



# Development and Course of Scars in the Comparison of Age-Related Macular Degeneration Treatments Trials

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**Purpose:** To describe risk factors for scar formation and changes to fibrotic scar through 5 years in the Comparison of Age-related Macular Degeneration Treatments Trials (CATT).

**Design:** Multicenter, prospective cohort study.

**Participants:** A total of 1061 subjects in CATT.

**Methods:** Color photographic and fluorescein angiographic images from baseline and 1, 2, and 5 years were evaluated. Incidence of scar formation was estimated with Kaplan–Meier curves. Risk factors were assessed with Cox regression models.

**Main Outcome Measures:** Scar formation, fibrotic scar area, and macular atrophy associated with fibrotic scar (“atrophy”).

**Results:** Cumulative proportion of eyes with scar was 32%, 46%, and 56% at years 1, 2, and 5, respectively. Baseline factors associated with increased risk (adjusted hazards ratio [aHR] and 95% confidence interval [CI]) were classic choroidal neovascularization (CNV) (aHR, 4.49; 95% CI, 3.34–6.04) versus occult, hemorrhage >1 disc area (DA) (aHR, 2.28; 95% CI, 1.49–3.47) versus no hemorrhage, retinal thickness >212  $\mu\text{m}$  (aHR, 2.58; 95% CI, 1.69–3.94) versus <120  $\mu\text{m}$ , subretinal tissue complex thickness >275  $\mu\text{m}$  (aHR, 2.64; 95% CI, 1.81–3.84) versus  $\leq 75$   $\mu\text{m}$ , subretinal fluid thickness >25  $\mu\text{m}$  (aHR, 1.31; 95% CI, 0.97–1.75) versus no fluid, visual acuity (VA) in fellow eye 20/20 (aHR, 1.72; 95% CI, 1.25–2.36) versus 20/50 or worse, retinal pigment epithelium elevation absence (aHR, 1.71; 95% CI, 1.21–2.41), and subretinal hyperreflective material (aHR, 1.72; 95% CI, 1.25–2.36). Among 68 eyes that developed fibrotic scar at year 1, VA decreased by a mean of additional 13 letters between years 1 and 5. Mean scar area was 1.2, 1.2, and 1.9 DA at 1, 2, and 5 years, respectively. Atrophy was present in 18%, 24%, and 54% of these eyes at years 1, 2, and 5, respectively; the mean areas were 1.6, 2.0, and 3.1 DA, respectively. Atrophy replaced fibrotic scar in 8 eyes at year 5. There was no significant correlation between scar growth and atrophy growth. The rate of growth for both was similar between the clinical trial and observation periods.

**Conclusions:** Several morphologic features, including classic CNV and large hemorrhage, are associated with scar formation. Rate of new scar formation declined after 2 years. Most fibrotic scars and accompanying macular atrophy expanded over time, reducing VA. *Ophthalmology* 2018;125:1037–1046 © 2018 by the American Academy of Ophthalmology



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Intravitreal anti-vascular endothelial growth factor (VEGF) treatment for neovascular age-related macular degeneration (nAMD) has become the standard of care based on the results of several multicenter, randomized clinical trials with generally good visual and morphologic outcomes.<sup>1,2</sup> The results of treatment are derived mostly from clinical trials that have been capped at 2 years. Subjects who completed a 2-year clinical trial continue to receive care from ophthalmologists, unrestricted from the protocol of the clinical trial. Some investigators have collected follow-up data from these clinical trial subjects 5 to 8 years after initiation of

anti-VEGF therapy, but their reports have been focused mainly on the visual status of these subjects.<sup>3</sup> A few studies have reported on the long-term outcomes of patients treated with anti-VEGF therapy in a real-world setting, but these too have dealt primarily with visual acuity (VA) outcomes.<sup>4,5</sup>

Scar and atrophy are the 2 most important morphologic features that influence visual outcomes in untreated nAMD, as well as in patients treated with anti-VEGF intravitreal injections.<sup>6,7</sup> Scars thicker than 0.2 mm have been associated with large-scale loss of the photoreceptors overlying

the scar tissue.<sup>8,9</sup> We have previously reported that both macular atrophy and foveal scar are the 2 foremost morphologic outcomes associated with poor VA in the Comparison of Age-related Macular Degeneration Treatments Trials (CATT).<sup>9</sup> Although long-term follow-up of geographic atrophy after anti-VEGF therapy, more recently referred to as “macular atrophy,” has been described, long-term follow-up of scars after the initiation of anti-VEGF therapy has not received much attention.<sup>10,11</sup>

The original CATT clinical trial was designed to assess differences between ranibizumab and bevacizumab, as well as differences between monthly and pro re nata dosing. At the end of the 2-year clinical trial period, the subjects were released from the systematic ocular examination and treatment specified by the study protocol.<sup>12,13</sup> After providing consent, subjects received ocular examinations and imaging approximately 5 years after initiation of anti-VEGF treatment. The results of the follow-up study detailing the vision outcomes have been published.<sup>14</sup> In this article, we report the incidence and risk factors of scar development through 5 years of follow-up, as well as the morphologic changes observed in and around fibrotic scars that had developed during the first year of the clinical trial.

## Methods

### Enrollment and Follow-up of Subjects

From 43 clinical centers in the United States, 1185 subjects who had untreated active (leakage on fluorescein angiogram [FA] and fluid on OCT) choroidal neovascularization (CNV) associated with age-related macular degeneration were enrolled in the CATT clinical trial between February 2008 and December 2009. The study eye was required to have CNV or fluid at the foveal center. Subjects were excluded if scar was located at the foveal center at enrollment, but study eyes with nonfoveal scars that were <50% of the total CNV lesions were included in the clinical trial. Additional eligibility criteria have been described previously.<sup>12</sup> Subjects were randomly assigned to treatment with intravitreal injections of ranibizumab or bevacizumab and to 1 of 3 dosing regimens for the initial 2 years of the study: monthly injections, monthly evaluation with injection only when signs of active neovascularization were present (pro re nata), or monthly injections for 1 year followed by pro re nata injections for 1 year.

During the clinical trial, color fundus photographs (CFPs), FA, and OCT were obtained. The CFPs and FA were obtained at baseline and 1 and 2 years, whereas OCT was obtained more frequently. The study was approved by the institutional review boards associated with each center, and all subjects provided written informed consent. The study was compliant with Health Insurance Portability and Accountability Act regulations. The CATT was registered with [clinicaltrials.gov](http://clinicaltrials.gov) (NCT00593450). At the end of the 2-year follow-up period of the clinical trial, subjects were released from the study protocol and managed according to best medical judgment. All 1117 patients in CATT who were alive at the end of the clinical trial were invited to participate in the CATT Follow-up Study approximately 5 years after initiation of treatment with the anti-VEGF therapy. Among the invited patients, 203 had died by the time of the follow-up study, and among the remaining 914 living patients, 647 (71%) participated. Nonparticipating patients were on average 2 years older, had VA 5 letters worse by the end of the clinical trial, and had 2 fewer injections during the clinical trial when they had been assigned to treatment as needed.<sup>14</sup> The percentage of participants with scar at 2 years was 44% and was

38% among nonparticipants ( $P = 0.10$ ).<sup>14</sup> Color fundus photographs, FA, and OCT were acquired at the time of the study visit.

### Assessment of Images

The methods used to grade the digital CFPs, FA images, and the OCT scans have been described previously.<sup>15,16</sup> At baseline, photographic images were evaluated at the fundus photograph reading center at the University of Pennsylvania for CNV type; contiguous hemorrhage, serous pigment epithelial detachment, or blocked fluorescence; and presence of scar or macular atrophy in both the study eye and the fellow eye. The CNV area and the total CNV lesion area were measured using ImageJ (available at <https://imagej.nih.gov/ij/>). Grading of year 1, 2, and 5 visit images was performed applying the same methods. Each image set was dual-reader graded for the various morphologic outcomes by trained nonphysician readers and the CATT fundus photographic reading center director (E.D.), all of whom were masked to demographic and clinical details. Discrepancies were adjudicated between the graders and the director of the reading center, and unresolved discrepancies were reviewed by the principal investigator (J.E.G.) to complete a final consensus grading form. Likewise, OCT evaluation was performed at the Duke University Reading Center, where a reader team, composed of 2 independent readers and a senior reader, evaluated each scan. Grading included the CATT OCT end points of total thickness at the foveal center point and intraretinal fluid, subretinal fluid, and sub-retinal pigment epithelium (RPE) fluid. The director of grading (C.A.T.) and the reading center director (G.J.J.) remained masked to subject identifiers and made final decisions on reader disagreements that remained controversial after arbitration.<sup>17</sup>

Scar was identified by CFP and FA as described previously.<sup>16</sup> Fibrotic scars were defined as obvious white or yellow mounds of fibrous-appearing tissue that were well defined in shape and appeared solid on color stereo images. Hyperfluorescence due to tissue staining or blocked fluorescence of the underlying choroid was identified from FA. Nonfibrotic scars were typically flat, small, well-circumscribed areas of pigmentation with varying degrees of central hypopigmentation on CFP images. The hypopigmented area was flat, and choroidal vessels were not visible. Hyperfluorescence of the depigmented area appeared early on FA and persisted or increased in intensity in the late phase. Hypofluorescence on FA surrounding the hyperfluorescence corresponded to the pigmented borders apparent on CFPs.

### Assessment of the Fibrotic Scar at 1, 2, and 5 Years

Additional evaluation was done only for fibrotic scars among eyes with images available for all visits (baseline and 1, 2, and 5 years). The reading center director assessed all year 1 CFPs and FA images that also had year 2 and year 5 visit images to identify fibrotic scars. Indeterminate or uncertain fibrotic scars were subjected to evaluation by a retina specialist and a senior reader, and consensus was obtained. With the use of ImageJ, measurements of area were obtained for the optic disc, fibrotic scar, and macular atrophy associated with fibrotic scar (atrophy) contiguous with or amidst the fibrotic scar. Atrophy had well-defined hypopigmented areas with exposed choroidal vessels observed on color images without visible fibrosis. The areas of fibrotic scar and atrophy were mutually exclusive, with fibrotic scar taking precedence over atrophy in instances when it was difficult to differentiate the 2 morphologic features. Hyperpigmentation on the fibrotic scar was also documented. These measurements and assessments were performed on the 2- and 5-year images for eyes that had fibrotic scar identified at 1 year (Fig 1).

## Candidate Risk Factors

Candidate risk factors for scar formation included baseline patient characteristics, such as age, gender, cigarette smoking, hypertension, diabetes, body mass index, dietary supplement use, cancers, hypercholesterolemia, and osteoarthritis. Ocular candidate risk factors were baseline VA in each eye; baseline morphologic features observed on color and fluorescein angiography, such as the type of CNV, hemorrhage, blocked fluorescence, nonfoveal scar and macular atrophy, and serous pigment epithelial detachment; baseline features observed on OCT images, such as intraretinal, subretinal, and sub-RPE fluid, vitreomacular adhesion and traction, subretinal hyper-reflective material, RPE elevation, subretinal tissue complex thickness (any combination of subretinal hyper-reflective material, pigment epithelium detachment, drusen material, and RPE), subretinal fluid thickness, and central retinal thickness; and the anti-VEGF drug and regimen used in the clinical trial period.

## Statistical Analysis

We used Kaplan–Meier estimates for the cumulative incidence of scar through 5-year follow-up. Subjects who did not participate in the CATT Follow-Up study were censored at 2 years. For subjects missing images during the first 2 years, the previous scar status was carried forward. We used univariate and multivariate Cox proportional hazards models to identify the baseline risk factors for scar development.

Risk factors were first evaluated by univariate analysis (without adjustment for any other risk factors) using a discrete time Cox proportional hazard model for time to scar formation. The factors with a *P* value <0.20 in the univariate analysis were included in a multivariate Cox proportional hazard model so that the independent effect of each risk factor could be assessed. The final multivariate model was created by applying a backward selection procedure that retained only those risk factors with a *P* value <0.05, with the exception of drug and regimen groups, which were included in all multivariate models. Adjusted hazard ratios (aHRs) for scar development during 5 years and their 95% confidence intervals (CIs) were calculated on the basis of the final multivariate models.

Among subjects who were identified with fibrotic scar at year 1 and followed up to year 5, we performed descriptive analysis for VA change over time, growth of fibrotic scar area over time, and hyperpigmentation changes over time, by using mean (standard deviation [SD]) for continuous measures and proportion for categorical measures. Fisher exact test was used for low-count frequency comparisons. All the statistical analyses were performed in SAS version 9.4 (SAS Institute Inc., Cary, NC), and *P* < 0.05 was considered to be statistically significant.

## Results

After excluding eyes with scar at baseline, ungradable scar status at baseline, or no gradable images after baseline, there were 1061 patients with at least 1 gradable set of images during follow-up (Fig S2, available at [www.aaojournal.org](http://www.aaojournal.org)). After excluding subjects who had missing values in 1 or more variables cited in the footnote of Table 1, there were 1020, 965, and 510 complete image sets available for scar assessment at 1, 2, and 5 years, respectively. The Kaplan–Meier estimates of the cumulative rates of scar were 32.0% at 1 year, 46.3% at 2 years, and 56.4% at 5 years (Fig 3).

Several baseline characteristics were associated with the development of scar through 5 years (Table 1). The presence of

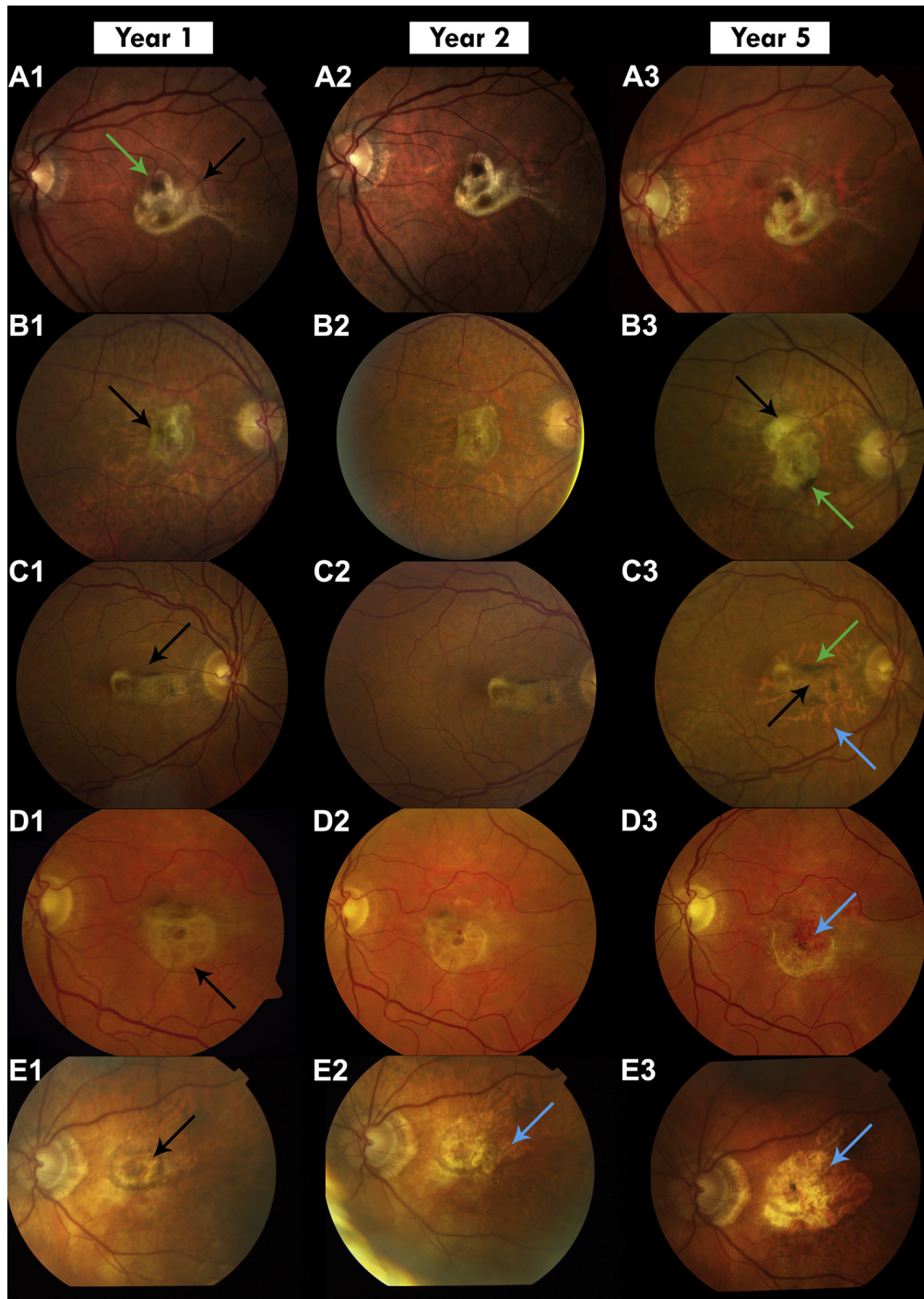
predominantly classic CNV was associated with 4.5-fold risk (aHR, 4.49; 95% CI, 3.34–6.04; *P* < 0.001) compared with occult CNV. Good baseline VA ( $\geq 20/20$ ) in the fellow eye was associated with increased risk of developing scar in the study eye (aHR, 1.34; 95% CI, 1.00–1.74; *P* = 0.04) compared with VA of 20/50 or worse. Large hemorrhages (>1 disc area [DA]) were associated with a more than 2-fold risk (aHR, 2.28; 95% CI, 1.49–3.47; *P* < 0.001) compared with no hemorrhages associated with the CNV. Eyes with central retinal thickness >212  $\mu\text{m}$  had increased risk (aHR, 2.58; CI, 1.69–3.94; *P* < 0.001) compared with eyes with central retinal thickness <120  $\mu\text{m}$ , and eyes with subretinal fluid thickness >0 to  $\leq 25$   $\mu\text{m}$  had increased risk (aHR, 1.84; 95% CI, 1.21–2.80; *P* = 0.01) compared with eyes without any subretinal fluid. Risk increased with the thickness of the subretinal tissue complex at the foveal center with a more than 2.5-fold risk for thickness >275  $\mu\text{m}$  (aHR, 2.64; 95% CI, 1.81–3.84; *P* < 0.001) compared with a thickness  $\leq 75$   $\mu\text{m}$ . The absence of RPE elevation (aHR, 1.71; 95% CI, 1.21–2.41; *P* = 0.002) and subretinal hyperreflective material (aHR, 1.72; 95% CI, 1.25–2.36; *P* < 0.001) increased the risk of scar by 70%. Incidence of scar was distributed similarly between the 2 drug groups and among the 3 dosing regimen groups (Table 1).

Photographic images at all 3 follow-up visits (1, 2, and 5 years) were available for 474 subjects, and 68 (14.3%) developed fibrotic scar in the study eye at 1 year. On average, the size of the scar changed slowly between years 1 and 5 (Fig 4). The change in size of fibrotic scars from year 1 to 2 and from year 2 to 5 is given in Table 2. The mean (SD) VA of these eyes was 61 [ $\approx 20/63$ ] (21) letters at 1 year, 63 [ $\approx 20/50$ ] (18) letters at 2 years, and 49 [ $\approx 20/100$ ] (26) at year 5. The mean (SD) VA was 38 [ $\approx 20/160$ ] (27) letters at year 5 in 8 eyes in which atrophy completely replaced the fibrotic scars (Table 3). The mean annual expansion rate of the fibrotic scar present in 68 eyes at year 1 was 0.02 (0.41) DA (range, –1.40 to 2.47; median, 0.004), whereas it was 0.20 (0.71) between year 2 and year 5 (range, –0.94 to 3.56; median, 0.01). The difference in the annual rate of expansion was not statistically significant (*P* = 0.33, Wilcoxon signed-rank test).

At 1 year, macular atrophy associated with fibrotic scar was observed in 12 eyes (18%), and the mean (SD) VA was 70 [ $\approx 20/40$ ] (15), whereas in eyes without macular atrophy associated with scar the mean (SD) VA was 59 [ $\approx 20/63$ ] (22) letters (*P* = 0.11). At 2 years, atrophy was observed in 16 eyes (24%) and the mean (SD) VA was 71 [ $\approx 20/40$ ] (13), whereas in eyes without atrophy the mean (SD) VA was 61 [ $\approx 20/63$ ] (19) letters (*P* = 0.04). At 5 years, atrophy was observed in 37 eyes (54%) and the mean (SD) VA was 44 [ $\approx 20/125$ ] (27), whereas in eyes without atrophy the mean (SD) VA was 53 [ $\approx 20/80$ ] (25) letters (*P* = 0.21). The average size of atrophy increased from 1.6 DA at year 1 to 2.0 DA in year 2 and to 3.1 DA in year 5 (Fig 5).

Among the 12 eyes with atrophy at year 1, the mean (SD) atrophy area increase was 0.73 (0.59) DA (range, 0.03–1.53 DA; median, 0.82 DA). Among the 16 eyes with atrophy at 2 years, the mean (SD) annual rate of area increase was 0.59 (0.53) (range, 0–1.53 DA; median, 0.51 DA). Among eyes that had both fibrotic scar and atrophy, there was no strong correlation between the area of the scar and the area of the atrophy, with correlation coefficients of 0.41 at year 1 (*N* = 12; *P* = 0.18), 0.35 at year 2 (*N* = 16; *P* = 0.18), and 0.01 at year 5 (*N* = 37 eyes; *P* = 0.96). The difference in the annual rate of expansion was –0.14 (0.7) DA (*P* = 0.79, Wilcoxon signed-rank test).

There were no significant associations with demographic or ocular characteristics between eyes with atrophy and eyes without atrophy in years 1, 2, or 5. Likewise, there were no significant associations with demographic or ocular characteristics between



**Figure 1.** Color images of fibrotic scar and macular atrophy associated with fibrotic scar (atrophy). **A**, Stable fibrotic scar: **A1** shows a fibrotic scar that has developed at year 1 (*black arrow*). It remains stable at years 2 and 5. There is hyperpigmentation on the scar (*green arrow*). **B**, Scar increasing in size: **B1** shows a fibrotic scar that shows no change in area from year 1 (**B1**) to year 2 (**B2**) but has a larger area in year 5 (**B3**) when there is growth superiorly (*black arrow*). There is also pigmentation on the scar (*green arrow*) at year 5. **C**, Scar with peripheral macular atrophy: **C1** shows a fibrotic scar at year 1 that undergoes thinning at year 2 (**B3**, *black arrow*) with an area of macular atrophy associated with fibrotic scar (atrophy) surrounding it in year 5 (**B3**, *green arrow*). Increased hyperpigmentation is also seen at year 5 (**B3**, *blue arrow*). **D**, Macular atrophy associated with fibrotic scar: **D1** shows a thick, round fibrotic scar at year 1 (*black arrow*). In year 5, the superior part of the fibrotic scar has been replaced by macular atrophy (**D3**, *blue arrow*). **E**, Scar completely replaced by macular atrophy: **E1** shows a fibrotic scar (*black arrow*) that develops atrophy in year 2 (**E2**, *blue arrow*), and eventually at year 5 the area of the fibrotic scar is replaced by an expanding macular atrophy (**E3**, *blue arrow*).

Table 1. Multivariable Model of Factors Associated with Incidence of Scar through Year 5

Baseline Characteristics	Eyes at Risk, N*	Scar, n (%)	Hazard Ratio (95% CI)	P Value
Drug				0.23
Ranibizumab	526	253 (48)	1.00	
Bevacizumab	484	256 (53)	1.15 (0.92–1.44)	
Dosing regimen during first 2 yrs				0.17
PRN for 2 yrs	504	248 (49)	1.00	
Switched from monthly to PRN at 1 yr	253	138 (55)	1.29 (0.98–1.69)	
Monthly for 2 yrs	253	123 (49)	1.02 (0.77–1.35)	
Baseline VA in fellow eye				0.04
≤20/50	308	146 (47)	1.00	
20/25–20/40	398	186 (47)	0.97 (0.74–1.28)	
≥20/20	304	177 (58)	1.34 (1.00–1.79)	
Lesion type				<0.001
Occult only	614	224 (36)	1.00	
Minimally classic	175	121 (69)	2.74 (2.04–3.69)	
Predominantly classic	221	164 (74)	4.49 (3.34–6.04)	
Hemorrhage associated with the lesion				<0.001
None	401	186 (46)	1.00	
≤1 DA	519	259 (50)	0.92 (0.73–1.18)	
>1 DA	90	64 (71)	2.28 (1.49–3.47)	
Retinal thickness at foveal center (μm)				<0.001
<120	103	44 (43)	1.00	
120–212	541	252 (47)	1.50 (1.00–2.24)	
>212	366	213 (58)	2.58 (1.69–3.94)	
Subretinal fluid thickness at foveal center (μm)				0.01
0	668	339 (51)	1.00	
>0–≤25	83	49 (59)	1.84 (1.21–2.80)	
>25	259	121 (47)	1.31 (0.97–1.75)	
Subretinal tissue complex thickness at foveal center (μm)				<0.001
>0–≤75	246	89 (36)	1.00	
>75–≤160	244	130 (53)	1.74 (1.23–2.46)	
>160–≤275	257	143 (56)	1.98 (1.38–2.82)	
>275	263	147 (56)	2.64 (1.81–3.84)	
RPE elevation				0.002
Yes	878	419 (48)	1.00	
No	132	90 (68)	1.71 (1.21–2.41)	
Subretinal hyperreflective material				<0.001
No	236	71 (30)	1.00	
Yes	774	438 (57)	1.72 (1.25–2.36)	

CI = confidence interval; DA = disc area; PRN = pro re nata; RPE = retinal pigment epithelium; VA = visual acuity.

P value from Cox proportional hazards model.

\*A total of 51 patients were not included in the multivariate model because of missing values in 1 or more of the following variables: lesion type, hemorrhage associated with the lesion, retinal thickness at foveal center (micrometers), subretinal fluid thickness at foveal center (micrometers), subretinal tissue complex thickness at foveal center (micrometers), RPE elevation, and subretinal hyperreflective material.

eyes with expanding atrophy and those without such expansion in years 1, 2, or 5 (Tables S4 and S5, available at [www.aajournal.org](http://www.aajournal.org)). Pigmentation on the fibrotic scars was seen in 13% of eyes at year 1, in 22% of eyes at year 2, and in 53% of eyes at year 5 (Fig 6).

## Discussion

Approximately one third of the CATT eyes developed retinal scar during the first year of treatment, and an additional 10% developed scar during the second year of treatment. At the completion of the 2-year clinical trial, the CATT subjects were released from their treatment protocol and were free to choose their ophthalmic care. Despite this change from the CATT clinical trial protocol and a longer follow-up period of 3 years, only an additional 10% of

subjects developed scar, indicating that in eyes with nAMD treated with anti-VEGF therapy, the majority of scars occur within the first year of treatment.

We had shown earlier that during the first 2 years of treatment of nAMD with anti-VEGF drugs, the risk factors present at baseline for developing a scar included predominantly the classic type of CNV, blocked fluorescence, thicker retina, larger foveal subretinal tissue complex thickness, foveal subretinal fluid, and subretinal hyperreflective material.<sup>16</sup> These risk factors, with the exception of blocked fluorescence, remained significantly associated with the development of scar through the additional 3 years of follow-up. However, 2 other baseline risk factors with a higher risk of scar were discovered: a better VA in the fellow eye and large hemorrhages. It is not entirely clear why a better VA in the fellow eye would be a risk factor for

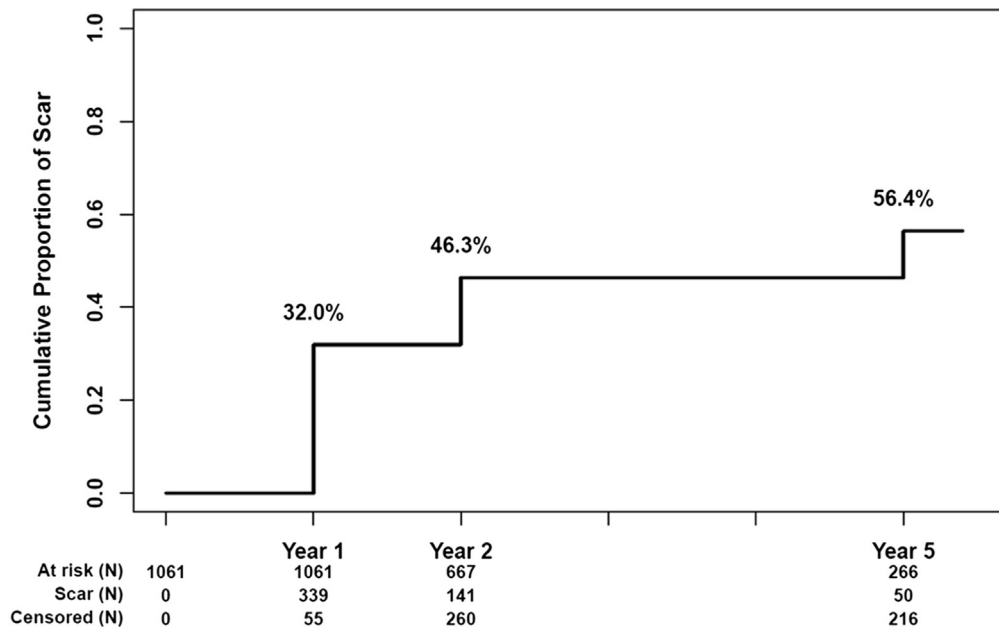


Figure 3. Kaplan–Meier graph showing the cumulative incidence of scar through 5 years.

development of scar in the study eye, but it is possible that it delayed the initial visit of the subject to an ophthalmologist and also might be less likely to be aggressively treated after the duration of the clinical trial.

The CATT study allowed recruitment of patients with nAMD having more than 50% hemorrhages relative to the total CNV lesion. Other major anti-VEGF clinical trials excluded such patients.<sup>18–20</sup> Therefore, the CATT cohort presented a unique opportunity to study eyes with hemorrhages that were more than 50% of the total CNV lesion, and many of the hemorrhages were larger than 1 DA. The VA in these eyes at the end of the 2-year clinical trial was similar to the eyes that did not have such large hemorrhages at enrollment.<sup>21</sup> However, the 5-year CATT Follow-Up study results show that relatively large hemorrhages present at enrollment, if observed over longer durations, more than double the risk of developing a scar. Apart from iron toxicity to the photoreceptors due to deposition of hemosiderin and the reduced nutrient flux, large hemorrhages promote the formation of scar and fibrin meshwork contraction that can further reduce vision by involving adjacent areas of the retina.<sup>22–29</sup>

We also found the risk for developing a scar due to predominantly classic lesions at enrollment increased from 3-fold at 2 years to 4.5-fold through 5 years. It is possible that this increased risk is caused by treated quiescent classic CNV lesions that relapsed over time and subsequently developed a scar. It is also possible that some occult lesions converted to classic lesions and increased the risk of developing a scar.<sup>30</sup>

Once a fibrotic scar developed during the first year after initiation of anti-VEGF therapy, several changes were observed in and around the scar over a period of time. By 5 years, only 15% of the fibrotic scars at year 1 remained stable without any observable changes in the color images. There was little change in the average size of fibrotic scar

between year 1 and 2, and the mean VA was maintained or slightly better at year 2 compared with year 1. However, over the time between the year 2 visit and the year 5 visit, the mean size of the fibrotic scar increased with a corresponding decrease in the mean VA in these eyes at year 5. The annualized rate of growth was similar from year 1 to 2 and year 2 to 5. The change due to difference in scar size and VA between the 2 periods could be attributed to a much longer time window in the second period and the difference in the type of care given during these 2 periods. During the first 2 years, the CATT clinical trial’s protocol required a monthly examination with anti-VEGF intravitreal injections given monthly or on a pro rata basis. At the end of 2 years, the CATT subjects were released from the protocol and were only seen after another 3 years. During this period, it is possible that reactivation of neovascularization occurred, resulting in extension of the scar area and reduction in vision.<sup>14</sup>

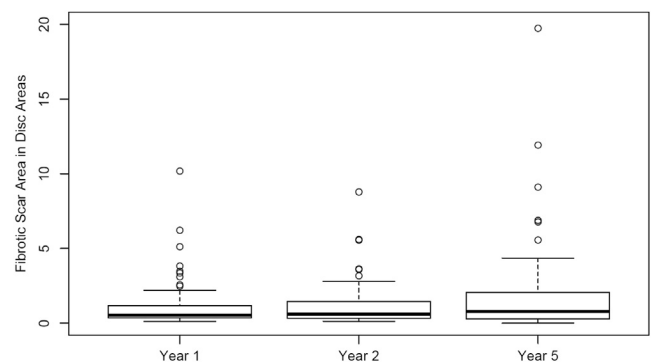


Figure 4. Box plot of fibrotic scar in disc areas over time among 68 eyes with fibrotic scar at year 1.

Table 2. Change in Fibrotic Scar Change over Time

Fibrotic Scar Size Change	N (%)	Mean (SD)	Median (Q1, Q3)
From year 1 to 2			
Increase	19 (27.9)	0.3 (0.6)	0.10 (0.07, 0.33)
Decrease	15 (22.1)	-0.3 (0.4)	-0.13 (-0.22, -0.08)
Same	34 (50.0)	NA	NA
From year 2 to 5			
Increase	33 (48.5)	1.8 (3.0)	0.94 (0.33, 1.48)
Decrease	23 (33.8)	-0.5 (0.6)	-0.37 (-0.65, -0.14)
Same	12 (17.6)	NA	NA
From year 1 to 5			
Increase	37 (54.4)	1.7 (2.8)	0.71 (0.21, 1.76)
Decrease	21 (30.9)	-0.7 (0.8)	-0.38 (-0.66, -0.13)
Same	10 (14.7)	NA	NA

NA = not available; Q = quartile; SD = standard deviation.

Macular atrophy associated with fibrotic scar develops within or adjacent to the scar and can encircle the scar partially or completely (Fig S2, available at [www.aaojournal.org](http://www.aaojournal.org)). Five years after enrollment, atrophy was observed in a little more than half of eyes that had developed a fibrotic scar at 1 year. As for fibrotic scar area expansion, the annualized increase in area was similar in the period of year 1 to year 2 and the period of year 2 to year 5. Mean VA in eyes that had atrophy at years 1 and 2 was good compared with eyes without atrophy but was reduced at 5 years. Expanding areas of atrophy are likely to produce scotomas and substantially affect vision when they involve the foveal center. Atrophy has been suggested to result from the remodeling of the choroid vasculature producing reduced blood flow around the scar and the subsequent ischemia causing RPE cell death.<sup>31</sup> It has also been suggested that anti-VEGF therapy may induce contracture of the CNV and the subretinal fibrosis and exert a traction force on the surrounding RPE and accelerate its destruction.<sup>32</sup> The changes within the fibrotic scar and in areas adjacent to it, such as the pigment accumulation and expanding macular atrophy, may be due to an aberrant wound-healing process influenced by the initial anti-VEGF treatment. Myopic CNV treated with anti-VEGF has been shown to have similar development of fibrotic scars and associated progressive chorioretinal atrophy with poor visual outcome.<sup>32</sup> However,

even before the start of the anti-VEGF era, Sarkis et al<sup>31</sup> had described the expanding macular atrophy associated with fibrotic scars developing from nAMD. They suggested that the expansion of such atrophy was faster during the earlier periods of follow-up, but the study was limited by its retrospective nature, with only a small number of eyes (n = 20) that had undergone treatment with laser photocoagulation, radiotherapy, intravitreal triamcinolone injections, or combinations of these.<sup>31</sup> Further, the measurements of atrophy in more than half of these commenced only after 2 years, unlike in our study that prospectively followed up fibrotic scars that had developed during the first year of therapy. It is not known whether the macular atrophy occurring as a result of nAMD without apparent fibrotic scar on color images is any different from this type of macular atrophy in terms of incidence, expansion, and association with VA. Reports on macular atrophy as a result of nAMD have not distinguished atrophy associated with fibrotic scar from macular atrophy without any preexisting fibrosis.<sup>4,5,10,33,34</sup>

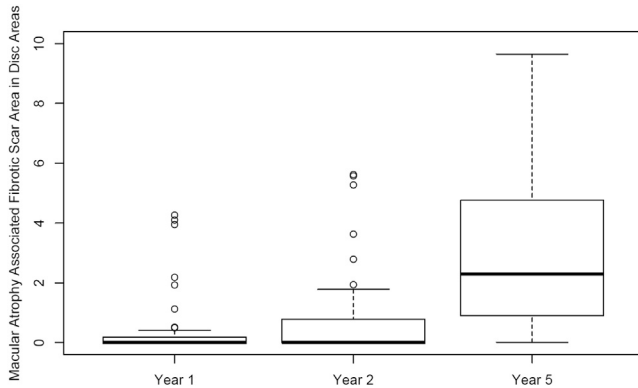
Our study had certain limitations. Although the follow-up at 2 years among living patients was high (93%), only 71% of living patients completed a follow-up study visit. The loss to follow-up may have resulted in inaccurate estimation of the incidence of scar from year 2 to year 5.

In our study, we were unable to find a strong correlation between scar area and atrophy area at all 3 follow-up time points when images were available for assessment. Also, limited by the small sample size, we were unable to identify any baseline demographic or ocular features that would predict the development and expansion of atrophy. It appears as though the expanding fibrotic scar and atrophy contribute to the decrease in VA in CATT study eyes at 5 years, even though they do not seem to substantially affect VA in year 2. Regular and long-term examinations of eyes to assess the development and progression of atrophy may be particularly important in clinical trials of antifibrotic agents to reduce the incidence of fibrotic scars after treatment of nAMD with anti-VEGF agents.<sup>35-38</sup> In one tenth of eyes with fibrotic scar at year 1, atrophy appears to completely replace the fibrotic scar by year 5. It is possible that the collagen fibers are phagocytosed by Bruch's membrane macrophages, which have been shown to be present in high counts in eyes with subclinical CNV.<sup>39</sup>

Table 3. Scar and Macular Atrophy Area and Visual Acuity at Years 1, 2, and 5 among Study Eyes with Fibrotic Scar at Year 1 (N = 68)

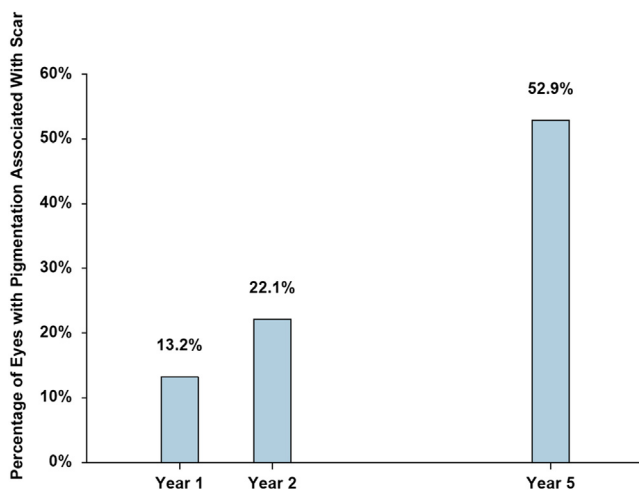
	Year	N	Size in Disc Area			Visual Acuity (Letters), Mean (SD)
			Mean (SD)	Median (Min, Max)	Q1, Q3	
Fibrotic scar	1	68	1.2 (1.6)	0.54 (0.11, 10.18)	0.36, 1.19	61.1 (21.0)
	2	68	1.2 (1.5)	0.60 (0.13, 8.78)	0.34, 1.44	63.2 (18.3)
	5	68	1.9 (3.1)	0.77 (0.00, 19.74)	0.29, 2.06	48.1 (26.5)
Macular atrophy associated with fibrotic scar	1	12	1.6 (1.6)	0.82 (0.14, 4.27)	0.29, 3.07	69.9 (14.7)
	2	16	2.0 (2.0)	1.12 (0.18, 5.62)	0.68, 3.21	71.4 (13.0)
	5	37	3.1 (2.6)	2.30 (0.01, 9.66)	0.90, 4.76	44.4 (27.1)

Max = maximum; Min = minimum; N = number of eyes; Q = quartile; SD = standard deviation.



**Figure 5.** Box plot of macular atrophy associated with fibrotic scar (atrophy) in disc areas at 1, 2, and 5 years among 68 eyes with fibrotic scar at year 1.

The number of treated eyes having pigmentation in or around the fibrotic scars was observed to increase proportionally with the years of follow-up, starting with 14% during the first year and involving more than half the subjects at year 5. This phenotypical presentation of pigmentation may be important, because it is believed that RPE cells undergo epithelial–mesenchymal transition and the melanotic cells that are unique to CNV are associated with atrophy with and without basal laminar deposits. This transdifferentiation of RPE cells from epithelial to mesenchymal phenotype can cause the RPE cells to adhere to and exert traction forces on the extracellular matrix and could be one of the factors contributing to the evolution of atrophy clinically.<sup>40–42</sup> The atrophy process increases with time and is consistent with a shift in biologic activities observed during continued passage of RPE cells in vitro.<sup>43</sup> The phenotypic diversity of RPE and its changing biological activity seen at a molecular level need to be understood clinically, and careful examination by different imaging



**Figure 6.** Bar diagram of percentages of eyes with fibrotic scar pigmentation in years 1, 2, and 5 among 68 eyes with fibrotic scar at year 1.

modalities of the evolution of nAMD into a fibrotic scar and its gradual erosion by atrophy in eyes treated with anti-VEGF injections offers this opportunity.<sup>44–46</sup>

In summary, a relatively small percentage of CATT subjects develop scar after 2 years compared with the first 2 years under anti-VEGF treatment. Large hemorrhages at enrollment appear to influence scar formation at later periods of follow-up. Fibrotic scars that developed at 1 year tended to change in size or be accompanied by atrophy and pigmentation, with only 15% remaining stable throughout the follow-up period. We observed a slow average increase in the area of fibrotic scar, probably due to ongoing organization of the collagen fibers or development of new areas of nAMD. Contiguous macular atrophy developed in an increasing number of eyes through 5 years, and the area expanded in size. We were unable to find any significant association with atrophy incidence or expansion with any of the baseline demographic or ocular characteristics.

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Abbreviations and Acronyms:

**aHR** = adjusted hazard ratio; **CATT** = Comparison of Age-related Macular Degeneration Treatments Trials; **CFP** = color fundus photograph; **CI** = confidence interval; **CNV** = choroidal neovascularization; **DA** = disc area; **FA** = fluorescein angiogram; **nAMD** = neovascular age-related macular degeneration; **RPE** = retinal pigment epithelium; **SD** = standard deviation; **VA** = visual acuity; **VEGF** = vascular endothelial growth factor.

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