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RETINAL DISORDERS

Hyperreflective material evolution patterns during long term anti-VEGF therapy in neovascular age-related macular degeneration

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Abstract

This retrospective, real-life cohort was analyzed to detect the frequency of different HRM evolution patterns and their correlation with MNV types, morphological and functional changes in exudative nAMD under long-term anti-VEGF therapy. We evaluated optical coherence tomography (OCT) volume scans in 143 eyes of 94 nAMD patients (start of anti-VEGF therapy 2009–2018, therapy until the last visit) and recorded the VA at all visits. HRM evolution patterns were differentiated: pattern 1 = no HRM, pattern 2 = subretinal HRM resolved during follow-up, pattern 3 = persistent subretinal HRM with new HRM-boundary remodeling [BR], pattern 4 = persistent subretinal HRM without HRM-BR. Pattern 1 was observed in 58 eyes (40.6%), 33 eyes (23.1%) showed pattern 2, 39 eyes (27.3%) pattern 3 and 13 eyes (9.1%) pattern 4. HRM pattern correlated with type 1–3 MNV ($p = 0.02$), especially pattern 1 with type 1 MNV and pattern 3 with type 2 MNV. Over time, a change of MNV types could be observed only from type 2 into type 1 MNV ($p = 0.0001$). Some eyes with HRM pattern 3 changed during follow-up into pattern 4, which was often associated with the presence of macular atrophy ($p = 0.0001$) and demonstrated a reduced mean VA compared to pattern 1–3 at baseline ($p = 0.0001$), year 1 ($p = 0.0001$) and final visit ($p = 0.02$).In this study, we characterized different HRM evolution patterns in a real-world dataset and demonstrated their associations with MNV transformation during long term anti-VEGF therapy. The HRM patterns may provide prognostic value with morphological and functional implications.

Key messages

What is known

- The presence of hyperreflective material (HRM) classified by different HRM evolution patterns has been discussed as a prognostic factor for short-term outcomes in patients with neovascular age-related macular degeneration (nAMD).

What is new

- The present study provides evidence that different HRM evolution patterns can be applied to real world cohorts and have prognostic value in predicting visual acuity (VA) during long-term intravitreal anti-vascular endothelial growth factor (VEGF) treatment.
- The specific HRM evolution pattern 3 (persistent subretinal HRM with new HRM-boundary remodeling) results in a transfer of MNV type 2 into MNV type 1.
- The specific HRM evolution pattern 4 (persistent subretinal HRM without HRM-boundary remodeling) is associated with the development of macular atrophy and reduced VA.

Keywords Neovascular age-related macular degeneration · Macular neovascularization · Subretinal hyperreflective material · Anti-VEGF therapy · Optical coherence tomography

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Introduction

To date, intravitreal anti-angiogenic therapy is the most effective treatment in exudative neovascular age-related macular degeneration (nAMD) [1]. In the initial treatment phase, an improvement in visual acuity (VA) and a decrease in mean central retinal thickness (CRT) due to fluid reduction can be observed in most patients [2–6]. However, about 50% of eyes develop fibrosis and macular atrophy 5–7 years after treatment initiation [7–9].

The introduction of spectral-domain optical coherence tomography (SD-OCT) offers the possibility to characterize pathological features of the retina in detail before and during treatment and enables long-term follow-up. It allows to locate and differentiate components of macular neovascularization (MNV) according to differences in reflectivity. This led to the introduction of a new classification system of MNV types based on localization of the MNV that can be used to describe changes over longer treatment periods [10].

Whereas serous fluid appears as hyporeflective areas in OCT, neovascular tissue elements, fibrous tissue and fluids containing proteinaceous and cellular components appear as hyperreflective regions [11]. Hyperreflective regions observed external to the neurosensory retina have been termed subretinal hyperreflective material (SHRM) and have been recognized as a biomarker of interest for MNV [12]. We recently proposed a classification of four different hyperreflective material (HRM) evolution patterns, in order to differentiate HRM changes during anti-VEGF treatment based on the presence and location of HRM at baseline and its subsequent resolution or remodeling of its boundary [13]. We had previously introduced the term HRM boundary remodeling (HRM-BR), defined as the appearance of a new, well-defined, hyperreflective band at the inner aspect of the SHRM that was continuous with the retinal pigment epithelium (RPE) layer adjacent to the lesion [13]. The different HRM evolution patterns were applied to the AVENUE trial image repository with 9 months follow-up and demonstrated the association of some HRM evolution patterns with visual prognosis in this short observational period.

The aim of the present study was to define the HRM evolution patterns that appear in long-term real-world data. In addition, the prognosis and transformation of the different patterns and their functional implication under long-term anti-VEGF therapy were analyzed.

Patients and methods

The present analysis is a single-center, retrospective cohort study that investigated SD-OCT volume scans of patients with nAMD for HRM presence and changes during therapy. Patients with new or ongoing anti-VEGF treatment for nAMD in 2018–2019 at the Department of Ophthalmology, St. Franziskus Hospital Muenster, Germany, were screened for study inclusion. The inclusion criteria were exudative nAMD with anti-VEGF-treatment and the availability of continuous follow-up until the last visit with consistent implementation of OCT-based retreatment criteria (IVAN PRN [5]) at all visits. Therefore, many patients with interruptions or discontinuations because of medical conditions like major hemorrhages or because of change of treatment center were excluded. Patients were included until 2022 and the morphologic analysis of MNV was performed only after an uninterrupted clinical course of treatment had been established during this follow-up to limit selection bias. All patients gave their written informed consent to anti-VEGF therapy. The need for informed consent for participation in this study was waived due to its retrospective design and anonymized data evaluation, which was approved by the local Institutional Ethics committee and adhered to the tenets of the Declaration of Helsinki for research involving human subjects. All data was anonymized and accessed for research purposes starting in 2022.

The diagnosis of nAMD was confirmed based on multimodal imaging acquired using Heidelberg Retina Angiograph 2 (HRA2) and Heidelberg Spectralis SD-OCT (both Heidelberg Engineering, Heidelberg, Germany) including obligatory fundus fluorescein angiography (FFA). The settings of the HE Spectralis SD-OCT B-scans were 6 × 6 mm OCT volume scans, consisting of 49 B-scans (appr. 125 µm between each scan) with 9 times averaging. Patients then were treated according to an "as needed" or "pro re nata" (PRN) protocol as described in the IVAN study [5]. Treatment was performed with either bevacizumab, ranibizumab or aflibercept at the treating physician's discretion. In case of insufficient response, a switch between agents was possible.

VA was recorded at all visits and MNV types 1–3 were classified at baseline and at the final visit in line with the CONAN consensus [10] by a single grader (DP). We analyzed the baseline, year 1 and final OCT volume scan to assess the presence of HRM and its subsequent resolution or remodeling of its boundary to differentiate the HRM evolution patterns (Table 1). For pattern 2, 3 and 4, the 6 months OCT were additionally analyzed for the presence or absence of HRM and boundary remodeling. The presence of complete RPE and outer retina atrophy (cRORA) was assessed on infrared (IR) en-face images and corresponding OCT B-scans.

Results are presented as mean ± standard deviation (SD) for continuous variables and as absolute and relative frequencies for categorical variables. The comparisons between initial and final HRM pattern as well as between initial and final MNV types were performed using Bowker's Symmetry Test.

To test the association between initial HRM pattern and initial MNV type, we used a generalized mixed linear model with MNV type as the dependent and HRM pattern as the independent variable using Cumulative Logit as the link function and a random intercept for patients.

Table 1 HRM evolution patterns [13]. HRM, hyperreflective material; HRM-BR, hyperreflective material boundary remodeling

HRM evolution pattern	Characteristics
1	no HRM at baseline or with sub-RPE HRM only
2	baseline subretinal HRM fully resolved during follow-up
3	persistent subretinal HRM with complete HRM-BR
4	persistent subretinal HRM with partial or absent HRM-BR

Linear mixed models were used to test the influence of initial HRM pattern on VA at baseline, after 1 year and at the final visit. Each model included the initial HRM pattern as an independent variable and a random intercept for the patient. Results are presented as estimated mean and 95% confidence interval for the mean.

Statistical analysis was performed using SAS (version 9.4, SAS Institute, Cary, North Carolina, USA) and R (version 4.3.0, https://www.r-project.org). P-values below 0.05 were regarded as statistically significant.

Results

In this single-center, retrospective cohort study 143 eyes of 94 nAMD patients (31 male, 63 female; initial age 55–97 years, mean age 75.9 ± 7.5 years) who started anti-VEGF therapy between 2009 and 2018 were included. Mean follow-up was 5.3 ± 2.9 years (range 1–14 years; mean follow-up pattern 1) and mean total number of injections was 33.3 ± 19.8 (range 6–90) with 7.0 ± 2.3 injections/year (range 3–12; mean injections/year: pattern 1 = 7.2 injections/year, pattern 2 = 7.3 injections/year, pattern 3 = 6.6 injections/year, pattern 4 = 6.4 injections/year; $p = 0.8$).

Distribution of the HRM evolution pattern

We found 58 eyes (40.6%) showing pattern 1, 33 eyes (23.1%) with pattern 2, 39 eyes (27.3.%) with pattern 3 and 13 eyes (9.1%) with pattern 4 (Table 2).

Comparison between HRM evolution patterns and MNV type 1–3 at baseline

Comparing HRM patterns with MNV types 1–3 of the respective eyes at baseline (Table 3), our data showed that HRM pattern 1 was most often associated with type 1 MNV and HRM pattern 3 with type 2 MNV. The correlation between the HRM evolution patterns and MNV type 1–3 at baseline was statistically significant ($p = 0.02$).

Comparison between baseline and final MNV types

In order to analyze the change of MNV types 1–3 associated with different HRM evolution patterns during follow-up, baseline MNV types were compared with final MNV types (at the last visit). Whereas we observed no change in eyes that were classified as type 1 MNV at baseline and only 2 eyes that changed from type 3 MNV to type 1 MNV, we found a frequent change from type 2 MNV to type 1 MNV (in 38/54 eyes) (Table 4), which was significantly more compared to the other 2 subgroups ($p < 0.0001$).

Comparison between baseline and final HRM evolution patterns

Upon comparison, our data show that HRM patterns established in the first year did not change during follow-up (comparison of follow-up between different patterns p=0.4), with the exception of pattern 3 (Table 5), where over time in 23 eyes (59.0%; mean follow up 5.6 years) the boundary remodeling was unchanged, while in 16 eyes (41.0%; mean follow up 5.8 y) a regression of the boundary remodeling could be observed. In these eyes with

Table 2 HRM pattern distribution. HRM, hyperreflective material

HRM evolution pattern	No. of eyes	Percentage
1	58	40.6%
2	33	23.1%
3	39	27.3%
4	13	9.1%

Table 3 Correlation between baseline HRM patterns and MNV types 1–3, HRM, hyperreflective material; MNV, macular neovascularization

	HRM pattern baseline				
MNV types baseline	1	2	3	4	Total
1	40 (28.0%)	11 (7.7%)	5 (3.5%)	3 (2.1%)	59 (41.3%)
2	6 (4.2%)	10 (7.0%)	29 (20.3%)	9 (6.3%)	54 (37.8%)
3	12 (8.4%)	12 (8.4%)	5 (3.5%)	1 (0.7%)	30 (21.0%)
Total	58 (40.6%)	33 (23.1%)	39 (27.3%)	13 (9.1%)	143 (100%)

Table 4 Baseline and final MNV types. MNV, macular neovascularization

	baseline MNV types			
final MNV types	1	2	3	Total
1	59 (41.3%)	38 (26.6%)	2 (1.4%)	99 (69.2%)
2	0 (0%)	16 (11.2%)	0 (0%)	16 (11.2%)
3	0 (0%)	0 (0%)	28 (19.6%)	28 (19.6%)
Total	59 (41.3%)	54 (37.8%)	30 (21.0%)	143 (100%)

a regression of the remodeled boundary, the HRM evolution pattern changed from pattern 3 to pattern 4 (Fig. 1a-f) (p=0.01).

Comparison between final HRM evolution patterns and development of cRORA

At the final visit, presence of HRM evolution pattern 4 was associated significantly more often with the development of cRORA above the MNV compared to other evolution patterns ($p < 0.0001$) (Table 6).

Influence of different HRM evolution patterns on function

We analyzed the association between baseline and final HRM evolution patterns 1–4 and mean VA (logMAR) at baseline, year 1 and final visit. This comparison showed a significantly poorer VA in pattern 4 compared to patterns 1–3 ($p = 0.001$ for baseline and year 1, $p = 0.02$ for final visit) (Table 7).

Discussion

SHRM has been identified as a risk factor for unfavorable visual outcomes in nAMD patients in previous studies [14–18]. During the 5 years follow-up of the CATT (Comparison of age-related macular degeneration treatment trials) study [17], presence of SHRM, amongst other pathological features such as foveal geographic atrophy and intraretinal fluid, was associated with worsening of VA. Similarly, Ehlers et al. found a significant correlation of SHRM with VA: eyes that showed only little variation in subretinal HRM volumes during the maintenance phase of anti-VEGF treatment showed greater gains in VA [18]. However, until recently, the composition, compartmental localization of HRM and its changes during disease progression with and without anti-angiogenic treatment had rarely been studied in detail.

By systematically characterizing HRM evolution during anti-angiogenic treatment on SD-OCT, we previously proposed a classification based on morphological characteristics that may serve as prognostic factors for functional outcomes [13]. In the current study, we analyzed HRM evolution pattern distribution in a real-life setting and with a longer follow-up. We were able to identify all four HRM patterns in our patient cohort. The most common was pattern 1 with 40.6%, while pattern 2 could be observed in 23.1%, pattern 3 in 27.3% and pattern 4 in 9.1% of the eyes. Previously, different growth of MNV size has been observed in eyes treated with PRN regimen compared to T&E regimen [19]. A growth of MNV under treatment was also observed in our cohort treated with IVAN-PRN [20], but appears independent of the presence of different HRM patterns.

In line with our previous study [13], we observed the development of a remodeled inner boundary (HRM evolution pattern 3) in a subset of eyes. This was found predominantly in type 2 MNV lesions (typically visible as HRM in the subretinal space) and often resulted in a transformation of MNV type 2 into an MNV type 1 lesion. During longer follow-up and under long-term effective anti-VEGF treatment, several eyes showed a transition of HRM pattern 3 into HRM pattern 4 due to loss of the inner boundary. This was significantly associated with the development of cRORA above the MNV and acute and long-term loss of VA. Therefore, the presence of HRM evolution pattern 4 may be characteristic of an MNV transformation into "fibrosis with impact on visual function" and associated development of cRORA above the MNV. Both aspects (i.e. fibrosis and cRORA) may therefore be considered as "two sides of the same coin" of MNV transformation under long-term anti-VEGF therapy with negative impact on function and therefore an important clinical characteristic for future therapeutic interventions [21]. The reason why some eyes demonstrate stable HRM pattern 3, while others

Table 5 Baseline and final HRM evolution pattern. HRM, hyperreflective material

	HRM pattern baseline				
HRM final	1	2	3	4	Total
1	58 (40.6%)	0 (0%)	0 (0%)	0 (0%)	58 (40.6%)
2	0 (0%)	32 (22.4%)	0 (0%)	0 (0%)	32 (22.4%)
3	0 (0%)	0 (0%)	23(16.1%)	0 (0%)	23(16.1%)
4	0 (0%)	1 (0.7%)	16 (11.2%)	13 (9.1%)	30 (21.0%)
Total	58 (40.6%)	33 (23.1%)	39 (27.3%)	13 (9.1%)	143

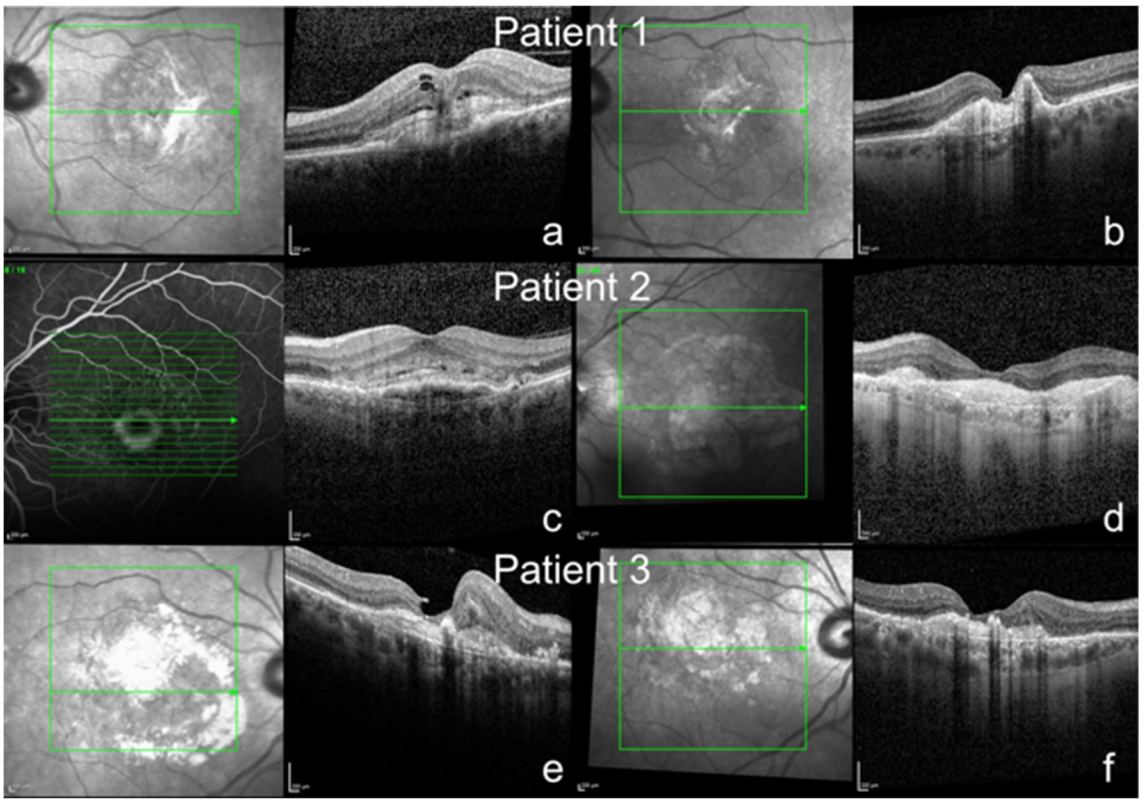

Fig. 1 Hyperreflective material (HRM) evolution patterns in three patients. Baseline (**a**, **c**, and **e**) and final visit (**b**, **d**, and **f**) optical coherence tomography images of three different female patients in their seventies under anti-vascular endothelial growth factor (VEGF) therapy for neovascular age-related macular degeneration. **a** - **b** . Patient 1 with 7 years of follow-up during which she received 44 injections (6.3 injections/year) showed pattern 3 (VA 0,6 logMAR) both at baseline (**a**) and at the final visit (VA 0,4 logMAR) (**b**) **c** - **d** . Patient 2 with 9 years of follow-up during which she received 55 injections (6.1 injections/year) showed pattern 3 (VA 0,5 logMAR) at baseline (**c**) and pattern 4 (0,8 logMAR) at the final visit (**d**) e-**f**. Patient 3 with 8 years of follow-up during which she received 44 injections (5.5 injections/year) showed pattern 4 (VA 0,3 logMAR) both at baseline (**e**) and at the final visit (VA 0,7 logMAR) (**f**) HRM, hyperreflective material; VEGF, vascular endothelial growth factor, VA, visual acuity

Table 6 Final HRM evolution patterns in correlation with the development of cRORA above the MNV at the final visit. HRM, hyperreflective material; cRORA, complete RPE and outer retina atrophy

	HRM pattern final				
	1	2	3	4	Total
cRORA final visit: no	27 (46.6%)	17 (53.1%)	16 (69.6%)	2 (6.7%)	62 (43.4%)
cRORA final visit: yes	31 (53.4%)	15 (46.9%)	7 (30.4%)	28 (93.3%)	81 (56.6%)
total	58 (40.6%)	32 (22.4%)	23 (16.1%)	30 (20.1%)	143

Table 7 Association between baseline (**a**) and final (**b**) HRM evolution patterns and the mean VA at baseline, year 1 and final visit. VA, visual acuity (logMar); HRM, hyperreflective material; *p*-value of mean VA between patterns1-3 and pattern 4: ANOVA

Baseline HRM pattern	HRM pattern 1	HRM pattern 2	HRM pattern 3	HRM pattern 4	*p* - value
VA baseline	0.43(0.36;0.50)	0.58 (0.49;0.68)	0.61 (0.53;0.70)	0.75 (0.60;0.89)	0.001
VA year 1	0.40 (0.32;0.49)	0.47 (0.37;0.58)	0.55 (0.45;0.64)	0.79 (0.62;0.95)	0.001
VA final	0.52 (0.42;0.63)	0.56 (0.42;0.69)	0.63 (0.51;0.75)	0.87 (0.66;1.07)	0.02
Final HRM pattern	HRM pattern 1	HRM pattern 2	HRM pattern 3	HRM pattern 4	*p* - value
VA baseline	0.43 (0.35;0.50)	0.59 (0.49;0.69)	0.62 (0.51;0.74)	0.66 (0.56;0.76)	0.001
VA year 1	0.40 (0.32;0.49)	0.47 (0.36;0.58)	0.51 (0.38;0.63)	0.68 (0.57;0.80)	0.002
VA final	0.53 (0.43;0.63)	0.56 (0.42;0.70)	0.55 (0.39;0.71)	0.78 (0.64;0.91)	0.02

transform early or late into HRM pattern 4, has to be investigated in the future.

In eyes that maintained HRM pattern 3 throughout the observation period, development and persistence of BR showed an OCT reflectivity and functional characteristics similar to the RPE band and may represent a new RPE band, an observation which has also been suggested in the RPE-free areas of RPE tears under long-term proactive anti-VEGF therapy [22, 23]. The development of the BR might serve as a stabilization process of the neovascular area with a similar nutritional function for the overlying retina as the RPE and could be regarded as part of a biological repair mechanism to preserve RPE and photoreceptor function [24]. By contrast, in eyes that demonstrated HRM pattern 4 or progressed to HRM pattern 4 from HRM pattern 3 during follow-up, no such hyperreflective boundary with RPE-like characteristics could be revealed and this MNV transformation ("fibrosis") might be the reason for the development of cRORA above the MNV often recognized as growing areas of cRORA during long-term anti-VEGF therapy [25].

Since SHRM may represent different components, e.g. type 2 MNV, subretinal hemorrhage, subretinal hyperreflective exudation or fibrosis [25], a further differentiation of HRM areas is necessary to assess the prognostic value of HRM. For this, OCT angiography (OCT-A) or polarization-sensitive OCT (PS-OCT) can be useful [26, 27]. Subretinal HRM that is due to fibrosis seems to be characterized by a greater thickness and volume compared to subretinal HRM based on other components [27]. Furthermore, subretinal HRM with fibrotic origin shows less reduction in thickness and volume in response to therapy. The reduction of subretinal HRM thickness may therefore serve as an additional prognostic marker for treatment response and MNV transformation [27].

When we analyzed functional implications of different HRM patterns under long-term anti-VEGF therapy, we found that the development and persistence of a BR (HRM pattern 3) was associated with better VA, which often remained stable during follow-up. Similarly to our previous study [13], we also observed a significantly lower mean VA (at baseline, year 1 and at the final visit) in HRM pattern 4 compared to patterns 1–3. Because pattern 4 is characterized by the absence of a hyperreflective RPE-like inner band, it appears – as mentioned before – that the development of this specific "fibrosis" of the MNV is associated with cRORA and consecutive loss of function. This is consistent with the observation of development of cRORA in several studies during long-term tanti-VEGF treatment [17, 20, 25, 28] and a reduced retinal sensitivity in microperimetry above the MNV in eyes with cRORA [24].

At least in our study, development of BR and presence of HRM pattern 3 frequently resulted in a transformation of MNV type 2 into MNV type 1. This may explain why in many prospective studies the initial MNV type has no prognostic impact for the later functional course of the eyes under anti-VEGF therapy [29–31].

In summary, we evaluated HRM evolution patterns in a real-world dataset under long-term anti-VEGF therapy and showed prognostic value for functional outcomes. HRM evolution pattern 4 appears to represent clinically relevant "fibrosis" of the MNV associated with the development of cRORA ("two sides of the same coin") and loss of retinal function. This observation and the reasons why exudative nAMD can be associated with these different HRM patterns should be evaluated in more detail in future studies and may be relevant for new interventions to prevent functional loss under long-term anti-angiogenic therapy in nAMD. By contrast, development and persistence of boundary remodeling may be a positive outcome for future treatments in nAMD.

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Declarations

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the (place name of institution and/or national research committee) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards, which was for the present study approved by the Ethics Committee of the Medical Association Westphalia-Lippe and the University Hospital Münster (2017-033-f-S).

Conflict of interest Daniel Pauleikhoff: clinical studies and advisory boards Bayer, Heidelberg Engineering, Novartis, Roche.
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Eike Bormann: no conflicts of interest.
Laurenz Pauleikhoff: no conflicts of interest.

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