Anti-VEGF–Resistant Subretinal Fluid Is Associated With Reduced Risk of Macular Atrophy and Better Visual Acuity: Drug-Induced Choroidal New Vessel Homeostasis?

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Presented at the Association for Research and Ophthalmology Annual Meeting 2020 | Baltimore, MD | May 3–7, 2020

Disclosures

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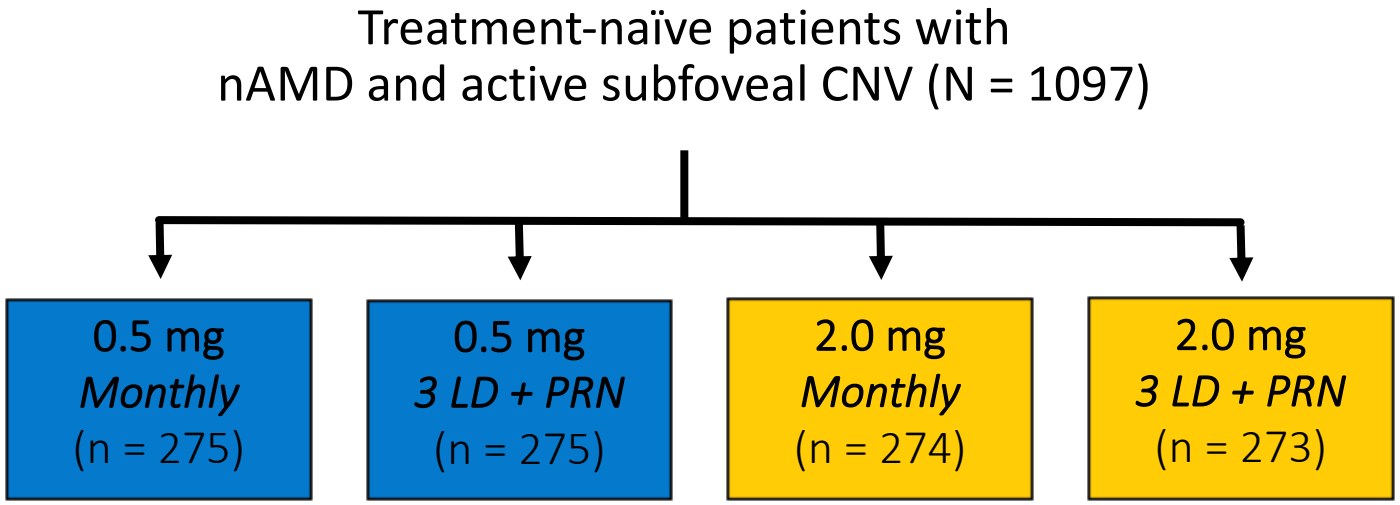
  Financial disclosures: ***Employment, Personal Financial Interest***: Genentech, Inc.

Background and Objective

- Clinical trial experience suggests that the best vision outcomes in nAMD are observed when the steady state induced by anti-VEGF treatment includes some residual (i.e., treatment-resistant) SRF[1-3]
- Using HARBOR data, we investigated the effect of SRF thickness on vision outcomes (BCVA, MA) using a 50-µm scale:
  - 0 µm
  - > 0–50 µm
  - > 50–100 µm
  - > 100 µm
- In HARBOR, all eyes were treated aggressively and SRF persisted **despite** aggressive therapy.

1. Jaffe GJ et al; Comparison of Age-related Macular Degeneration Treatments Trials Research Group. *Ophthalmology*. 2013;120(9):1860-1870. 2. Sharma S et al; Comparison of Age-related Macular Degeneration Treatments Trials Research Group. *Ophthalmology*. 2016;123(4):865-875. 3. Holekamp N et al. Presented at: Annual Macula Society Meeting; February 13–16, 2019; Bonita Springs, FL.
nAMD, neovascular age-related macular degeneration; SRF, subretinal fluid; VEGF, vascular endothelial growth factor.

The HARBOR Trial (NCT00891735) Compared Monthly and PRN Ranibizumab in nAMD for 24 Months



Re-treatment criteria for the PRN groups:

≥ 5-letter decrease in BCVA from previous visit
or any evidence of disease activity on SD-OCT
(SRF, IRF, or subretinal pigment epiretinal fluid)

BCVA, best-corrected visual acuity; CNV, choroidal neovascularization; IRF, intraretinal fluid; LD, loading dose; nAMD, neovascular age-related macular degeneration; PRN, as-needed; SD-OCT, spectral-domain optical coherence tomography; SRF, subretinal fluid.

Study Design

- Post hoc analysis of HARBOR (NCT00891735)
- All treatment arms pooled, and analysis limited to eyes with SRF at screening, baseline, or week 1 (n = 785)
- Outcomes:
  - **SRF** presence and thickness evaluated using SD-OCT imaging
    - Eyes grouped according to SRF thickness:
      - 0 µm, > 0–50 µm, > 50–100 µm, or > 100 µm
  - **BCVA** assessed using standard ETDRS protocols
  - **MA** presence determined from fluorescein angiograms and color fundus photographs by masked graders

BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; MA, macular atrophy; SD-OCT, spectral-domain optical coherence tomography; SRF, subretinal fluid.

Reading Center Definitions and Protocols: Subretinal Fluid and Macular Atrophy

Subretinal Fluid

- Definition: exudation occurring between the photoreceptor layer and the RPE
- Determined from all B-scans for each patient
- All evaluations assessed by 2 masked graders
- A third grader adjudicated any discrepancies between the first 2 assessments

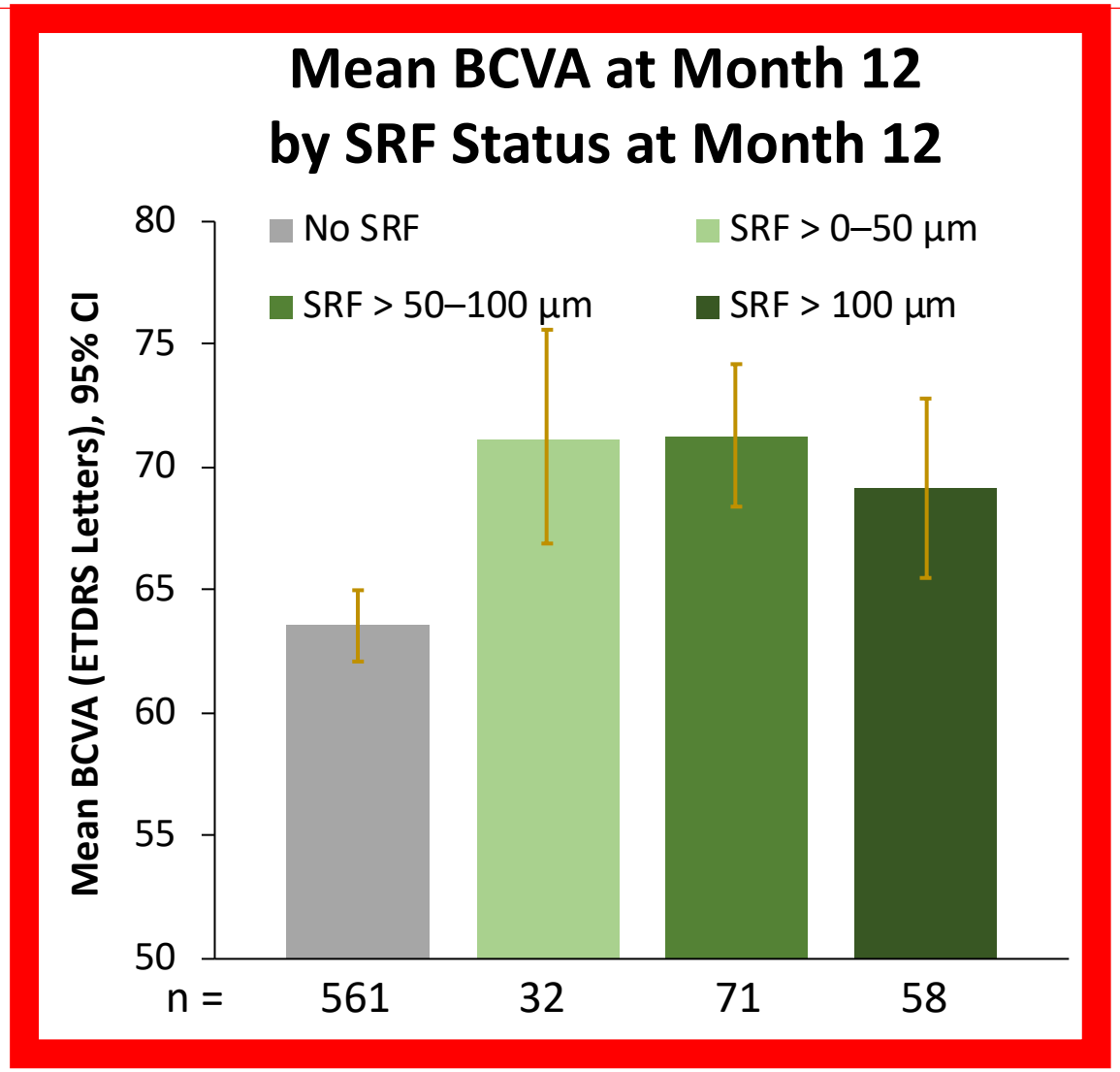
Macular Atrophy[1]

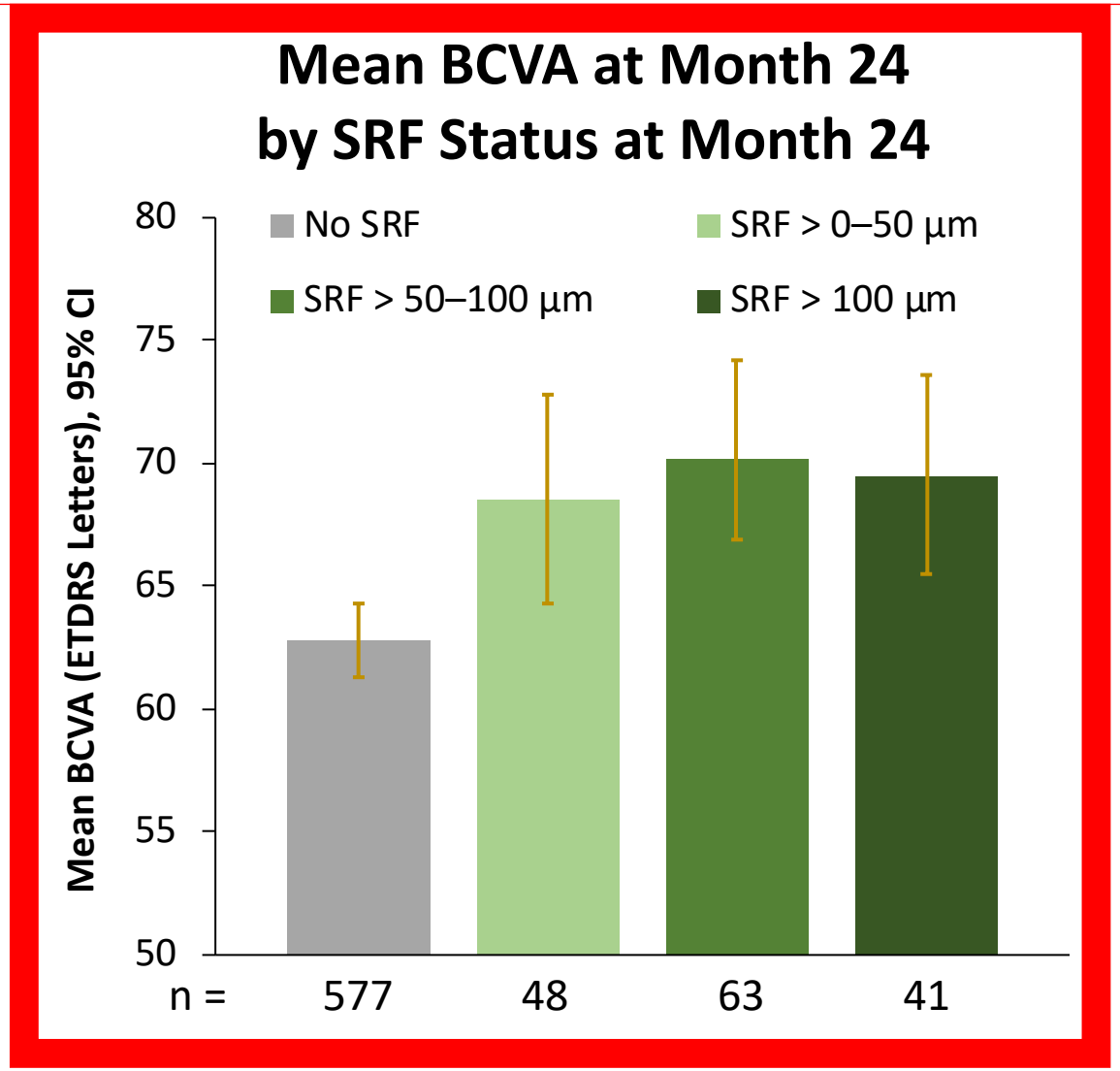
- Definition: sharply demarcated areas of RPE depigmentation with increased visibility of choroidal vessels through the lesion on CFP or FA, ≥ 250-µm diameter, corresponding to flat areas of well-demarcated staining on FA
  - Included all atrophy immediately within, adjacent to, and nonadjacent to CNV lesions (active or regressed)

1. Sadda SR et al. *Ophthalmology.* 2018;125(6):878-886.

CFP, color fundus photograph; CNV, choroidal neovascularization; FA, fluorescein angiography; RPE, retinal pigment epithelium.

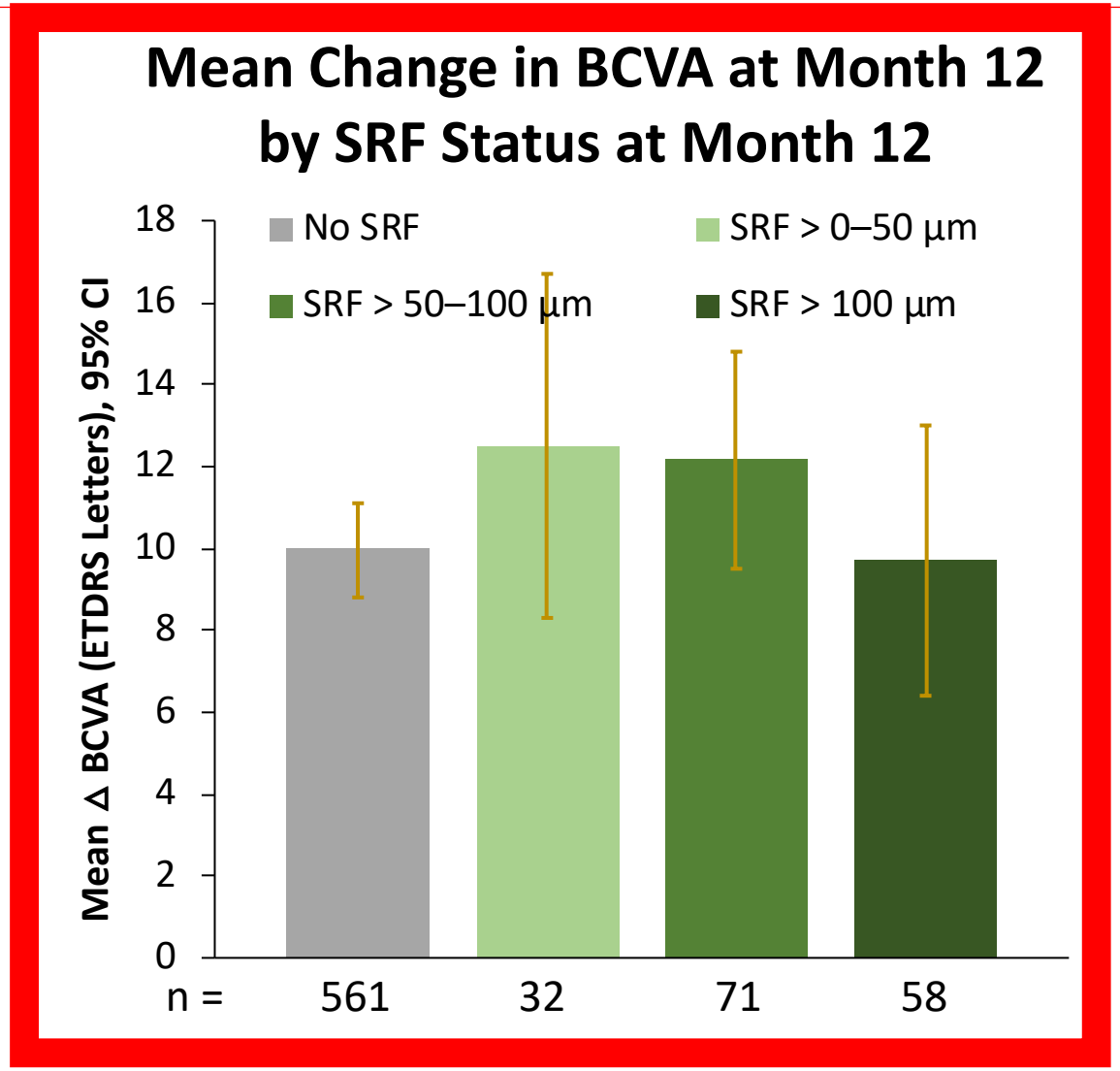
Ranibizumab-Treated Eyes With Residual SRF Had Greater Mean BCVA Than Eyes With No SRF Regardless of SRF Thickness

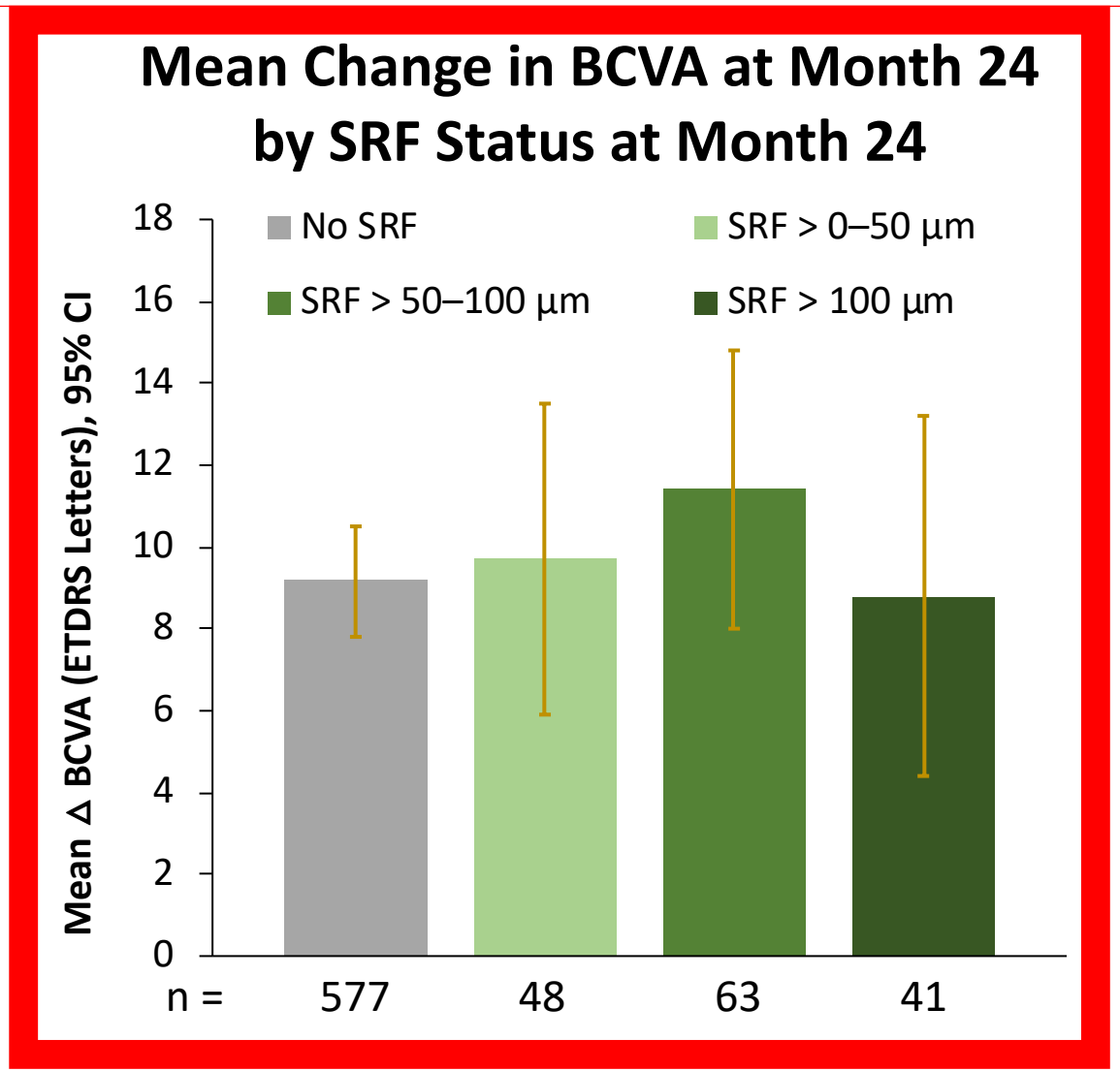




BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; SRF, subretinal fluid.

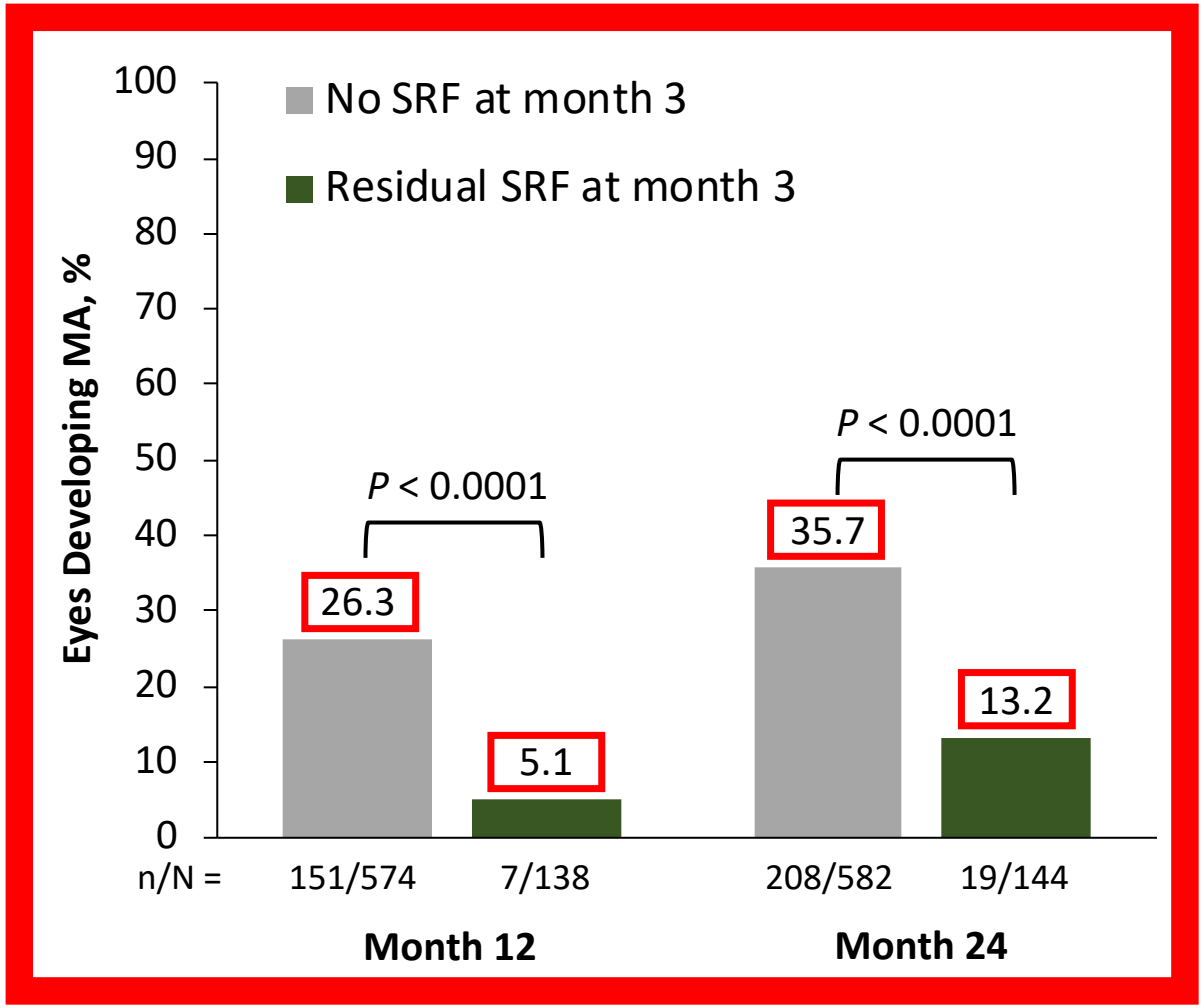
Mean Change in BCVA Was Similar Between Eyes With or Without Residual SRF

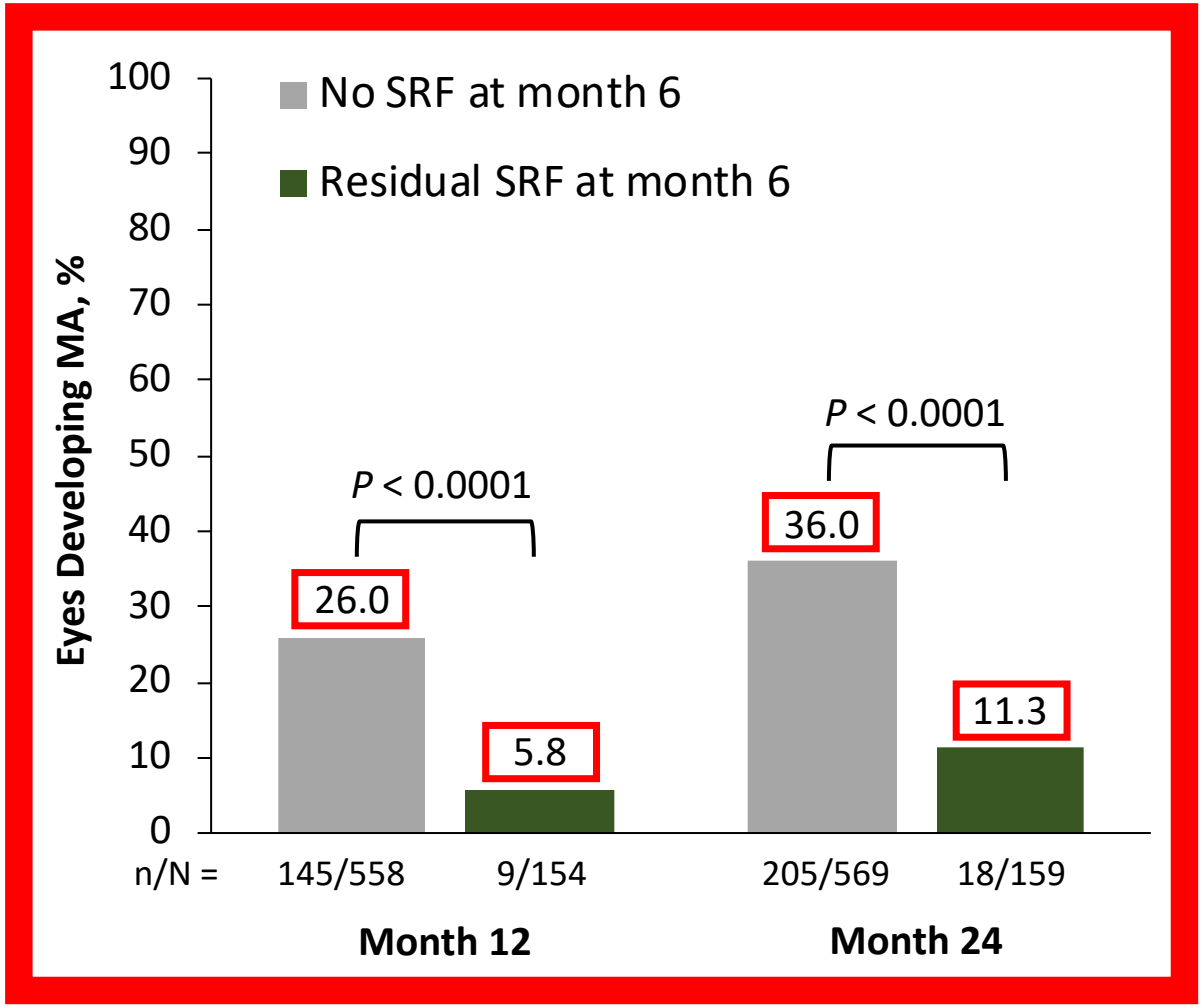




BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; SRF, subretinal fluid.

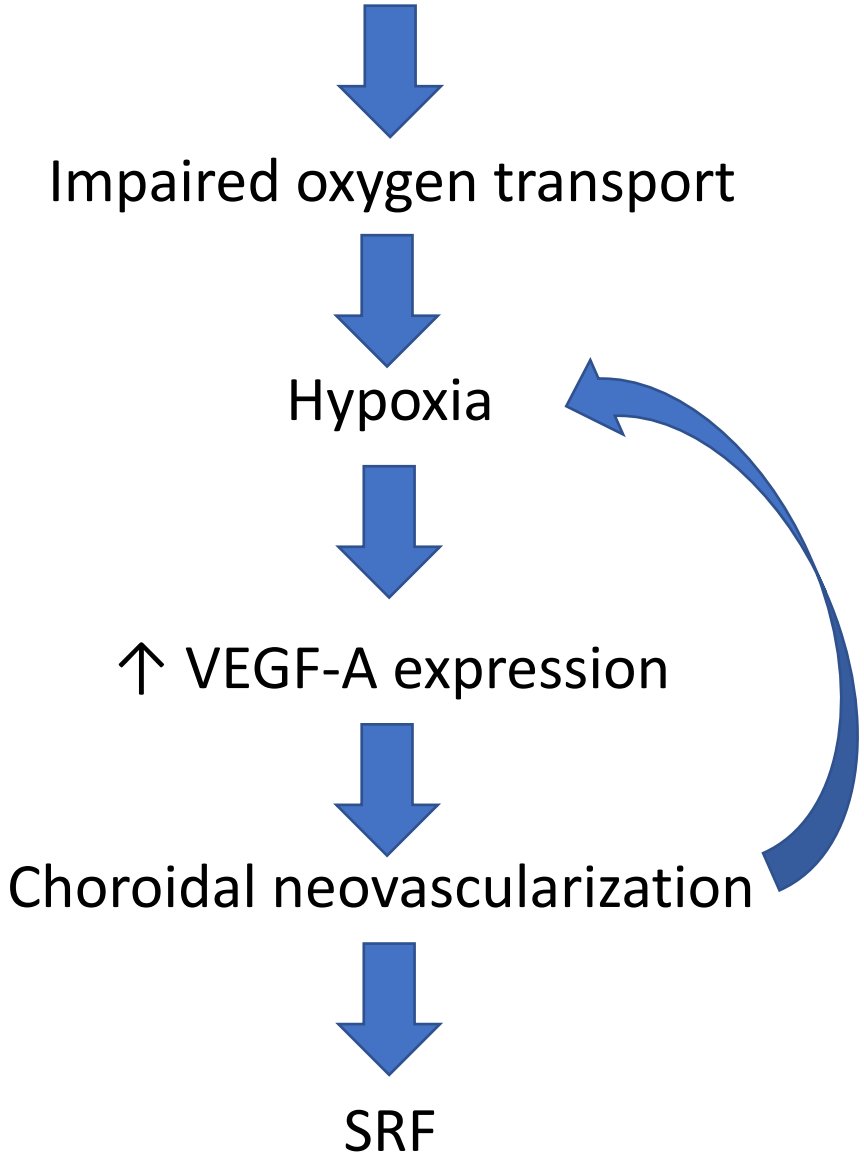
In Eyes With No MA at Baseline, Residual SRF Was Associated With Reduced Risk of Developing MA





MA, macular atrophy; SRF, subretinal fluid.

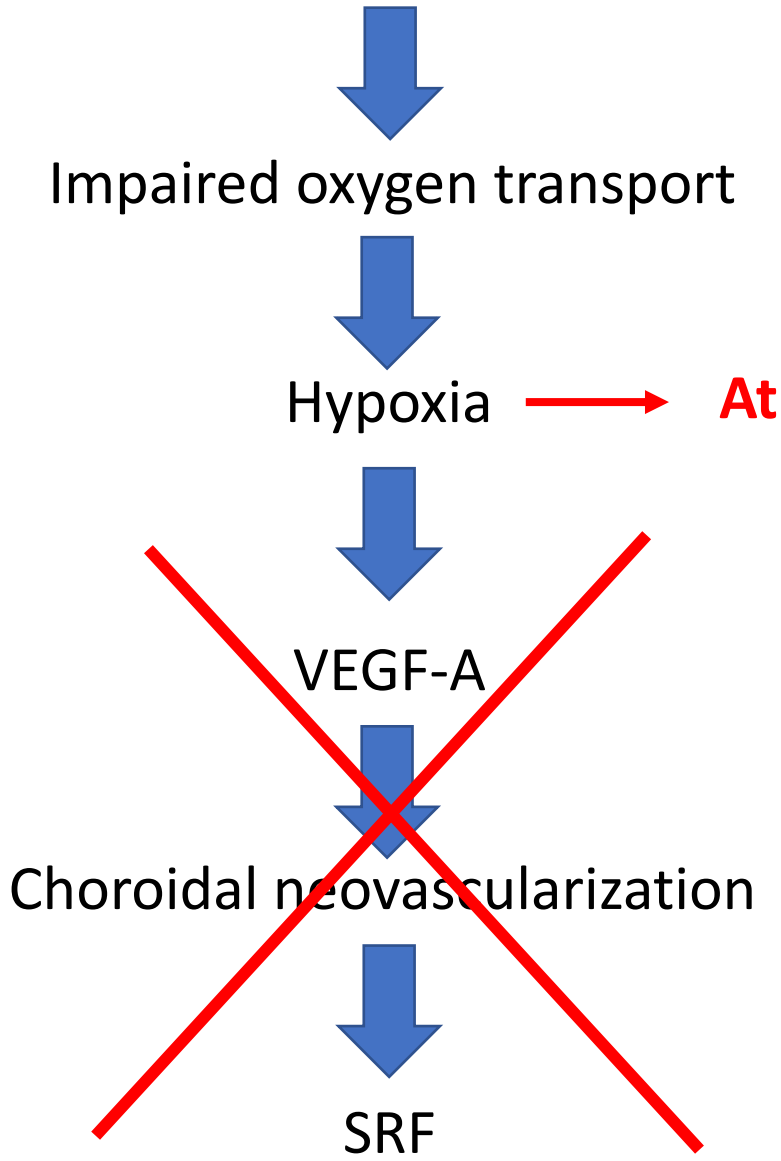
AMD-related changes in the retina/choroid interface



The SRF could potentially be a manifestation of an imperfect yet critical "survival mechanism" for the degenerating macula

1. **Sarks et al.** Eye. 1997;11:515-522; 2. **Grossniklaus HE, Green WR.** Am J Ophthalmol. 2004;137:496-503; 3. **Miller et al.** Ophthalmology 2013;120:106–114; 4. **Querques et al.** Invest Ophthalmol Vis Sci. 2013;54:6886-6892; 5. **Dansingani et al.** Ophthalmic Surg Lasers Imaging Retina. 2015;46:907-912; 6. **Roisman et al.** Ophthalmology. 2016;123:1309-1319; 7. **Capuano et al.** Am J Ophthalmol. 2017;182:45-55.
AMD, age-related macular degeneration; SRF, subretinal fluid; VEGF-A, vascular endothelial growth factor-A.

AMD-related changes in the retina/choroid interface



The cessation or absence of this imperfect "survival mechanism" may be a harbinger of the development of atrophic changes

AMD, age-related macular degeneration; SRF, subretinal fluid; VEGF-A, vascular endothelial growth factor-A.

Conclusions

- We analyzed SRF in 50-µm increments and found no threshold detrimental to vision outcomes over 2 years
- Rates of MA were significantly higher in the absence of SRF
- These findings are consistent with earlier analyses[1-3]
- Persistent SRF in the course of anti-VEGF treatment may be a sign of persistent choroidal new vessel perfusion with transudation, which may operate as an imperfect compensatory mechanism that maintains the function of the degenerating macula[1-15]

1. **Grunwald et al.** Ophthalmology 2017;124:97-104; 2. **Sadda et al.** Ophthalmology 2018;125:878-86; 3. **Guymer et al.** Ophthalmology 2019;126:723-34; 4. **McLeod DS, Lutty GA**. Invest Ophthalmol Vis Sci. 1994;35:3799-3811; 5. **Sarks et al.** Eye. 1997;11:515-522; 6. **Grossniklaus HE, Green WR**. Am J Ophthalmol. 2004;137:496-503; 7. **Querques et al.** Invest Ophthalmol Vis Sci. 2013;54:6886-6892; 8. **Dansingani et al.** Ophthalmic Surg Lasers Imaging Retina. 2015;46:907-912; 9. **Dhrami-Gavazi et al.** Int J Retina Vitreous 2015;1:15; 10. **Xu et al.** Retina. 2015;35:176-186; 11. **Channa et al.** Am J Ophthalmol. 2015;159:9-19; 12. **Roisman et al.** Ophthalmology. 2016;123:1309-1319; 13. **Capuano et al.** Am J Ophthalmol. 2017;182:45-55; 14. **Christenbury et al.** Retina. 2018;38:1276-1288; 15**. Chen et al.** Ophthalmology 2020; doi: https://doi.org/10.1016/j.ophtha.2020.01.040.

MA, macular atrophy; SRF, subretinal fluid; VEGF, vascular endothelial growth factor.