations of intraretinal fluid (IRF) and subretinal fluid (SRF) have shown distinct functional implications in various analyses by determining fluid presence or absence without including precise quantitative measurements. So far, there has been no correlation of automatically measured fluid volumes with function in nAMD.

Although detrimental effects on visual acuity have been attributed to IRF, several reports suggest that the presence of SRF corresponds to preserved visual acuity.<sup>7-9</sup> Investigations correlating objective quantitative fluid measurements with best-corrected visual acuity (BCVA) are required to provide robust conclusions, which can contribute toward establishing reliable guidelines for more efficient patient management in nAMD. In this analysis, we



# PERSISTENT IRF

Post hoc analysis of the CATT study , 365 eyes with nAMD. (2022)

- **Persistent IRF up to 12 weeks:** higher risk of long-term IRF persistence and more rapid recurrences.
- **Persistent IRF up to one year:** worse functional prognosis compared to eyes without PP-IRF, but not an independent risk factor for worse visual outcomes.
- **Persistent IRF up to two years:** independent risk factor for worse long-term visual outcomes and an increased risk of scar development.



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**Main Outcome Measures:** Predominantly persistent intraretinal fluid through week 12, year 1, and year 2; VA score and VA change; and scar development at year 2.

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**Conclusions:** Approximately one quarter of eyes had PP-IRF through year 2. Predominantly persistent intraretinal fluid through year 1 was associated with worse long-term VA, but the relationship disappeared after adjustment for baseline predictors of VA. Predominantly persistent intraretinal fluid through year 2 was independently associated with worse long-term VA and scar development. *Ophthalmology Retina* 2022;6:771-785 © 2022 by the American Academy of Ophthalmology



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# PERSISTENT SRF

Post hoc analysis of the CATT study , 359 eyes with nAMD. (2021)

- **Persistent SRF up to 12 weeks:** faster average recurrence time (8 weeks).
- **Persistent SRF up to one year:** no impact on visual functional outcomes.
- **Persistent SRF up to two years:** no impact on visual functional outcomes and lower risk of atrophy (protective barrier between the outer segments of photoreceptors and pathological RPE).



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**Methods:** Graders evaluated monthly OCT scans for SRF. Predominantly persistent SRF through week 12 was defined as SRF at baseline and weeks 4, 8, and 12. Predominantly persistent SRF through 1 or 2 years was defined as SRF in 80% or more of visits by years 1 or 2, respectively. Linear regression models including baseline predictors of VA and predominantly persistent intraretinal fluid (IRF) were used to evaluate mean differences in vision outcomes.

**Primary Outcome Measures:** Predominantly persistent SRF through year 1, adjusted VA score and VA change, and foveal SRF thickness.

**Results:** Among 406 eyes with baseline SRF, SRF persisted in 108 eyes (26.6%) through week 12, in 94 eyes (23.2%) through year 1, and in 77 eyes (19.0%) through year 2. Adjusted VA means at year 1 were similar between eyes with predominantly persistent versus nonpersistent SRF by week 12 (68.1 vs. 70.2 letters;  $P = 0.18$ ), year 1 (67.6 vs. 70.2 letters;  $P = 0.11$ ), and year 2 (71.4 vs. 70.9 letters;  $P = 0.78$ ). Adjusted changes in mean VA at year 1 were similar between eyes with predominantly persistent versus nonpersistent SRF by week 12 (6.3 vs. 7.6 letters;  $P = 0.38$ ), year 1 (5.5 vs. 7.8 letters;  $P = 0.14$ ), and year 2 (8.1 vs. 7.7 letters;  $P = 0.78$ ). Among eyes with predominantly persistent SRF through year 1, foveal SRF was absent in 46 eyes (48.9%), thickness was 1 to 200  $\mu\text{m}$  in 48 eyes (50.0%) and more than 200  $\mu\text{m}$  in 1 eye (1.1%) at year 1.

**Conclusions:** Eyes with predominantly persistent and nonpersistent SRF through week 12, year 1, or year 2 showed similar VA outcomes after adjustment for baseline covariates and persistent IRF. At the foveal center, predominantly persistent SRF was most commonly absent or present in small quantities. *Ophthalmology Retina* 2021;5:962-974 © 2021 by the American Academy of Ophthalmology



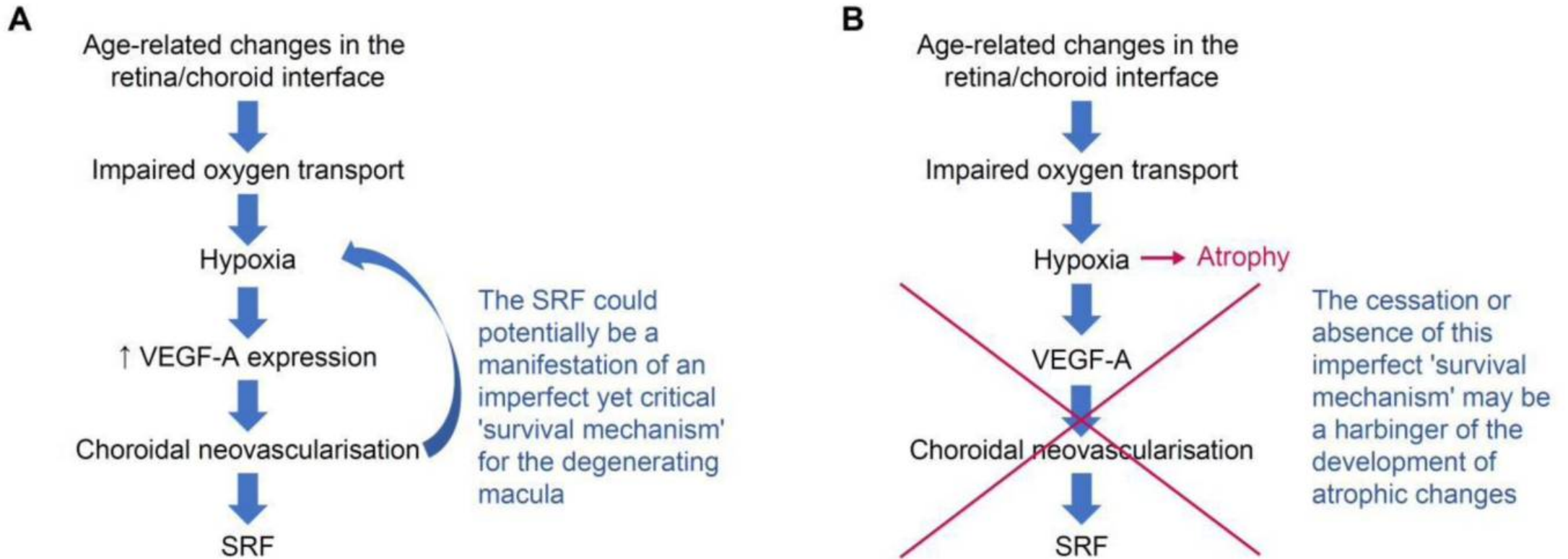
Supplemental material available at [www.ophtalmologyretina.org](http://www.ophtalmologyretina.org).

Neovascular age-related macular degeneration (nAMD) involves the formation of immature, leakage-prone blood vessels with fluid accumulation within or below the retina, often resulting in reduced visual acuity (VA) through incompletely characterized mechanisms.<sup>1,2,4</sup> Intravitreal injections of anti-vascular endothelial growth factor (VEGF) agents are highly effective for improving and preserving VA and are the current standard of care.<sup>3-8</sup> Most treatment approaches are guided by the presence of fluid on OCT to identify ongoing neovascular activity.<sup>5,10</sup> Almost all large-scale clinical trials evaluating the efficacy of anti-VEGF therapies have used a zero-tolerance approach to fluid, with any amount of subretinal fluid (SRF) or intraretinal

fluid (IRF), and in some cases sub-retinal pigment epithelium (RPE) fluid, serving as an indication for re-treatment.<sup>3,5,11-13</sup>

Recent studies found SRF at both baseline and long-term follow-up visits to be predictors of better long-term VA outcomes,<sup>14-18</sup> challenging the assumption that any fluid in the context of nAMD is detrimental to vision. It is important to understand the functional consequences of fluid that persists despite aggressive anti-VEGF therapy to determine whether treatment modification should be sought to eliminate fluid and preserve vision. To accomplish this, SRF presence and its effect on VA must be examined not only cross-sectionally as previously described but also

# PERSISTENT SRF AND MACULAR ATROPHY





# IRF AND SRF QUANTIFICATION

HARBOR study, 1094 eyes with nAMD (2022)

- **Foveal IRF** consistently shows a negative correlation with BCVA at baseline and subsequent visits.
- **Foveal SRF** correlated with better BCVA at baseline and subsequent visits

IRF is associated with more permanent damage to the neurosensory tissue compared to SRF.



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## Impact of Intra- and Subretinal Fluid on Vision Based on Volume Quantification in the HARBOR Trial

Sophie Riedl, MD, Wolf-Dieter Vogl, PhD, Sebastian M. Waldstein, MD, PhD, Ursula Schmidt-Erfurth, MD, Hrvoje Bogunović, PhD

**Purpose:** To investigate the functional associations of intraretinal fluid (IRF) and subretinal fluid (SRF) volumes at baseline and after the loading dose as well as fluid change after the first injection with best-corrected visual acuity (BCVA) in patients with neovascular age-related macular degeneration (nAMD) who received an anti-VEGF treatment over 24 months.

**Design:** Post hoc analysis of a phase III, randomized, multicenter trial in which ranibizumab was administered monthly or in a pro re nata regimen (HARBOR).

**Participants:** Study eyes of 1094 treatment-naïve patients with nAMD.

**Methods:** IRF and SRF volumes were segmented automatically on monthly spectral domain OCT images. Fluid volumes and changes thereof were included as covariates into longitudinal mixed-effects models, which modeled BCVA trajectories.

**Main Outcome Measures:** BCVA estimates corresponding to baseline, follow-up, and persistent IRF/SRF volumes after the loading dose; BCVA estimates of change in fluid volumes after the first injection; and marginal and conditional R<sup>2</sup>.

**Results:** Analysis of 22 494 volumetric scans revealed that foveal IRF consistently shows a negative correlation with BCVA at baseline and subsequent visits (−3.23 and −4.32 letters/100 nL, respectively). After the first injection, BCVA increased by +2.13 letters/100 nL, decrease in foveal IRF. Persistent IRF was associated with lower baseline BCVA and less improvement. Foveal SRF correlated with better BCVA at baseline and subsequent visits (+6.52 and +1.42 letters/100 nL, respectively). After the first injection, SRF decrease was associated with significant vision gain (+5.88 letters/100 nL). Foveal fluid correlated more with BCVA than parafoveal IRF/SRF.

**Conclusions:** Although IRF consistently correlates with decreased function and recovery throughout therapy, SRF is associated with a more pronounced functional improvement. Moreover, SRF resolution provides increased benefit. Fluid-function correlation represents an essential base for the development of personalized treatment regimens, optimizing functional outcomes, and reducing treatment burden. *Ophthalmology Retina* 2022;6:291-297 © 2021 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).



Supplemental material available at [www.ophtalmologyretina.org](http://www.ophtalmologyretina.org).

Artificial intelligence (AI)—based analysis of OCT images has become a promising perspective in the field of retinal diseases, improving knowledge on disease activity, and therapeutic strategies.<sup>1</sup> In neovascular age-related macular degeneration (nAMD), exudative fluid, identifiable on OCT, represents the morphologic hallmark. After the introduction of AI-based methods in ophthalmic research, automated quantification of fluid volumes has accelerated scientific progress and is expected to replace manual evaluation in large-scale image-based analyses.<sup>2-4</sup> Once patients have received their loading dose, flexible treatment decisions, such as pro re nata and treat-and-extend protocols, are largely based on the identification of retinal fluid as the indicator of disease activity.<sup>5,6</sup>

Numerous investigations of intraretinal fluid (IRF) and subretinal fluid (SRF) have shown distinct functional implications in various analyses by determining fluid presence or absence without including precise quantitative measurements. So far, there has been no correlation of automatically measured fluid volumes with function in nAMD.

Although detrimental effects on visual acuity have been attributed to IRF, several reports suggest that the presence of SRF corresponds to preserved visual acuity.<sup>7-9</sup> Investigations correlating objective quantitative fluid measurements with best-corrected visual acuity (BCVA) are required to provide robust conclusions, which can contribute toward establishing reliable guidelines for more efficient patient management in nAMD. In this analysis, we

# PERSISTENT BALAD



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## Long-Term Outcomes of Bacillary Layer Detachment in Neovascular Age-Related Macular Degeneration

Prithvi Ramtohul, MD,<sup>1</sup> Ariane Malclès, MD,<sup>2</sup> Edward Gigon, MD,<sup>2</sup> K. Bailey Freund, MD,<sup>3,4</sup> Ugo Intorini, MD,<sup>5</sup> Francesco Bandello, MD, PhD,<sup>5,6</sup> Maria Vittoria Cicinelli, MD<sup>5,6</sup>

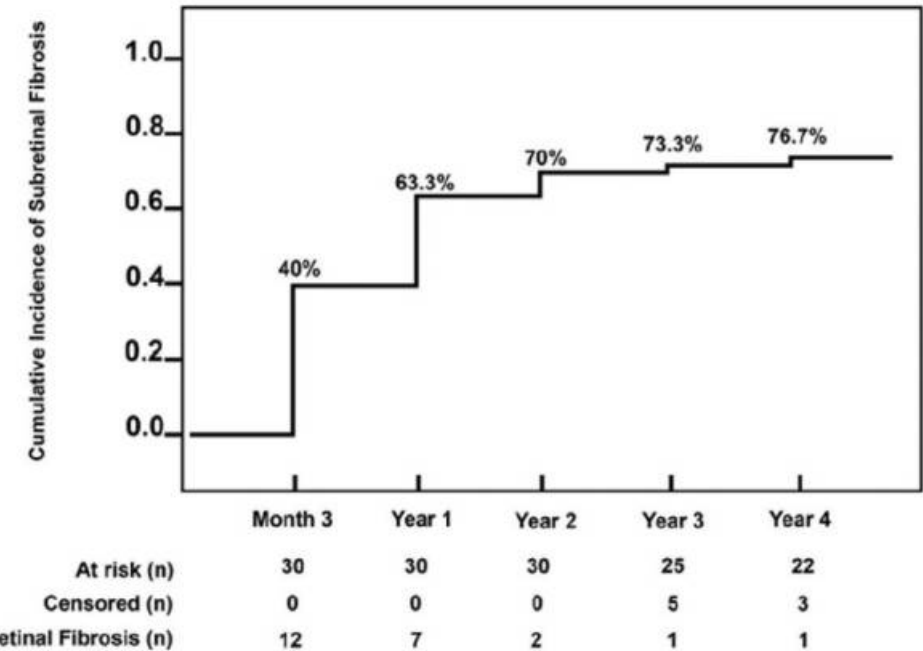
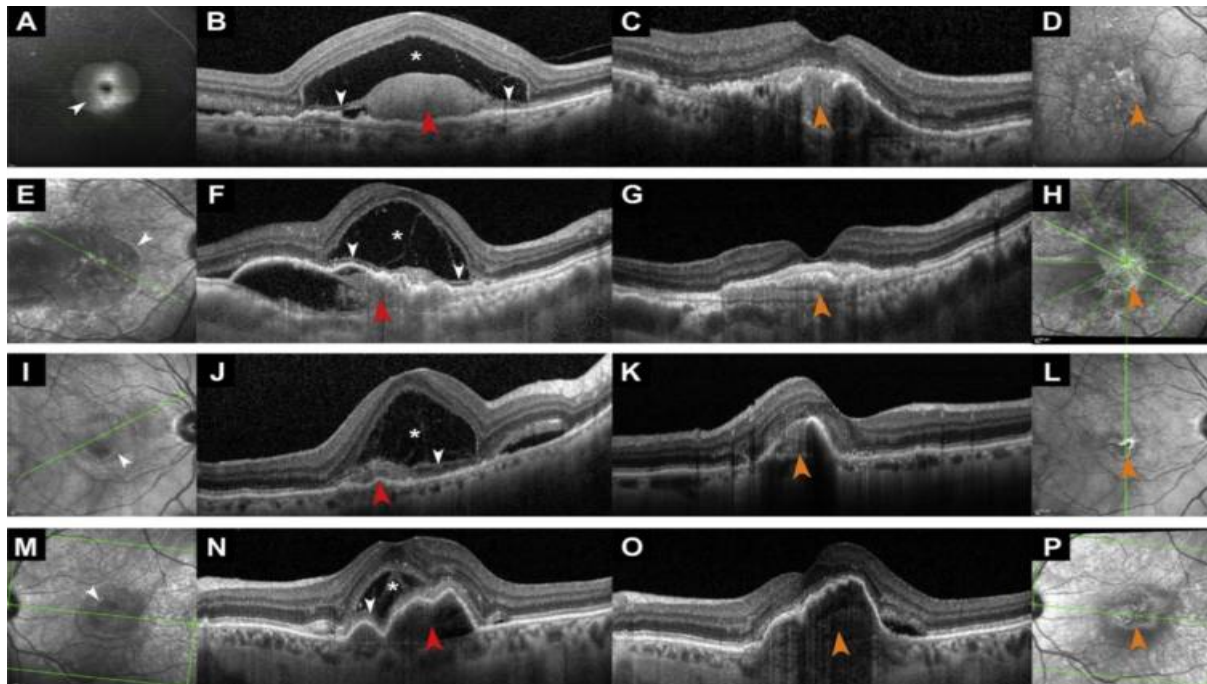
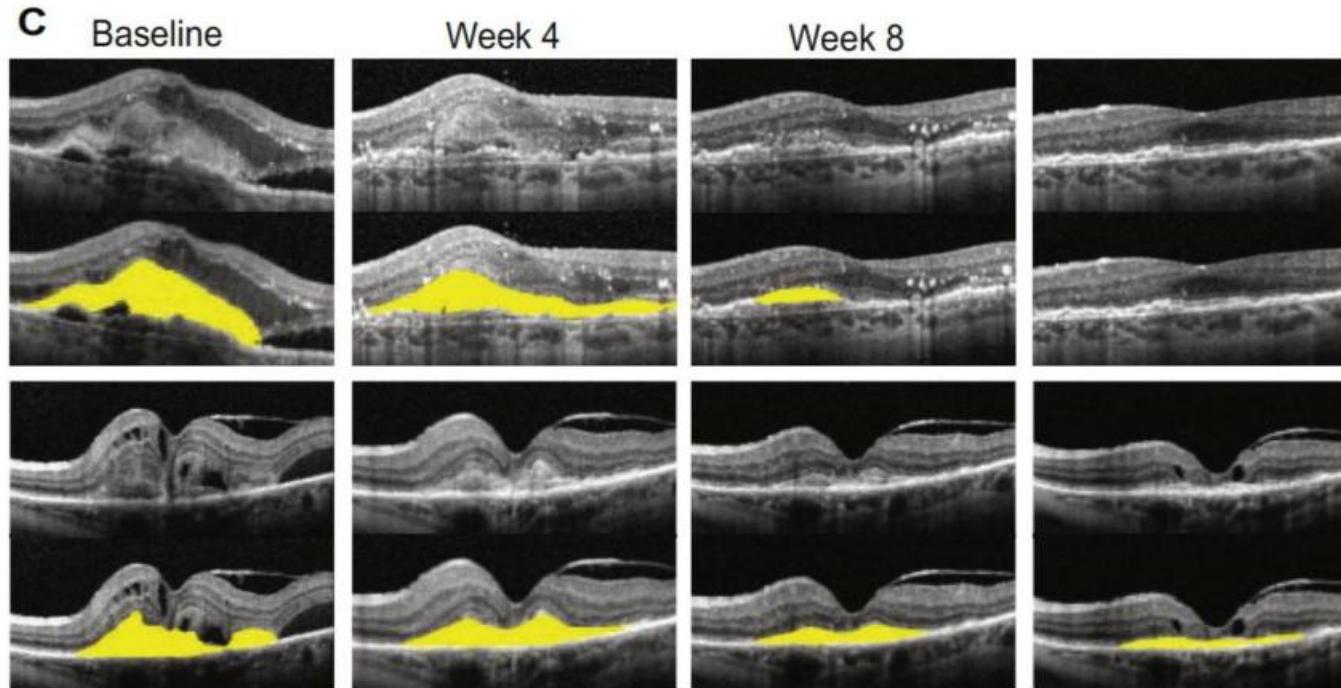


Figure 5. Kaplan–Meier graph showing the cumulative incidence of subretinal fibrosis through 4 years.

The cumulative risk of **subretinal fibrosis** was **77% at 4 years**.



# PERSISTENT SHRM / SHE



Significant negative correlation between SHRM volume and visual acuity within the first year.



## Longitudinal Assessment of Ellipsoid Zone Integrity, Subretinal Hyperreflective Material, and Subretinal Pigment Epithelium Disease in Neovascular Age-Related Macular Degeneration

Justis P. Ehlers, MD,<sup>1,2</sup> Robert Zahid, PharmD, MBA,<sup>3</sup> Peter K. Kaiser, MD,<sup>2</sup> Jeffrey S. Heier, MD,<sup>4</sup> David M. Brown, MD,<sup>5</sup> Xiangyi Meng, PhD,<sup>2</sup> Jamie Reese, BSN,<sup>2</sup> Thuy K. Le, BA,<sup>1,2</sup> Leina Lunasco,<sup>1,2</sup> Ming Hu, PhD,<sup>1,6</sup> Sunil K. Srivastava, MD<sup>1,2</sup>

**Purpose:** To assess longitudinally the effect of anti-vascular endothelial growth factor (VEGF) treatment on ellipsoid zone (EZ) integrity, subretinal hyperreflective material (SHRM), and the sub-retinal pigment epithelium (sub-RPE) compartment in eyes with neovascular age-related macular degeneration (AMD).

**Correlation between Subretinal Hyperreflective Material Metrics and Best-Corrected Visual Acuity.** The correlations between each of the SHRM metrics and BCVA for each study visit are shown in Figure 2. A significant negative correlation was found between SHRM volume and BCVA at baseline and most subsequent study visits ( $P < 0.05$ , excluding weeks 20, 24, 40, and 56). Also a significant negative correlation was found between SHRM CST and BCVA at baseline and weeks 4, 8, 28, and 32 ( $P < 0.05$ ). The significant correlations were weak to moderate for both SHRM volume ( $0.40 \leq r \leq 0.62$ ) and SHRM CST ( $0.38 \leq r \leq 0.59$ ).

Change in BCVA from baseline to week 56 showed a significant weak correlation with change in SHRM volume from baseline to week 56 ( $r = 0.44$ ;  $P = 0.02$ ) and from baseline to week 4 ( $r = 0.41$ ;  $P = 0.04$ ), suggesting that greater decrease in SHRM volume was associated weakly with greater increase in BCVA. Change in BCVA from baseline to week 56 was not correlated significantly with change in SHRM CST from baseline to week 56 ( $r = 0.32$ ;  $P = 0.10$ ) or from baseline to week 4 ( $r = 0.36$ ;  $P = 0.07$ ).



# THE ROLE OF FLUID IN NEOVASCULAR AMD

1. Is the type of fluid related to the prognosis?

2. What is the impact of persistent fluid on the patient's VA?



- **The Good** : SRF (exudative and probably degenerative pathway)
- **The Bad** : IRF
- **The Ugly** : both SHRM/BALAD ending in fibrotic scars

# ROLE OF FLUID IN NEOVASCULAR AMD

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**3. Are there fluids that should not be treated?**



# ROLE OF FLUID IN NEOVASCULAR AMD

Practice Guideline > Ophthalmology. 2020 Jan;127(1):P1-P65.

doi: 10.1016/j.ophtha.2019.09.024. Epub 2019 Sep 25.

## Age-Related Macular Degeneration Preferred Practice Pattern®

Christina J Flaxel<sup>1</sup>, Ron A Adelman<sup>2</sup>, Steven T Bailey<sup>1</sup>, Amani Fawzi<sup>3</sup>, Jennifer I Lim<sup>4</sup>, G Atma Vemulakonda<sup>5</sup>, Gui-Shuang Ying<sup>6</sup>

Review > Br J Ophthalmol. 2014 Sep;98(9):1144-67. doi: 10.1136/bjophthalmol-2014-305702.

## Guidelines for the management of neovascular age-related macular degeneration by the European Society of Retina Specialists (EURETINA)

Ursula Schmidt-Erfurth<sup>1</sup>, Victor Chong<sup>2</sup>, Anat Loewenstein<sup>3</sup>, Michael Larsen<sup>4</sup>, Eric Souied<sup>5</sup>, Reinier Schlingemann<sup>6</sup>, Bora Eldem<sup>7</sup>, Jordi Monés<sup>8</sup>, Gisbert Richard<sup>9</sup>, Francesco Bandello<sup>10</sup>, European Society of Retina Specialists

Editorial > Eye (Lond). 2022 Nov;36(11):2078-2083. doi: 10.1038/s41433-022-02095-2.

Epub 2022 May 27.

## The Royal College of Ophthalmologists Commissioning guidelines on age macular degeneration: executive summary

Shruti Chandra<sup>1</sup>, Martin McKibbin<sup>2</sup>, Sajjad Mahmood<sup>3</sup>, Louise Downey<sup>4</sup>, Beth Barnes<sup>5</sup>, Sobha Sivaprasad<sup>6</sup>; AMD Commissioning Guidance Development Group

The **presence of fluid** on OCT is considered an indication of active disease, and thus a new treatment is recommended whenever fluid is detected.



# ROLE OF FLUID IN NEOVASCULAR AMD

**CATT study**  
**HARBOR study**

**FLUID study**

Randomized Controlled Trial > N Engl J Med. 2011 May 19;364(20):1897-908.  
doi: 10.1056/NEJMoa1102673. Epub 2011 Apr 28.

**Ranibizumab and bevacizumab for neovascular age-related macular degeneration**

CATT Research Group; Daniel F Martin, Maureen G Maguire, Glenn J Jaffe

Clinical Trial > Ophthalmology. 2013 May;120(5):1046-56. doi: 10.1016/j.ophtha.2012.10.014. Epub 2013 Jan 23.

**Twelve-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration**

Brandon G Busbee<sup>1</sup>, Allen C Ho, David M Brown, Jeffrey S Heier, Ivan J Sufer, Zhengrong Li, Roman G Rubio, Phillip Lai; HARBOR Study Group

Collaborators, Affiliations + expand  
PMID: 23352196 DOI: 10.1016/j.ophtha.2012.10.014

OCT evidence of **fluid in any compartment**:  
a criterion for retreatment.

Clinical Trial > BMC Ophthalmol. 2016 Mar 24;16:31. doi: 10.1186/s12886-016-0207-3.

**The role of sub-retinal fluid in determining treatment outcomes in patients with neovascular age-related macular degeneration--a phase IV randomised clinical trial with ranibizumab: the FLUID study**

Jennifer J Arnold<sup>1</sup>, Caroline M Markey<sup>2</sup>, Nicol P Kura

Clinical Trial > Ophthalmology. 2019 May;126(5):723-734. doi: 10.1016/j.ophtha.2018.11.025. Epub 2018 Nov 29.

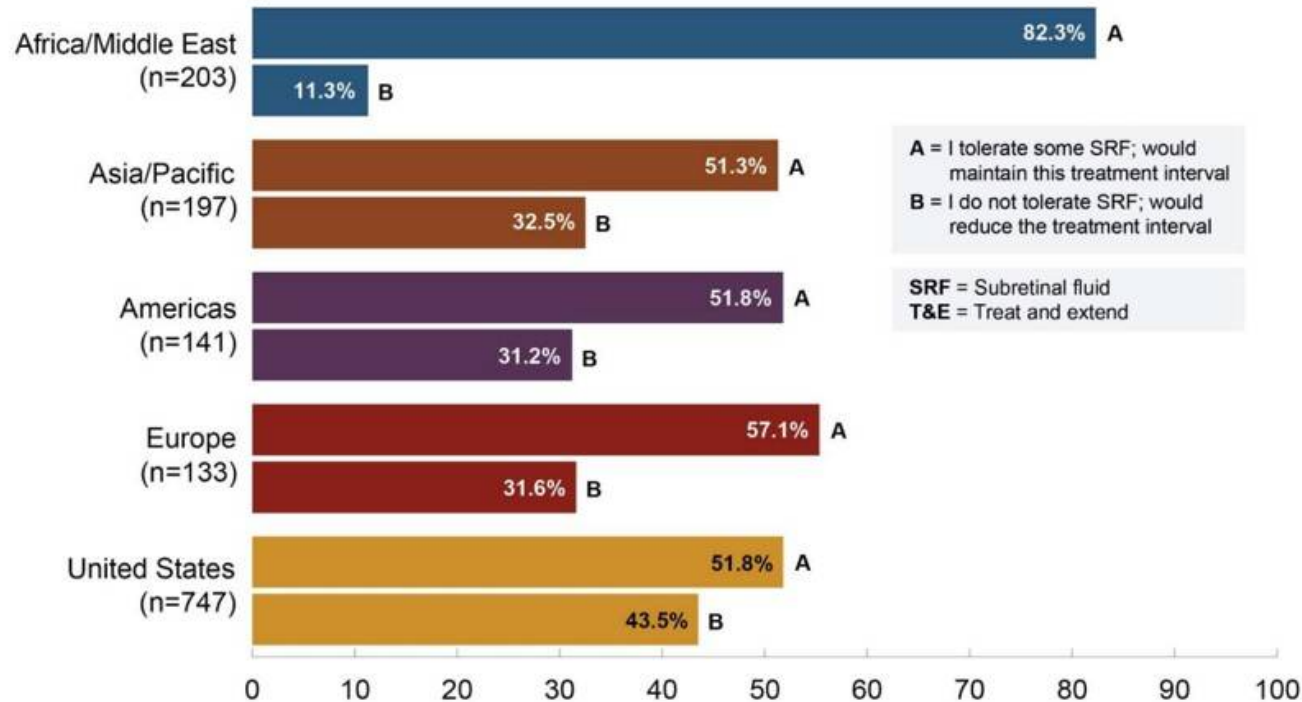
**Tolerating Subretinal Fluid in Neovascular Age-Related Macular Degeneration Treated with Ranibizumab Using a Treat-and-Extend Regimen: FLUID Study 24-Month Results**

Robyn H Guymer<sup>1</sup>, Caroline M Markey<sup>2</sup>, Ian L McAllister<sup>3</sup>, Mark C Gillies<sup>4</sup>, Alex P Hunyor<sup>5</sup>, Jennifer J Arnold<sup>6</sup>; FLUID Investigators

**Tolerant approach** towards small amounts of **SRF** residual (up to 200 µm subfoveal). "Relaxed' Treat & Extend regimen."

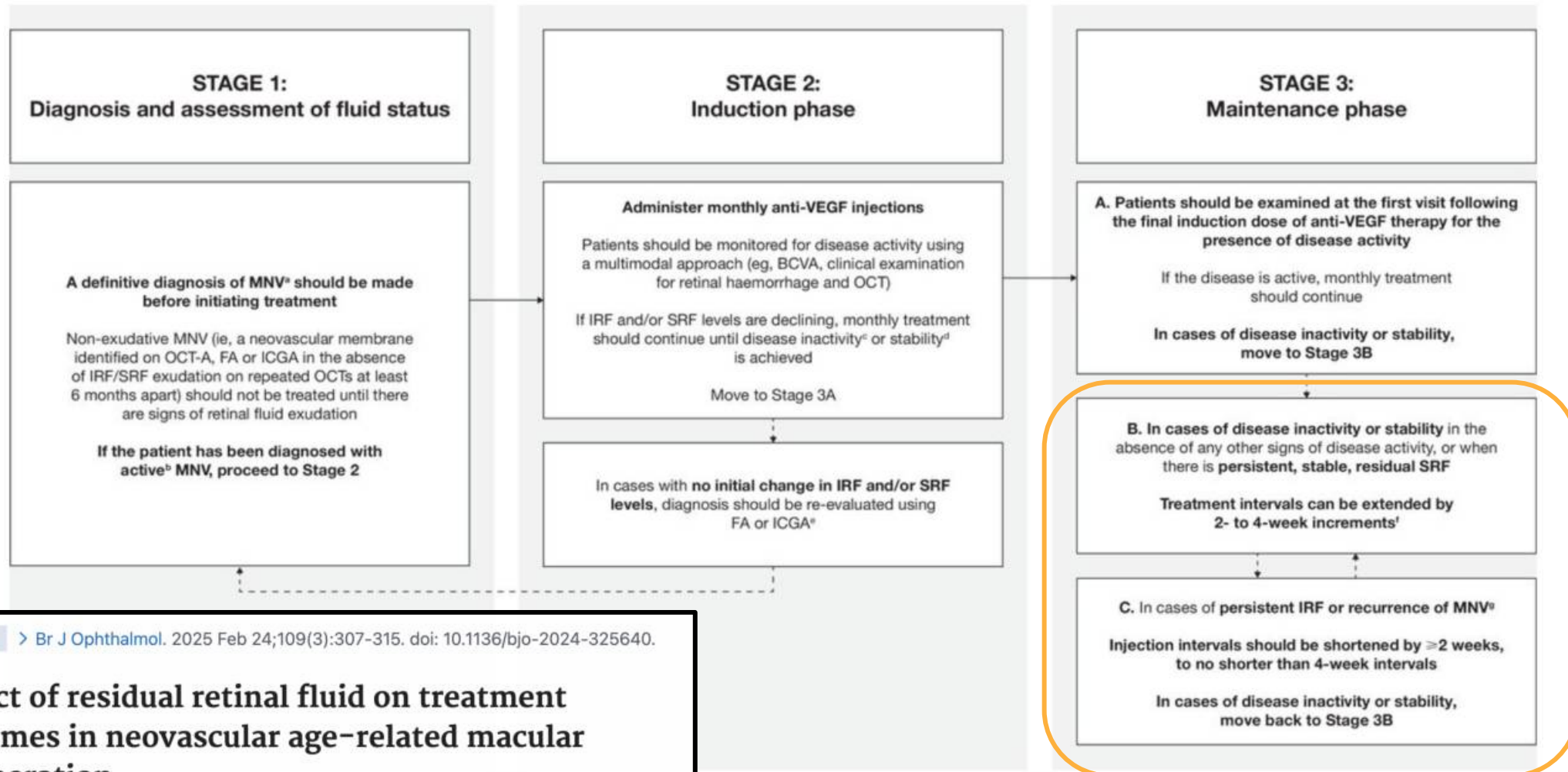
# TREATMENT IN NEOVASCULAR AMD

**How much recurrent extrafoveal SRF would you tolerate in a recently diagnosed wet-AMD patient on a T&E protocol?**



→ More than 50% would have tolerated a small amount of extrafoveal SRF and maintained the treatment intervals.

# TREATMENT IN NEOVASCULAR AMD



Review > Br J Ophthalmol. 2025 Feb 24;109(3):307-315. doi: 10.1136/bjo-2024-325640.

## Impact of residual retinal fluid on treatment outcomes in neovascular age-related macular degeneration

Dinah Zur <sup>1</sup>, Robyn Guymer <sup>2</sup>, Jean-François Korobelnik <sup>3 4</sup>, Lihteh Wu <sup>5</sup>, Francesco Viola <sup>6 7</sup>,



# TREATMENT IN NEOVASCULAR AMD

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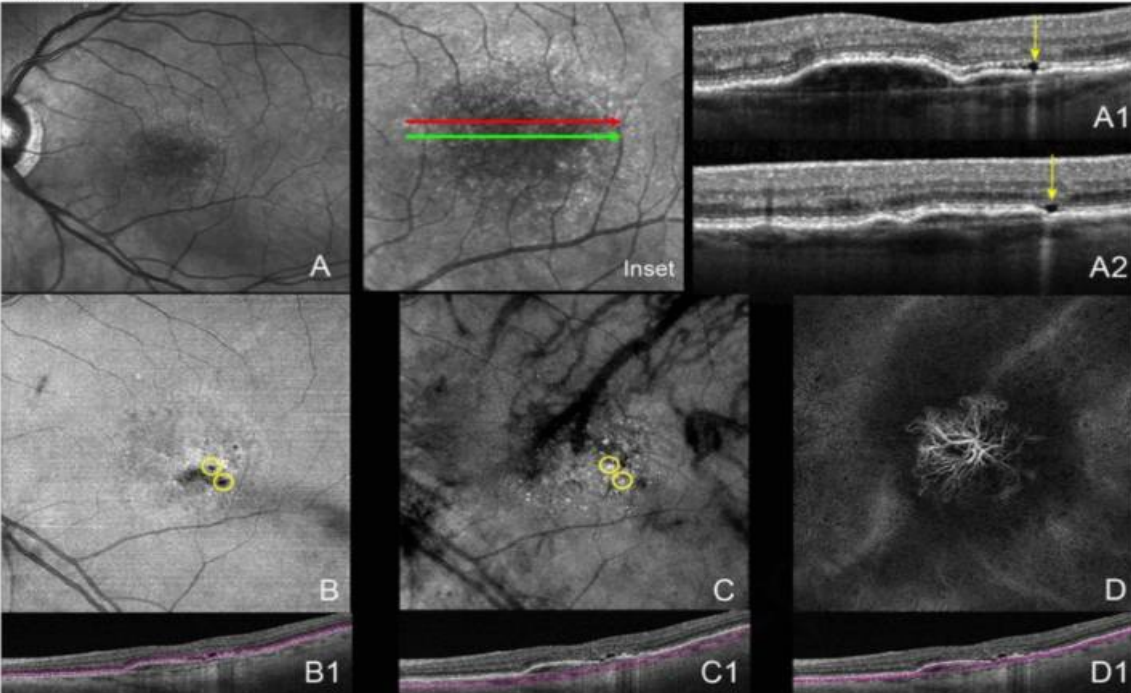
**.....HOWEVER, HYPOREFLECTIVE SPACES ARE NOT ALWAYS INDICATIVE OF FLUID ACCUMULATION DUE TO ACTIVE NEOVASCULAR AMD (nAMD).**

# SUBRETINAL LIPID GLOBULE ( SLG)

Hyporeflective round lesions ranging in size from 31 to 157  $\mu\text{m}$ , located between the ellipsoid zone and the retinal pigment epithelium/Bruch's membrane complex. They exhibit a characteristic hypertransmission tail.

## Multimodal imaging features and clinical relevance of subretinal lipid globules.

Pedro Fernández-Avellaneda, K. Bailey Freund, Ruikang K. Wang, Qinghua He, Qinqin Zhang, Serena Fragiotta, Xiaoyu Xu, Gerardo Ledesma-Gil, Yoshimi Sugiura, Mark P. Breazzano, Lawrence A. Yannuzzi, Sandra Liakopoulos, David Sarraf, Rosa Dolz-Marco



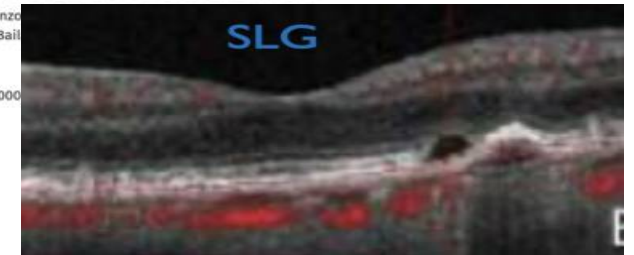
ORIGINAL STUDY

## SUBRETINAL LIPID GLOBULES AN EARLY BIOMARKER OF MACULAR NEOVASCULARIZATION IN EYES WITH INTERMEDIATE AGE-RELATED MACULAR DEGENERATION

Frangiotta, Serena PhD<sup>1</sup>; Parravano, Mariacristina MD<sup>2</sup>; Costanzo Monica MD<sup>3</sup>; Fernández-Avellaneda, Pedro MD<sup>1</sup>; Freund, K. Bailey MD<sup>4</sup>

Author Information ©

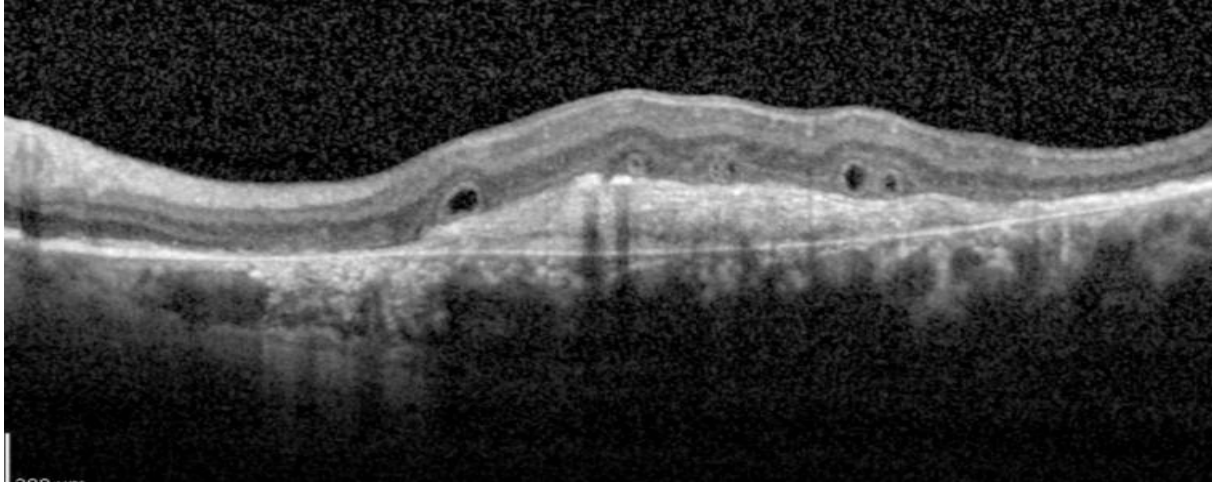
Retina 43(6):p 913-922, June 2023. | DOI: 10.1097/IAE.0000000000000000



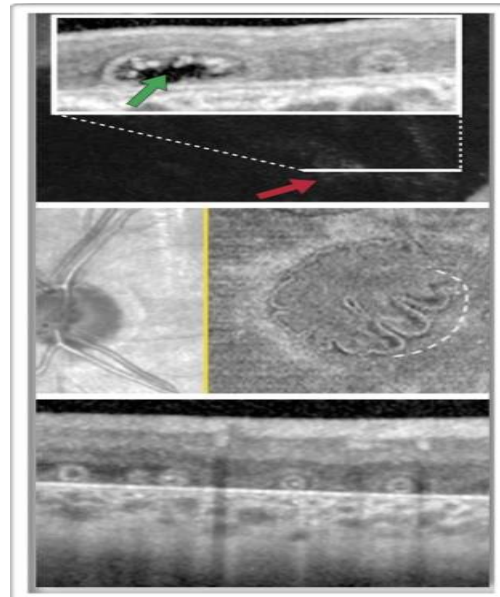
It should **not be considered an exudative sign**, as it is not associated with exudation in 75% of eyes with neovascular AMD.

It may even be present in eyes with early-stage AMD

# OUTER RETINAL TUBULATION (ORT)



Photoreceptor rearrangement following retinal injury. ORT presents with a distinctive hyperreflective border, is located within the outer retina, and remains stable over time.

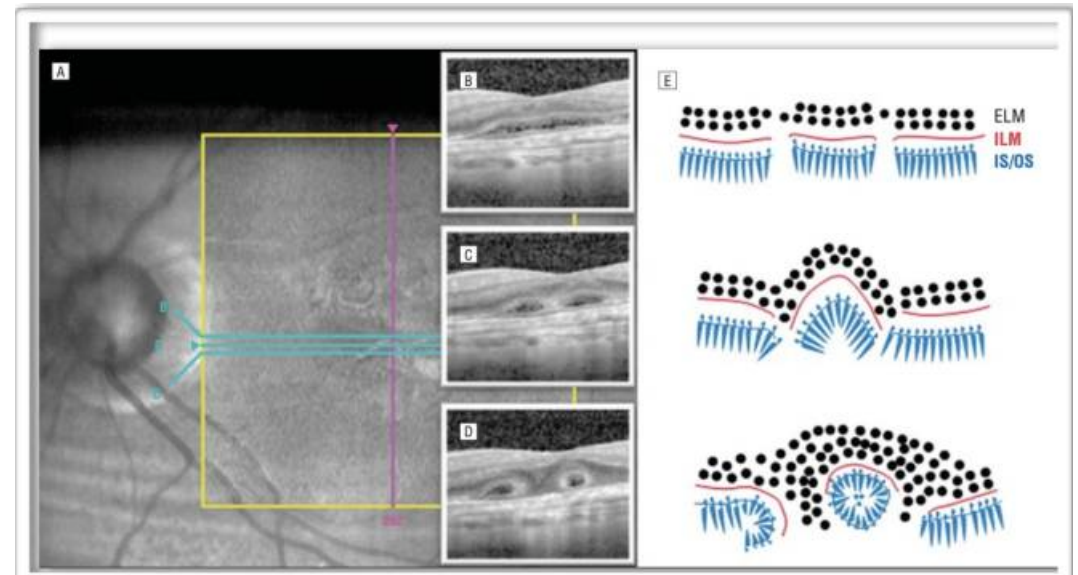


## Outer Retinal Tubulation

### *A Novel Optical Coherence Tomography Finding*

Sandrine A. Zweifel, MD; Michael Engelbert, MD, PhD; Ketan Laud, MD;  
Ron Margolis, MD; Richard F. Spaide, MD; K. Bailey Freund, MD  
ARCH OPHTHALMOL/VOL 127 (NO. 12), DEC 2009

**No treatment** is required when observed in patients with neovascular AMD, as it indicates inactive disease.

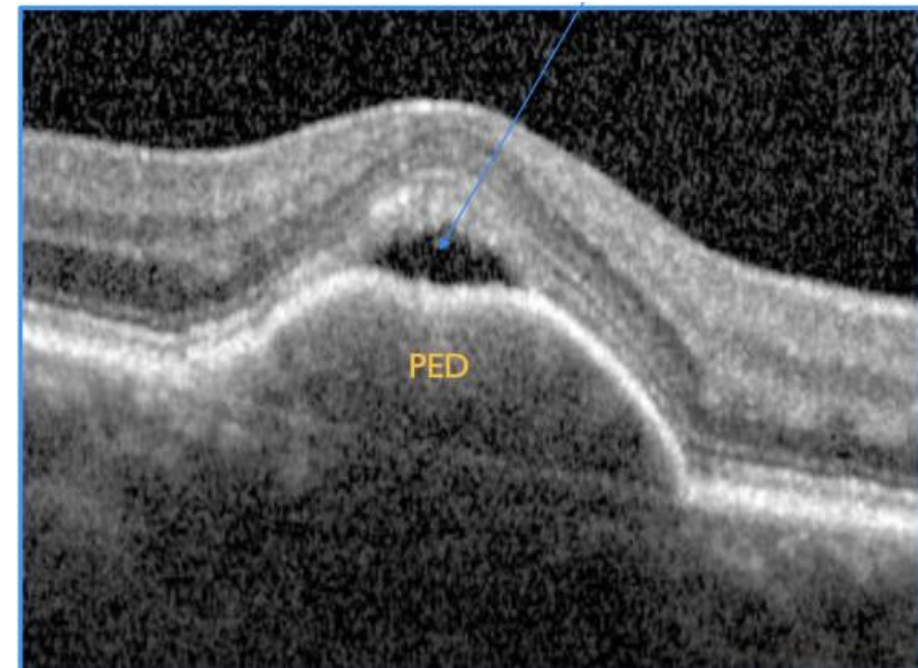
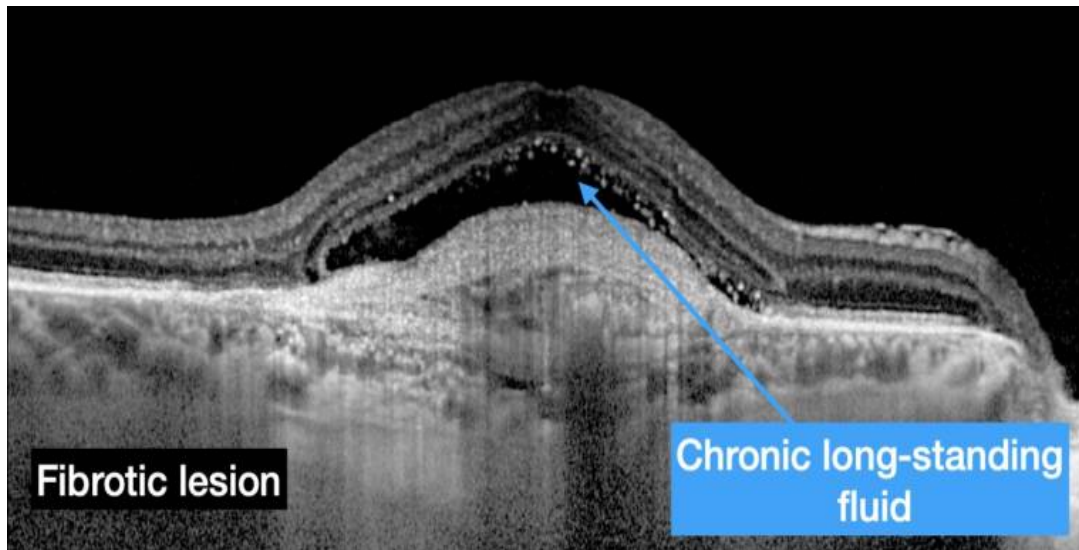




# NON-EXUDATIVE SUBRETINAL FLUID

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SRF may result from **non-exudative processes** and does not necessarily indicate the need for anti-VEGF treatment.



# TAKE HOME MESSAGE



- **THE TYPE OF FLUID IS RELATED TO PROGNOSIS:** IRF, BALAD, and SHE are associated with worse prognosis due to the risk of fibrotic evolution; SRF may have a protective effect and is generally associated with a more favorable prognosis.
  - **TREATMENT STRATEGIES SHOULD REFLECT FLUID DIFFERENTIATION:** Intensive treatment is recommended for non-tolerable fluid types (IRF, PED, BALAD, SHE); A more tolerant approach can be considered for small amounts of SRF.
  - **NOT ALL HYPOREFLECTIVE SPACES SHOULD BE INTERPRETED AS FLUID:** structures such as ORT and SLG do not require treatment.
  - **NOT ALL FLUID IS EXUDATIVE IN ORIGIN:** accurate differential diagnosis is crucial to avoid unnecessary or inappropriate treatments.
- ✓ A modern approach to managing patients with nAMD requires an understanding of the **biological implications of retinal fluid**. The goal is not merely to dry the retina, but to do so selectively and intelligently, in order to best preserve long-term visual function

THANK'S

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