

Incidence of Choroidal Neovascularization in the Fellow Eye in the Comparison of Age-Related Macular Degeneration Treatments Trials

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Objective: To assess the influence of drug; dosing regimen; and traditional, nontraditional, and genetic risk factors on the incidence of choroidal neovascularization (CNV) in the fellow eye of patients treated for CNV with ranibizumab or bevacizumab.

Design: Cohort study of patients enrolled in a multicenter, randomized clinical trial.

Participants: Patients with no CNV in the fellow eye at the time of enrollment in the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT).

Methods: Eligibility criteria for the clinical trial required that study eyes have evidence on fluorescein angiography and optical coherence tomography of CNV secondary to age-related macular degeneration (AMD) and visual acuity between 20/25 and 20/320. Treatment for the study eye was assigned randomly to either ranibizumab or bevacizumab and to 3 different regimens for dosing over a 2-year period. The genotypes for 4 single nucleotide polymorphisms (SNPs) associated with risk of AMD were determined. Only patients without CNV in the fellow eye at baseline were considered at risk. The CATT ophthalmologists examined patients every 4 weeks through 2 years and recorded treatment for CNV in the fellow eye.

Main Outcome Measures: Development of CNV in the fellow eye.

Results: Among 1185 CATT participants, 727 (61%) had no CNV in the fellow eye at enrollment. At 2 years, CNV had developed in 75 (20.6%) of 365 patients treated with ranibizumab and in 60 (16.6%) of 362 patients treated with bevacizumab (absolute difference, 4.0%; 95% confidence interval [CI], -1.7% to 9.6%; $P = 0.17$). The risk ratio for pro re nata dosing relative to monthly dosing was 1.1 (95% CI, 0.8–1.6). Greater elevation of the retinal pigment epithelium and fluid in the foveal center of the study eye were associated with increased incidence of CNV in the fellow eye. Incidence was not associated with genotype on rs1061170 (*CFH*), rs10490924 (*ARMS2*), rs11200638 (*HTRA1*), and rs2230199 (*C3*; $P > 0.35$).

Conclusions: Through 2 years, there was no statistically significant difference between ranibizumab and bevacizumab in incidence of CNV in the fellow eye. Genotype on 4 SNPs previously found to be associated with AMD did not affect the risk of CNV in the fellow eye among CATT patients.

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The presence of choroidal neovascularization (CNV) in 1 eye of a patient with age-related macular degeneration (AMD) is an established and strong risk factor for development of CNV in the contralateral (fellow) eye.^{1–5} In previous large-scale studies, the annual incidence of CNV in fellow eyes ranged from 4% to 19%.^{3,4,6–8} Variation in incidence rates may reflect differences in the method of identifying CNV, for example, clinical examination versus reading center interpretation, as well as differences among patient groups with respect to risk factors such as large

drusen, pigmentary abnormalities, genetic background, and intake of foods or supplements with high levels of antioxidant vitamins and zinc.⁹

Between 2005 and 2011, nearly all patients with newly diagnosed CNV secondary to AMD in the United States were treated with intravitreal injections of ranibizumab (Lucentis; Genentech, Inc, South San Francisco, CA) or bevacizumab (Avastin; Genentech).^{10,11} These drugs bind vascular endothelial growth factor (VEGF) and are derived from similar monoclonal antibodies. Results from the

Comparison of Age-Related Macular Degeneration Treatments Trials (CATT), a multicenter, randomized clinical trial of the efficacy and safety of ranibizumab and bevacizumab for the treatment of CNV secondary to AMD, showed that through 2 years of treatment, the drugs have equivalent effects on visual acuity and that dosing on a pro re nata (PRN) basis resulted in less gain in visual acuity (mean, 2.4 letters) than monthly dosing.^{12,13}

However, the effects of the drugs differed in several areas. At 1 and 2 years after initiation of treatment, eyes treated with ranibizumab had less fluid on optical coherence tomography and had less retinal thickness.^{12,13} In addition, CATT patients treated with bevacizumab had more serious adverse events during 2 years than patients treated with ranibizumab (39.9% vs. 31.7%; $P = 0.004$). In a multicenter clinical trial conducted in Great Britain with a study design similar to that of CATT, patients with bevacizumab had more serious adverse events within 1 year than those treated with ranibizumab, but not to a statistically significant degree (12.5% vs. 9.6%; $P = 0.25$).¹⁴ In CATT, most adverse events were conditions that have not been associated with VEGF inhibition in clinical trials for patients with cancer. As a consequence, the interpretation of the adverse event findings was not clear, and instead raised questions regarding different systemic effects with the 2 drugs.

The possibility that ranibizumab and bevacizumab may have systemic effects has prompted interest in possible therapeutic effects in the fellow eye after intravitreal injection in one eye. A retrospective evaluation of the incidence of CNV in fellow eyes from 2 clinical trials involving sham injections or treatment with photodynamic therapy, which has no known effect on VEGF, found no evidence of a reduction in incident CNV with monthly injections of ranibizumab.⁷ However, there are reports of resolution of retinal neovascularization, diabetic macular edema, and uveitic cystoid macular edema in the fellow eye after unilateral intravitreal treatment with bevacizumab.^{15–17}

The data collected on patients participating in CATT provide the opportunity to explore whether systemic effects of intravitreal injections on the incidence of CNV in the fellow eye differ between ranibizumab and bevacizumab. In addition, morphologic features of the study eye and genotypes of single nucleotide polymorphisms (SNPs) within genes associated with AMD may be evaluated as risk factors.

Patients and Methods

Study Population for the Clinical Trial

Details of the design and methods for CATT have been published previously.¹² Only features relevant to the evaluation of incidence of CNV in the fellow eye are noted here. Patients were enrolled through 43 clinical centers in the United States between February 2008 and December 2009. Only 1 eye per patient, the study eye, needed to be eligible for the clinical trial and only that eye was assigned. Inclusion criteria included age 50 years or older, presence in the study eye of previously untreated active CNV secondary to AMD, and visual acuity between 20/25 and 20/320 in the study eye. Active CNV was considered present when both leakage on fluorescein angiography and fluid on time-domain

optical coherence tomography (OCT) were documented through central review of images. Fluid on OCT could be within or beneath the retina or beneath the retinal pigment epithelium (RPE). Either neovascularization, fluid, or hemorrhage needed to be under the fovea. For the CNV to be considered secondary to AMD, at least 1 druse larger than 63 μm needed to be present in either the study eye or fellow eye, or the fellow eye needed to have CNV or geographic atrophy. The study was approved by an institutional review board associated with each center. All patients provided written informed consent.

Treatment of the Study Eye

At enrollment, patients were assigned with equal probability to 1 of 4 treatment groups defined by drug (ranibizumab or bevacizumab) and by dosing regimen (monthly or PRN). At 1 year, patients initially assigned to monthly treatment retained their drug assignment but were reassigned randomly, with equal probability, to either monthly or PRN treatment. Patients initially assigned to PRN treatment had no change in assignment; that is, they retained both their drug assignment and PRN dosing regimen for year 2.

Study Procedures

During the initial visit, patients provided a medical history and were examined by a study-certified ophthalmologist. The ophthalmologist indicated whether there was a history of CNV or active CNV in the nonstudy eye. Patients underwent bilateral color stereoscopic fundus photography and fluorescein angiography that included stereo images of the macula of the fellow eye at 2 and 10 minutes after dye injection. Study eyes also were imaged at the initial visit with time-domain OCT. Follow-up examinations were scheduled every 28 days for 2 years. During each examination, the study ophthalmologist completed case report forms with specific questions regarding whether there had been any treatment for CNV in the nonstudy eye since the last CATT examination or whether treatment was scheduled on the day of the examination. Color fundus photography and fluorescein angiography were performed at 52 weeks and 104 weeks.

Certified graders at the CATT fundus photograph reading center and the CATT OCT reading center reviewed images acquired at the initial and follow-up visits. Morphologic features of the study eyes at baseline were evaluated.^{18,19} Graders at the photograph reading center were required to indicate whether there were signs at the initial visit of CNV or scar in the fellow eye or to indicate that no determination could be made because of missing or poor-quality images. The following signs were considered evidence of CNV or scar: leakage or late staining of fluorescein on angiography or fibrous tissue on color photographs.

Between July 2010 and September 2011, CATT patients were invited to provide blood samples for genetic studies. Blood samples from patients were sent to the CATT genetics laboratory for DNA extraction. Four SNPs previously associated with risk and progression of AMD were evaluated: (1) complement factor H (*CFH*) Y402H (rs1061170), (2) age-related maculopathy susceptibility 2 (*ARMS2*; also called *LOC387715*) A69S (rs10490924), (3) high temperature requirement factor A2 (*HTRA1*; rs11200638), and (4) complement component 3 (*C3*) R80G (rs2230199).^{20,21}

Definitions of Patients at Risk and Development of Choroidal Neovascularization

Patients were at risk of incident CNV if there was documentation of CNV secondary to AMD in the study eye and neither the enrolling ophthalmologist nor the reading center graders detected evidence of CNV or scar in the fellow eye. Choroidal neovascularization in the

fellow eye was considered present at the earliest follow-up visit when the examining ophthalmologist indicated that treatment for CNV in the fellow eye had occurred since the last study examination or would occur on the day of the study visit.

Statistical Analyses

Estimates of the cumulative proportion of patients in whom CNV developed in the fellow eye were calculated by the Kaplan-Meier method, and differences between treatment groups were assessed with the log-rank test. The discrete-time Cox proportional hazards model, with the exact method for handling ties in time of onset of CNV, was used to estimate relative hazard rates. Dosing regimen was a time-dependent covariate to accommodate the rerandomization at 1 year of patients assigned to monthly treatment at the time of enrollment. The proportional hazards assumption for drugs was tested by including an interaction term involving drug and log ($t + 4$, where t is the number of weeks since baseline). The following factors were included in the models as established, traditional risk factors for developing CNV: older age, female gender, cigarette smoking, the Age-Related Eye Disease Study (AREDS) simple risk score, and not taking β carotene, vitamin C, vitamin E, or zinc.²² Genotype was summarized as the number of risk alleles present. Statistical computations were performed with SAS software version 9.3 (SAS Inc, Cary, NC).

Results

In a total of 135 (18.6%) patients, CNV developed in the fellow eye among the 727 patients who were at risk. At 1 year, the proportion of patients with CNV was similar among those treated with ranibizumab (7.9%) and bevacizumab (7.2%; $P = 0.76$). At 2 years, in 75 (20.6%) of 365 patients in the ranibizumab group and in 60 (16.6%) of 362 patients in the bevacizumab treatment group, CNV had developed in the fellow eye. The difference in rates was 4.0% (95% confidence interval [CI], -1.7% to 9.6% ; $P = 0.17$). The Kaplan-Meier estimates of cumulative incidence show that most of the difference between drug groups occurred during year 2 ($P = 0.20$; Fig 1). In an analysis of time to CNV with the Cox model, the hazard ratio for CNV among those treated with bevacizumab compared with those treated with ranibizumab was 0.8 (95% CI, 0.6–1.2; Table 1). Adjustment for factors previously associated with incidence of CNV had little influence on the estimates. Among the factors, only female gender, higher AREDS risk score, and use of dietary supplements were associated significantly with higher incidence of CNV in the fellow eye. The hazard ratio in the multivariate model for CNV among those treated PRN compared with those treated monthly was 1.1 (95% CI, 0.8–1.6).

Morphologic characteristics of the study eye at the initial visit, as captured on color fundus photography, fluorescein angiography, and OCT, were evaluated as risk factors for development of CNV in the fellow eye. The characteristics evaluated included area of CNV, area of the CNV lesion, subfoveal CNV, angiographic type of CNV (occult, classic, both), CNV lesion composition, presence of retinal angiomatous proliferation, area of hemorrhage associated with the CNV lesion, geographic atrophy in the study eye, retinal thickness, subretinal thickness, sub-RPE thickness, presence of intraretinal fluid, presence of subretinal fluid, presence of sub-RPE fluid, presence of fluid in the foveal center on OCT, maximum height of RPE elevation, and presence of subretinal hyperreflective material. Among these, only the presence of fluid in the fovea and greater height of RPE elevation were associated with increased risk of CNV in the fellow eye after adjustment for other known risk factors (Table 1, last 2 columns).

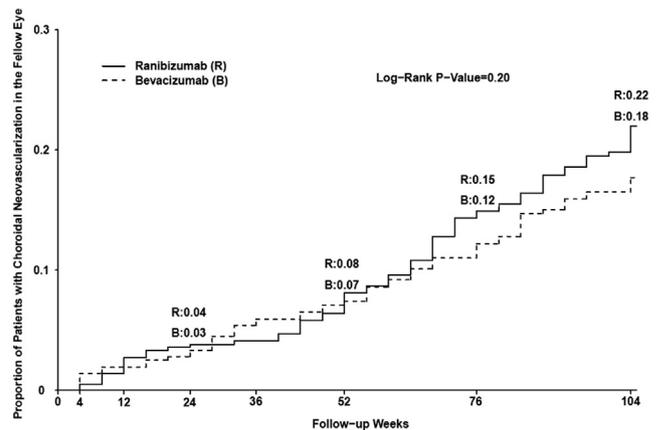


Figure 1. Kaplan-Meier estimates of cumulative incidence of choroidal neovascularization in the fellow eye by assigned drug.

The association between development of CNV and genotype for the 4 SNPs previously associated with risk and progression of AMD was evaluated within the 518 patients who had genotyping (Table 2). Overall, the proportion of patients developing CNV in the fellow eye did not decrease with a lower number of risk alleles. Adjusting for the age, gender, and smoking habits of patient did not alter the results.

Discussion

The overall incidence of CNV in the fellow eye among CATT patients was approximately 10% per year, comparable with the rates observed in large-scale studies relying on central interpretation of photographs for identifying CNV.^{2–6} Comparison of the 2-year incidence of CNV in fellow eyes of CATT patients treated unilaterally with either ranibizumab or bevacizumab did not reveal a statistically significant difference between drugs. At 1 year, the rates for ranibizumab (7.9%) and bevacizumab (7.2%) were virtually identical. By 2 years, the rate for ranibizumab (20.6%) was numerically higher than that for bevacizumab (16.6%), but not to a statistically significant degree (4.0% absolute difference; 95% CI, -1.7% to 9.6%). Nonetheless, the difference is intriguing because of reports of higher systemic VEGF suppression by bevacizumab than ranibizumab and the plausibility of a lag time between the initiation of therapy and an effect on clinically apparent neovascularization.^{14,23–25}

Several findings from other studies support the plausibility that intravitreal bevacizumab may have an effect in the fellow eye that is different from that of ranibizumab.^{23,24} In animals, bevacizumab has a longer half-life in the vitreous and only bevacizumab has been found in fellow eyes of animals receiving unilateral injections.^{23,24,26–32} After the drugs reach the bloodstream, there is a sizable difference between the serum elimination half-lives of ranibizumab (approximately 2 hours) and bevacizumab (20 days).³³ In humans, serum VEGF levels are reduced after intravitreal injections of bevacizumab in patients with proliferative diabetic retinopathy, retinopathy of prematurity, and neovascular AMD.^{34–38} In a comparative study of 62 patients, the plasma level of VEGF among those treated for

Table 1. Risk Factors for Incidence of Choroidal Neovascularization in the Fellow Eye from the Cox Proportional Hazards Model

Characteristic	No.	Choroidal Neovascularization, n (%)	Model with Traditional Risk Factors Only		Model with All Risk Factors	
			Rate Ratio (95% Confidence Interval)	P Value*	Rate Ratio (95% Confidence Interval)	P Value*
Drug						
Ranibizumab	365	75 (20.6)	1.0	0.32	1.0	0.34
Bevacizumab	362	60 (16.6)	0.8 (0.6–1.2)		0.8 (0.6–1.2)	
Dosing regimen [†]						
Monthly	358	66 (18.4)	1.0	0.61	1.0	0.62
PRN	369	69 (18.7)	1.1 (0.8–1.6)		1.1 (0.8–1.6)	
Age (yrs)						
50–69	96	14 (14.6)	1.0	0.29	1.0	0.39
70–79	268	49 (18.3)	1.4 (0.7–2.5)		1.2 (0.7–2.3)	
80–89	323	64 (19.8)	1.5 (0.8–2.7)		1.3 (0.7–2.4)	
≥90	40	8 (20.0)	1.4 (0.6–3.8)		1.4 (0.6–3.3)	
Gender						
Female	446	98 (22.0)	1.0	0.01	1.0	0.03
Male	281	37 (13.2)	0.6 (0.4–0.9)		0.6 (0.4–0.95)	
Cigarette smoking						
Never	297	56 (18.9)	1.0	0.44	1.0	0.32
Quit	369	67 (18.2)	1.3 (0.9–1.8)		1.2 (0.9–1.8)	
Current	61	12 (19.7)	1.3 (0.7–2.6)		1.6 (0.8–3.0)	
Definite hypertension						
Normal	166	28 (16.9)	1.0	0.62	1.0	0.61
Suspect	58	12 (20.7)	1.4 (0.7–2.8)		1.4 (0.7–2.8)	
Definite	503	95 (18.9)	1.1 (0.7–1.6)		1.2 (0.7–1.8)	
AREDS risk score						
0	37	2 (5.4)	1.0	0.004	1.0	0.01
1	111	12 (10.8)	2.0 (0.4–8.9)		1.9 (0.4–8.6)	
2	552	117 (21.2)	3.9 (1.0–15.8)		3.6 (0.9–14.5)	
Dietary supplements						
None	70	6 (8.6)	1.0	0.02	1.0	0.01
Antioxidants [‡] and zinc	464	81 (17.5)	1.7 (0.7–4.0)		1.7 (0.7–4.0)	
Other supplements	193	48 (24.9)	2.6 (1.1–6.0)		2.8 (1.2–6.6)	
Fluid in foveal center						
No	136	14 (10.3)	—	—	1.0	0.03
Yes	590	121 (20.5)	—	—	1.9 (1.1–3.3)	
RPE elevation (mm)						
≤3.0	215	27 (12.6)	—	—	1.0	0.01
>3.0–≤5.0	138	23 (16.7)	—	—	1.2 (0.7–2.0)	
>5.0–≤11.5	175	38 (21.7)	—	—	1.4 (0.9–2.4)	
>11.5	175	45 (25.7)	—	—	1.8 (1.1–3.0)	

- = Characteristic not included in the model; rate ratio and P value not applicable; AREDS = Age-Related Eye Disease Study; PRN = pro re nata; RPE = retinal pigment epithelium.

*P value for test of linear trend for age, AREDS risk score, and RPE elevation.

[†]No. and percentage based on the original dosing assignment; hazard ratio, confidence interval, and P value based on dosing regimen as a time-dependent covariate in the model.

[‡]Antioxidants: beta carotene, vitamin C, and vitamin E.

neovascular AMD with 3 consecutive monthly injections decreased in patients treated with bevacizumab, but not in patients treated with ranibizumab.²⁵ In the Alternative Treatments to Inhibit VEGF in Age-Related Choroidal Neovascularization trial, a randomized clinical trial of 610 patients, serum levels of VEGF were reduced with both ranibizumab and bevacizumab after 1 year of treatment; however, the levels in patients treated with bevacizumab were approximately half those in patients treated with ranibizumab.¹⁴

Among the traditional risk factors evaluated, the strongest gradient in risk was seen with the AREDS risk score based on large drusen and pigmentary abnormalities

(Table 1). Females had a higher risk than males; female gender has been an inconsistent risk factor for CNV in previous studies.²⁰ Although the risk ratios for developing CNV increased with age and current smoking status, these factors were not statistically significant within this group of patients with unilateral CNV at baseline. The range of risk within CATT is restricted because there are no low-risk eyes. The constrained differences in risk between groups and the relatively small proportion of eyes in which CNV developed limit the power to detect statistically significant effects of traditional, as well as nontraditional, risk factors. Both patients who took β carotene, vitamin C, vitamin E, and zinc in some amount and patients who used

Table 2. Association of Choroidal Neovascularization in Fellow Eye with Genotype for 4 Single Nucleotide Polymorphisms Associated with Age-Related Macular Degeneration

Single Nucleotide Polymorphism	Genotype*	No. (N = 518)	Choroidal Neovascularization, n (%)	Survival Analysis	
				Unadjusted, Rate Ratio (95% Confidence Interval) [†]	Adjusted, Rate Ratio (95% Confidence Interval) [‡]
CFH (rs1061170)	CC	174	28 (16.1)	1.0	1.0
	TC	246	57 (23.2)	1.5 (1.0–2.4)	1.4 (0.9–2.2)
	TT	98	19 (19.4)	1.2 (0.7–2.2)	1.2 (0.7–2.1)
P value				0.36	0.48
ARMS2 (rs10490924)	TT	99	21 (21.2)	1.0	1.0
	GT	249	50 (20.1)	0.9 (0.6–1.5)	0.9 (0.6–1.6)
	GG	170	33 (19.4)	0.9 (0.5–1.5)	0.8 (0.5–1.4)
P value				0.64	0.48
HTRA1 (rs11200638)	AA	95	21 (22.1)	1.0	1.0
	AG	245	49 (20.0)	0.9 (0.5–1.5)	0.9 (0.5–1.5)
	GG	178	34 (19.1)	0.8 (0.5–1.4)	0.8 (0.4–1.4)
P value				0.51	0.38
C3 (rs2230199)	GG	41	7 (17.1)	1.0	1.0
	CG	188	36 (19.2)	1.1 (0.5–2.5)	1.0 (0.4–2.2)
	CC	289	61 (21.1)	1.2 (0.6–2.7)	1.0 (0.4–2.2)
P value				0.49	0.91
No. of risk alleles	0–1	79	15 (19.0)	1.0	1.0
	2	84	20 (23.8)	1.3 (0.7–2.5)	1.4 (0.7–2.7)
	3	113	21 (18.6)	1.0 (0.5–1.9)	1.1 (0.6–2.1)
	4	104	20 (19.2)	1.0 (0.5–2.0)	1.1 (0.6–2.2)
	≥5	138	28 (20.3)	1.1 (0.6–2.1)	1.3 (0.7–2.5)
P value				0.86	0.74

*The risk alleles are C for CFH, T for ARMS2, A for HTRA1, and G for C3.

[†]Cox model with genotype coded according to the number of risk alleles.

[‡]Cox model adjusted for age, gender and smoking status.

other dietary supplements had higher rates of CNV. This finding seems to contradict the results of the AREDS, in which patients randomly assigned to these antioxidant vitamins and zinc showed decreased risk of late AMD developing.⁹ Patients who choose to take these supplements may have worse health or other factors that both increase their risk of CNV developing in the fellow eye and increase the likelihood that they take supplements.

Two morphologic features of the study eye at baseline were identified as risk factors from among 17 features evaluated. Eyes with greater RPE elevation or fluid in the foveal center on OCT had higher rates of CNV in the fellow eye. Replication of these findings is required before these 2 features can be established as true risk factors.

Patients within CATT with more risk alleles for each of 4 SNPs associated with an increased risk of AMD (CFH, ARMS2, HTRA1, and C3) did not have increased risk of CNV developing in the fellow eye. Findings from a recent report involving 207 Japanese patients showed a strong association of incidence of CNV in the fellow eye with ARMS2 A69S.³⁹ Patients with a TT genotype had a much higher risk than those with a GG genotype (rate ratio, 2.7; 95% CI, 1.4–5.5). Approximately 60% of the CNV in the study group was polypoidal choroidal vasculopathy, a form of neovascular macular degeneration much more common in Asian populations than other racial groups. The results from a study of 108 patients from The Netherlands did not find an association between genotype for CFH, ARMS2, or C3 and risk of CNV in the fellow

eye.⁴⁰ In the CATT, the CIs for the rate ratios comparing those with no risk alleles with those with 2 risk alleles included 0.5 (approximately a halving of risk) as well as 2.0 (approximately a doubling of risk). It is possible that 1 or more of the SNPs evaluated may have a clinically meaningful impact on risk of fellow eye involvement that was not detected with the CATT data.

The strengths of this investigation include being able to exclude fellow eyes identified by the examining ophthalmologist or the reading center graders as already having CNV at baseline, having close monitoring of the fellow eye through monthly examination of patients, and having accurate information on several important risk factors for CNV. One weakness of this study is that there were no untreated patients for comparison. Another weakness is the limited precision in estimating risk provided by CATT's sample size. The CIs show that large differences in risk between drugs, risk factor levels, or genotypes are unlikely, but that modest increases or decreases in risk truly may exist.

Analysis of the data on incidence of CNV in the fellow eye of CATT patients through 2 years did not identify a differential effect of ranibizumab and bevacizumab or effects of genotype on 4 previously identified risk alleles. The components of the AREDS simple scale, large drusen and pigmentary abnormalities, again were shown to be strong predictors of risk and are easily available to ophthalmologists when discussing prognosis with patients having 1 eye with CNV.

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A listing of the CATT Research Group can be found in [Appendix 1](#) (available at <http://aojournal.org>).

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