Risk Factors for Choroidal Neovascularization and Geographic Atrophy in the Complications of Age-Related Macular Degeneration Prevention Trial

The Complications of Age-related Macular Degeneration Prevention Trial (CAPT) Research Group

Objective: To determine risk factors for choroidal neovascularization (CNV) and of geographic atrophy (GA) in eyes with large drusen.

Design: Cohort study within a multicenter, randomized clinical trial of laser treatment for the prevention of vision loss from advanced age-related macular degeneration.

Participants: One thousand fifty-two participants with 10 or more large drusen (≥125 μm) and visual acuity of 20/40 or better in each eye.

Methods: At baseline, participants provided a brief medical history. Trained readers evaluated baseline color photographs for drusen characteristics and pigmentary abnormalities. One eye of each participant was assigned to laser treatment and the contralateral eye was assigned to observation. The Complications of Age-Related Macular Degeneration Prevention Trial (CAPT) Reading Center readers identified CNV and endpoint GA from color photographs and fluorescein angiograms obtained during follow-up visits scheduled for 5 or 6 years. Estimates of relative risks (RRs) and 95% confidence intervals (CIs) were obtained from survival analyses of observed and treated eyes, considered separately and combined.

Main Outcome Measures: Development of CNV and of endpoint GA.

Results: Choroidal neovascularization developed in 141 observed eyes and 141 treated eyes, including 57 patients affected bilaterally. Statistically significant risk factors for CNV in the multivariate model for all eyes were older age (RR, 2.81 [95% CI, 1.33–5.94] for >79 years vs. 50–59 years), cigarette smoking (RR, 1.98 [95% CI, 1.16–3.39] for current vs. never), and focal hyperpigmentation (RR, 1.84 [95% CI, 1.22–2.76] for ≥250 μm vs. none). Among eyes free of GA at baseline, endpoint GA developed in 61 observed eyes and in 58 treated eyes, including 29 patients affected bilaterally. Statistically significant risk factors for GA in the multivariate model for all eyes were older age (RR, 6.39 [95% CI, 1.64–24.9] for >79 years vs. 50–59 years), greater retinal area covered by drusen (RR, 5.10 [95% CI, 2.57–10.1] for ≥25% vs. <10%), retinal pigment epithelium (RPE) depigmentation (RR, 2.64 [95% CI, 1.26–5.53), and focal hyperpigmentation (RR, 10.4 [95% CI, 4.51–24.0] for ≥250 μm vs. none).

Conclusions: Among CAPT participants, increased age and focal hyperpigmentation were risk factors for the development of CNV and for GA. Cigarette smoking was significantly associated with CNV only, whereas retinal area covered by drusen and RPE depigmentation were associated significantly with GA only.

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People having eyes with many large drusen face substantial risk of progressing to choroidal neovascularization (CNV), geographic atrophy (GA), or both, which are the advanced stages of age-related macular degeneration (AMD) frequently responsible for severe loss of vision. The Complications of Age-Related Macular Degeneration Prevention Trial (CAPT) found that light-intensity laser treatment did not reduce the risk of the development of CNV, GA, or loss of visual acuity.[1]

Results from many earlier studies have addressed risk factors for CNV or for advanced AMD, that is, either CNV or GA.[2] However, the only previous study to have sufficient incident cases of advanced late AMD to support examination of risks of CNV and GA separately was the Age-Related Eye Disease Study (AREDS), and most of the eyes in AREDS did not have the high number of large drusen required for entry into CAPT.[3] To determine the extent to which previously identified risk factors extend to eyes that have already progressed well beyond the threshold for early AMD, this study analyzed the association between baseline participant demographic and medical history information, as well as features of early and intermediate AMD on color

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fundus photographs and fluorescein angiograms, and the subsequent incidence of CNV and GA in CAPT participants.

Patients and Methods

Details of the design and methods and a description of the baseline characteristics of the participants have been reported previously.[1,4,5] In September 1999, CAPT was registered with ClinicalTrials.gov (NCT00000167). Only the major features of CAPT relevant to the evaluation of risk factors for CNV and GA are described here.

Participants were enrolled through 22 clinical centers between May 1999 and March 2001. The institutional review board associated with each center approved the study protocol, and written informed consent was obtained from each participant. Data management was compliant with the Health Insurance Portability and Accountability Act guidelines. The conduct of the clinical trial adhered to the tenets of the Declaration of Helsinki. Major eligibility criteria included the presence of 10 or more drusen at least 125 μm in diameter within 2 disc diameters of the fovea and a standardized visual acuity measurement of 20/40 or better in each eye. Neither eye was to have evidence of CNV, serous pigment epithelial detachment, GA within 500 μm of the foveal center or total area of more than 1 Macular Photocoagulation Study (MPS) disc area, or other ocular conditions that were likely to compromise visual acuity or contraindicate application of laser treatment. Participants had to be 50 years of age or older and free of conditions likely to preclude 5 years of follow-up.

During the initial visit, participants provided information on demographic characteristics, history of diabetes mellitus, history of cigarette smoking, current use of aspirin, and current use of antihypertensive medications. Blood pressure (BP) was measured once while the participant was sitting. Depending on the time of enrollment, patients were scheduled for either 5 or 6 years of follow-up. At the initial visit and annually thereafter, certified photographers adhering to a standardized protocol for field definition and image sequencing obtained stereoscopic, color fundus photographs on film, and a fluorescein angiogram on film, with frames from each eye. Color photographs also were obtained at 6 months.

All photographic images were graded by trained readers in the CAPT Reading Center using a system that incorporated methods from the Wisconsin Age-Related Maculopathy Grading System[6] and the International Classification and Grading System for Age-Related Maculopathy and Age-Related Macular Degeneration.[7] Photographs were graded independently by 2 readers who later discussed their discrepancies openly to arrive at consensus. At baseline, the fundus features described in the grading included: number of drusen, largest drusen size, percent of area covered by drusen, drusen confluence, focal hyperpigmentation, and retinal pigment epithelium (RPE) depigmentation. These evaluations were made for each of 3 areas of the retina (within 500 μm, 500–1500 μm, and 1500–3000 μm of foveal center). Additionally, predominant drusen size within 3000 μm of the foveal center and percent of global area covered by drusen within 3000 μm of the foveal center were evaluated.

Readers in the CAPT Reading Center evaluated the follow-up images for the presence of CNV and GA. Fluorescein angiograms were used to identify CNV, defined as expansion or persistent staining of an area of hyperfluorescence as the time from injection increased. Geographic atrophy was considered present when the color photographs showed an area of atrophy of the RPE with a diameter of at least 250 μm with 2 of the following 3 features: visible choroidal vessels, sharp edges, and a more or less circular shape. Endpoint GA was defined as the development of a total of more than 1 MPS disc area of new, additional atrophy when all areas of GA within 3000 μm of the foveal center were combined.

Reproducibility of the Reading Center consensus gradings was assessed by having samples of photographs regraded by readers masked to results of the original evaluation. Baseline photographs of each eye of 25 patients were regraded once for drusen and pigmentary characteristics. Follow-up photographs of each eye of 35 patients were regraded on 4 different occasions during the follow-up period of the study for presence of CNV and endpoint GA.

Data Analysis

Hypertension was classified according to the BP measured at initial visit and the reported use of antihypertensive medications. Definite hypertension was defined as systolic BP of 160 mmHg or more, diastolic BP of 95 mmHg or more, or current use of antihypertensive medications. Suspect hypertension was defined as either systolic BP of 140 mmHg or more but less than 160 mmHg or diastolic BP of 90 mmHg or more but less than 95 mmHg in participants not taking antihypertensive medications.

The percent of exact agreement between pairs of gradings and the weighted κ statistic were calculated to describe the reproducibility of photograph grading. Qualitative terms for agreement as measured by κ statistics followed the guidelines put forth by Landis and Koch.[8] Analyses to identify risk factors were performed separately for data from observed eyes and from treated eyes, as well as for the combined data. Eyes with CNV identified by the Reading Center from review of baseline photographs (n = 20) were excluded from the analysis of development of CNV. Eyes with CNV (n = 20), serous pigment epithelial detachment (n = 2), or any GA (n = 66) identified by the Reading Center from review of baseline photographs or no photographs permitting assessment of GA during follow-up (n = 28) were excluded from the analysis of development of endpoint GA. In addition, eyes were excluded from specific analyses and tables if the value of an involved factor was unknown. Cox proportional hazards modeling was used to calculate the relative risk estimates and their associated 95% confidence intervals. The association of each risk factor with the outcome of interest (CNV or endpoint GA) was analyzed first with only a single risk factor in the model (univariate analysis). Risk factors associated with a significance level of less than 0.10 from the univariate analysis were entered simultaneously into a multivariate model. The multivariate model then was simplified through stepwise selection until all the risk factors in the multivariate model were statistically significant ($P \leq 0.05$). For the analysis of the combined data from observed and treated eyes, assigned treatment was included as a covariate. The correlation between paired eyes of participants was accommodated by using a robust estimator of variance.[9] Differences in risk estimates between treated and observed eyes were assessed by including interaction terms for treatment group and the risk factors in the model. All analyses were conducted using SAS software version 9.1 (SAS, Inc., Cary, NC).

Results

The baseline participant and ocular characteristics have been reported previously.[1,5] The mean age of CAPT participants at enrollment was 71 years, 99% were white, 47% had definite hypertension, and 6% were currently smoking cigarettes (Table 1, available at http://aaojournal.org). With respect to ocular characteristics, 70% of eyes had largest drusen size of 250 μm or more, 47% had predominant drusen size of 125 μm or more, 33% had an area of 10% or more covered by drusen within 3000 μm of the foveal center, 70% had focal hyperpigmentation, and 5% had RPE

Table 3. Statistically Significant Risk Factors for Choroidal Neovascularization from Multivariate Analysis*

Baseline Characteristic	Observed		Treated		Combined†	
	Relative Risk (95% Confidence Interval)	P *Value*	*Relative Risk (95% Confidence Interval)*	P *Value*	*Relative Risk (95% Confidence Interval)*	P *Value*
Age (yrs)		0.19‡		0.04§		0.01§
50–59	1.00		1.00		1.00	
60–69	1.35 (0.62–2.94)	0.45	3.48 (1.24–9.78)	0.02	2.06 (1.06–3.97)	0.03
70–79	1.90 (0.91–3.99)	0.09	3.90 (1.42–10.8)	0.008	2.61 (1.39–4.92)	0.003
>79	1.65 (0.68–3.99)	0.27	4.98 (1.66–15.0)	0.004	2.81 (1.33–5.94)	0.007
Cigarette smoking		0.05§		0.04§		0.04§
Never	1.00		1.00		1.00	
Quit	0.88 (0.62–1.25)	0.47	1.19 (0.83–1.70)	0.35	1.01 (0.76–1.35)	0.93
Current	1.89 (1.03–3.47)	0.04	1.95 (1.00–3.81)	0.05	1.98 (1.16–3.39)	0.01
Hypertension		0.004§		0.34‡		0.02§
Normal	1.00		1.00		1.00	
Suspect	0.68 (0.38–1.23)	0.20	0.74 (0.43–1.27)	0.27	0.69 (0.45–1.07)	0.10
Definite	1.55 (1.07–2.25)	0.02	1.08 (0.74–1.58)	0.69	1.23 (0.90–1.68)	0.19
Focal hyperpigmentation		0.31‡		0.009§		0.01§
None/questionable	1.00		1.00		1.00	
<250 μm	1.12 (0.75–1.67)	0.59	1.50 (0.98–2.29)	0.06	1.28 (0.94–1.75)	0.11
≥250 μm	1.49 (0.89–2.51)	0.13	2.25 (1.34–3.79)	0.002	1.84 (1.22–2.76)	0.003

*Only the statistically significant risk factors were kept in the final multivariate model.
†Cox model of time to development of choroidal neovascularization with the correlation from paired eyes accounted for, treatment was included as a covariate.
‡Risk factor is not statistically significant in the multivariate model that includes significant risk factors and this specific nonsignificant risk factor.
§Test for any difference among all levels of the factor, from final multivariate model that includes significant risk factors only.

depigmentation (Table 2, available at http://aaojournal.org). Through 5 years of follow-up, 5891 (97.2%) visits were completed of the 6061 6-month and annual visits scheduled for surviving CAPT participants.

The percent exact agreement between gradings of the baseline drusen characteristics noted in this report ranged from 78% to 94%, with the corresponding weighted κ statistics ranging from 0.55 to 0.87 (moderate to almost perfect). The percent exact agreement and weighted κ statistic were 71% and 0.54 (moderate), respectively, for focal hyperpigmentation and 96% and 0.48 (moderate), respectively, for RPE depigmentation. For presence of CNV, estimates of exact agreement and weighted κ statistic ranged between 85% to 95% and 0.64 to 0.86 (substantial to almost perfect), respectively, on 4 different quality assurance gradings. Estimates of exact agreement and weighted κ statistic for the presence of endpoint GA ranged from 85% to 98% and 0.32 to 0.44 (fair to moderate), respectively.

During the CAPT study period, CNV developed in 141 (13.5%) of 1044 observed eyes and in 141 (13.6%) of 1040 treated eyes. CNV developed in a total of 225 patients, and in 57 (25.3%), both eyes were affected. On consideration of each factor separately for the observed eyes, definite hypertension ($P = 0.03$) and current cigarette smoking ($P = 0.04$) were statistically associated with increased risk of CNV; risk increased with age, but not to a statistically significant degree ($P = 0.10$; Table 1). For the laser-treated eyes with each factor considered separately, increased age ($P = 0.003$) and focal hyperpigmentation of 250 μm or more ($P = 0.003$) were associated significantly with an increased risk of CNV. The risk of CNV increased with current cigarette smoking, but not to a statistically significant degree ($P = 0.12$; Table 1). With simultaneous consideration of candidate risk factors in observed eyes, definite hypertension and current cigarette smoking maintained their associations with CNV (Table 3). With simultaneous consideration of candidate risk factors in treated eyes, increased age, current cigarette smoking, and focal hyperpigmentation of 250 μm or more had statistically significant associations with CNV (Table 3). The relative risk estimates for treated and observed eyes were not statistically significantly different for any of the risk factors. When the data from observed and treated eyes were combined, all 4 of the above-mentioned risk factors were statistically significantly associated with the development of CNV. Notably, largest drusen size, number of drusen within 500 μm of foveal center, percent of global area covered by drusen, and RPE depigmentation were not significantly associated with development of CNV in any of the groups of eyes (Table 2).

Endpoint GA (>1 MPS disc area of geographic atrophy within 3000 μm of the foveal center) developed in 61 (6.2%) of 989 observed eyes and in 58 (5.8%) of 999 treated eyes; in 4 of these treated eyes and in 4 of these observed eyes, CNV later developed. In a total of 90 participants, GA developed, and in 29 (32.2%), both eyes were affected. On consideration of each participant-level factor separately for the observed eyes, only definite hypertension ($P = 0.03$) was statistically significantly associated with an increased risk of GA (Table 4, available at http://aaojournal.org). For the laser-treated eyes with each factor considered separately, only suspect hypertension ($P = 0.02$) was significantly associated with an increased risk of GA (Table 4). Whether considering observed eyes only, treated eyes only, or the data from both eyes, most drusen and pigmentary features examined in Table 5 (available at http://aaojournal.org) were associated with the development of GA. With simultaneous consideration of candidate risk factors, percent retinal area covered by drusen and focal hyperpigmentation were significantly associated with the development of GA whether observed eyes only, treated eyes only, or all eyes were considered (Table 6). Associations between age and GA, between hypertension and GA, and between RPE depigmentation and GA seemed less consistent between treatment groups, yet none of the differences in risk estimates between treatment groups were statistically significantly different. Age was statistically significant when all eyes were considered, although the estimated risk ratios did not increase with each higher age category. Systemic hypertension was not statistically significant when all eyes were con-

Table 6. Statistically Significant Risk Factors for Geographic Atrophy from Multivariate Analysis*

Baseline Characteristic	Observed		Treated		Combined†	
	Relative Risk (95% Confidence Interval)	P *Value*	*Relative Risk (95% Confidence Interval)*	P *Value*	*Relative Risk (95% Confidence Interval)*	P *Value*
Age (yrs)		0.04‡		0.19§		0.03‡
50–59	1.00		1.00		1.00	
60–69	14.5 (1.81–116)	0.01	2.67 (0.80–8.93)	0.11	6.09 (1.72–21.5)	0.01
70–79	9.81 (1.23–78.2)	0.03	1.78 (0.54–5.90)	0.35	4.12 (1.18–14.4)	0.03
>79	15.6 (1.76–138)	0.01	3.39 (0.87–13.2)	0.08	6.39 (1.64–24.9)	0.01
Hypertension		0.20§		0.02‡		0.12§
Normal	1.00		1.00		1.00	
Suspect	1.59 (0.67–3.78)	0.30	2.45 (1.20–5.01)	0.01	1.94 (1.02–3.68)	0.04
Definite	1.86 (0.94–3.69)	0.08	1.20 (0.63–2.28)	0.58	1.46 (0.84–2.55)	0.18
Percent of area covered by drusen		<0.001‡		0.01‡		<0.001‡
<10%	1.00		1.00		1.00	
10%–24%	2.27 (1.18–4.34)	0.01	2.42 (1.31–4.46)	0.005	2.39 (1.44–3.97)	0.001
≥25%	8.94 (4.26–18.7)	<0.001	2.26 (0.89–5.75)	0.09	5.10 (2.57–10.1)	<0.001
Focal hyperpigmentation		<0.001‡		<0.001‡		<0.001‡
None/questionable	1.00		1.00		1.00	
<250 μm	4.21 (1.28–13.9)	0.02	2.68 (1.05–6.81)	0.04	2.82 (1.30–6.12)	0.009
≥250 μm	17.9 (5.27–61.0)	<0.001	8.03 (3.01–21.4)	<0.001	10.4 (4.51–24.0)	<0.001
RPE depigmentation						
No	1.00		1.00		1.00	
Yes	2.55 (1.06–6.10)	0.04‡	2.24 (0.81–6.19)	0.12†	2.64 (1.26–5.53)	0.01‡

RPE = retinal pigment epithelium.
*Only the statistically significant risk factors were kept in the final multivariate model.
†Cox model of time to development of geographic atrophy with the correlation from paired eyes accounted for, treatment was included as a covariate.
‡Test for any difference among all levels of the factor from the final multivariate model that includes the significant risk factors only.
§Test for any difference among all levels of the factor from the multivariate model that includes all significant risk factors and this specific nonsignificant risk factor.

sidered. Retinal pigment epithelium depigmentation was associated significantly with increased risk of GA when all eyes were combined.

In eyes that had less than 1 MPS disc area of GA at baseline, additional GA during follow-up was likely to develop. New GA of more than 1 MPS disc area developed in 17 (47%) of 36 observed eyes and in 16 (53%) of 30 treated eyes.

Discussion

The CAPT provides an excellent opportunity to analyze risk factors for the development of CNV and GA over 5 to 6 years in a large cohort of participants (n = 1052). Participants were followed up prospectively and color photographs and fluorescein angiograms were obtained at least yearly by certified photographers following a standard protocol. Photographs were interpreted at a central reading center where the readers showed high reliability, comparable with the level achieved in AREDS, in identifying baseline fundus features as well as the outcomes of CNV and GA.[10] Follow-up was nearly complete, with an overall missed visit rate of 3%. One of the inclusion criteria for the study was at least 10 large (≥125 μm) drusen in both eyes. Therefore, these participants had a substantial drusen burden in each eye and were at high risk for progression of their disease when they entered the study.

Candidate risk factors were examined within treatment groups separately and then with the data from the groups combined. Laser treatment may have altered the association of candidate risk factors with the development of late AMD in an eye; therefore, relationships were examined first within treatment group. Although there was some variation between observed and treated groups in the estimated risk ratios, none of the differences were statistically significant for any of the factors. Thus, combining the data from both eyes, with appropriate statistical treatment of the correlation between eyes, was justified and provided more precise estimates of risk. The results from the analysis of all eyes, were the main source for the conclusions below regarding candidate risk factors.

Increased age, cigarette smoking, and systemic hypertension have been the 3 most consistently identified nonocular risk factors for advanced AMD in previous studies.[2] Overall in CAPT, increased age was associated with the development of CNV as well as of GA. The estimated risk of developing CNV was greater with each successively older age group in the analysis of all eyes combined (Table 3). The risk of developing GA was very low among patients younger than 60 years (Table 4) compared with the risk in the older age groups; however, there did not seem to be additional risk of developing GA with age beyond 60 years (Tables 4 and 6).

Current cigarette smoking was associated with an increased risk of CNV (Tables 1 and 3). Increased risk for CNV, however, was not seen in participants who identified themselves as former smokers. One explanation for this finding may be that cigarette smoking increases the risk of CNV by an active stimulus, perhaps mediated through in-

flammation. In this study, former cigarette smoking did not seem to cause irreversible damage that led to CNV. Because CNV may lead to a rapid decline in vision, an increased risk of CNV in active smokers should be yet another incentive for smoking cessation in participants with early or intermediate AMD. Although the estimated relative risk for developing GA for current smokers was more than 1, the elevated risk was not statistically significant (Table 4).

The presence of definite systemic hypertension at study entry was associated with increased risk of CNV in the observed and combined groups, but no such association was found in the treated group. In addition, the risk of CNV in the suspected hypertension group was lower than the risk of CNV in the no hypertension group in all 3 analyses. Overall, hypertension was not a very strong risk factor for either CNV or GA in this cohort. This may imply that hypertension does not play a role in the pathogenesis of advanced AMD. Alternatively, a true association may have been attenuated because the control of systemic blood pressure over time was not taken into consideration in the analysis.

Each of the drusen features (largest drusen size, predominant drusen size, percent of area covered by drusen, and confluence of drusen) was associated strongly with an increased risk of GA in the univariate analysis for observed, treated, and combine groups of eyes. Sarks[11] described histopathologic evidence showing the development of GA in which macrophages invaded drusen, drusen contents were replaced by fibrous tissue, and pigment epithelium overlying the drusen disappeared, leaving small areas of atrophy that gradually expanded and coalesced. The AREDS allowed prospective photographic monitoring of participants in whom GA developed during the follow-up period. A reanalysis showed that the most common course preceding the appearance of GA consisted of increasing size and confluence of drusen, development of hyperpigmentation, subsequent depigmentation, and ultimately atrophy in the same area.[12] The results from this cohort of participants are consistent with the above findings in that drusen area, focal hyperpigmentation, and RPE depigmentation each were independent risk factors for the development of GA (Table 6). In addition, approximately half the eyes that entered the study with a small area of GA went on to demonstrate at least 1 MPS disc area of new atrophy over the 5 to 6 years of follow-up. Geographic atrophy may be the end stage of drusen evolution; however, many eyes with drusen do not progress to GA over prolonged follow-up periods.

In CAPT, there was no association between any of the drusen measurements and the risk of developing CNV after adjustment for age, smoking, and focal hyperpigmentation. However, the results of many previous population-based and clinic-based studies have shown a strong relationship between number, size, area of drusen, or a combination thereof and risk of CNV or of late AMD.[2] Explanations for this apparent disparity include the fact that the eyes enrolled in CAPT would have been in the highest risk group in nearly all of these studies. For example, investigators in AREDS examined the relation between fundus features and the 5-year risk of advanced AMD.[13] Similar to the experience in the CAPT, increased risk for advanced AMD leveled off at the highest levels of drusen area. The risk of CNV in AREDS was 9%, 12%, and 13%, respectively, among eyes with drusen area classified into the 3 categories: (1) standard grading circle of 0 to 2 or more (area of approximately 13 soft, indistinct drusen) and less than 0.5 disc areas (DAs); (2) 0.5 or more DA and less than 1.0 DAs; and (3) 1.0 or more DAs. Eyes of participants in the CAPT already may have been above the threshold for risk from drusen to develop CNV, and therefore the quantity of drusen was inconsequential.

In CAPT, there was an association of drusen area with development of GA. GA is more likely to occur in the latest stages of drusen evolution when very large, confluent drusen are present,[12] and the risk for developing GA may continue to increase at higher levels of drusen area relative to the risk of developing CNV. This is consistent with prevalence studies of AMD, which indicate that drusen area is strongly related to age and that GA tends to occur at a slightly older age than CNV.[14,15] However, the 5-year incidence rates in AREDS for central GA for eyes falling into the top 3 categories of drusen area noted above were 4%, 13%, and 12%.[13] Determining whether risk of GA actually plateaus after a particular area of drusen accumulates in an eye will require study of more eyes with very high areas of drusen.

This study showed no difference in the incidence of CNV between the observed and treated groups of eyes, even though the laser-treated group had more resolution of drusen in the first few years of follow-up.[1] Although genetic and environmental factors are present for years, AMD typically does not cause phenotypic changes until the sixth or seventh decade of life, with vision loss occurring even later. The presence of extensive amounts of large drusen represents a fairly advanced state of AMD and by that point, the risk for CNV may not be increased by the development of more drusen nor decreased by the resolution of drusen after laser.

Hyperpigmentation was associated with an increased risk of CNV (Table 3) and was strongly associated with increased risk of GA (Table 6). Hyperpigmentation represents migration and accumulation of pigment into the subretinal space and retina. It is a manifestation of degeneration of the RPE and a relatively advanced stage of drusen evolution that can be followed by the development of either CNV or GA. Follow-up of participants in the AREDS showed that hyperpigmentation as well as depigmentation was associated strongly with the risk of progression to advanced AMD (CNV or GA).[13,16]

Retinal pigment epithelium depigmentation often occurs when drusen evolve into flat atrophic areas. Therefore, it is not surprising that in this study, RPE depigmentation was associated with an increased risk of atrophy (Table 5). Although statistical significance was not reached, eyes with RPE depigmentation had a lower rate of CNV (Table 2). This is consistent with Sarks'[11] contention that the risk of CNV decreases as RPE atrophy develops.

In conclusion, the results reported in this paper offer insight into the risk factors for choroidal neovascularization and GA for a cohort of patients at relatively high risk of progression to advanced AMD. Studies are underway to

define further the role of these risk factors along with genetic influences in the development of advanced AMD.

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Footnotes and Financial Disclosures

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A listing of the Complications of Age-Related Macular Degeneration Prevention Trial (CAPT) Research Group is available in Appendix 1 at http://aaojournal.org.

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Table 1. Association of Baseline Participant Characteristics with the Risk of Choroidal Neovascularization: Univariate Analysis by Treatment Group and Combined

	Observed			Treated			Combined*
Baseline Characteristic	*No.*	*Choroidal Neovascularization (%)*	*Relative Risk (95% Confidence Interval)*	*No.*	*Choroidal Neovascularization (%)*	*Relative Risk (95% Confidence Interval)*	*Relative Risk (95% Confidence Interval)*
Age (yrs)							
As continuous (10-yr increase)	1044	(13.5)	1.21 (0.96–1.52)	1040	(13.6)	1.44 (1.14–1.83)	1.32 (1.11–1.56)
As categorical							
50–59	89	(9.0)	1.00	89	(4.5)	1.00	1.00
60–69	297	(12.1)	1.43 (0.66–3.10)	294	(14.0)	3.41 (1.22–9.58)	2.09 (1.10–3.97)
70–79	539	(15.4)	1.97 (0.95–4.10)	538	(14.3)	3.68 (1.34–10.1)	2.54 (1.38–4.69)
>79	119	(11.8)	1.67 (0.69–4.01)	119	(16.0)	4.81 (1.62–14.2)	2.70 (1.32–5.52)
Sex							
Male	408	(12.5)	1.00	413	(13.1)	1.00	1.00
Female	636	(14.2)	1.07 (0.75–1.51)	627	(13.9)	0.99 (0.70–1.40)	1.03 (0.77–1.37)
Hypertension							
Normal	364	(11.8)	1.00	360	(13.1)	1.00	1.00
Suspect	186	(8.06)	0.68 (0.37–1.22)	189	(10.6)	0.81 (0.48–1.38)	0.75 (0.49–1.14)
Definite	487	(16.8)	1.52 (1.05–2.21)	485	(15.3)	1.22 (0.84–1.77)	1.36 (1.01–1.85)
Cigarette smoking							
Never	476	(13.7)	1.00	471	(12.3)	1.00	1.00
Quit	511	(12.3)	0.91 (0.64–1.29)	511	(14.1)	1.17 (0.82–1.66)	1.03 (0.78–1.37)
Current	57	(22.8)	1.86 (1.02–3.43)	58	(19.0)	1.69 (0.87–3.25)	1.77 (1.06–2.96)
Aspirin use							
Never	372	(12.9)	1.00	369	(12.5)	1.00	1.00
Occasionally	249	(14.9)	1.14 (0.74–1.76)	247	(11.7)	0.90 (0.56–1.44)	1.02 (0.70–1.48)
Regularly	423	(13.2)	1.02 (0.69–1.50)	424	(15.6)	1.25 (0.85–1.83)	1.13 (0.83–1.54)
Diabetes							
No	951	(13.4)	1.00	950	(13.9)	1.00	1.00
Yes	88	(15.9)	1.30 (0.74–2.28)	85	(9.41)	0.70 (0.34–1.45)	1.00 (0.61–1.63)

*From the Cox model for time to development of choroidal neovascularization with the correlation from paired eyes accounted for. The model was not adjusted by any other covariates.

Table 2. Association of Baseline Ocular Characteristics with the Risk of Choroidal Neovascularization: Univariate Analysis by Treatment Group and Combined

Baseline Ocular Characteristic	Observed			Treated			Combined*
	No.	*Choroidal Neovascularization (%)*	*Relative Risk (95% Confidence Interval)*	*No.*	*Choroidal Neovascularization (%)*	*Relative Risk (95% Confidence Interval)*	*Relative Risk (95% Confidence Interval)*
Largest drusen (μm)							
<250	297	(13.5)	1.00	276	(12.3)	1.00	1.00
≥250	730	(13.6)	1.00 (0.69–1.45)	750	(13.9)	1.11 (0.75–1.64)	1.05 (0.79–1.40)
Predominant drusen size (μm)							
<125	540	(14.1)	1.00	507	(11.8)	1.00	1.00
≥125	483	(13.0)	0.96 (0.69–1.35)	511	(14.9)	1.34 (0.95–1.89)	1.13 (0.87–1.47)
Percent of area covered by drusen							
<10%	689	(13.6)	1.00	679	(12.1)	1.00	1.00
10%–24%	284	(13.4)	0.95 (0.65–1.39)	286	(15.7)	1.33 (0.92–1.92)	1.13 (0.85–1.49)
≥25%	54	(13.0)	0.89 (0.41–1.93)	60	(18.3)	1.46 (0.77–2.77)	1.17 (0.67–2.04)
Confluent drusen							
<10 pairs	482	(12.5)	1.00	467	(11.6)	1.00	1.00
≥10 pairs	526	(14.6)	1.15 (0.82–1.62)	533	(14.8)	1.27 (0.90–1.81)	1.21 (0.93–1.57)
Focal hyperpigmentation							
None/questionable	299	(12.0)	1.00	320	(9.69)	1.00	1.00
<250 μm	581	(13.6)	1.15 (0.77–1.71)	553	(13.9)	1.52 (1.00–2.32)	1.32 (0.97–1.79)
≥250 μm	145	(17.2)	1.55 (0.92–2.59)	146	(19.2)	2.19 (1.30–3.68)	1.84 (1.23–2.75)
RPE depigmentation							
No	974	(13.8)	1.00	972	(13.6)	1.00	1.00
Yes	55	(10.9)	0.81 (0.35–1.84)	52	(11.5)	0.85 (0.37–1.94)	0.83 (0.45–1.52)
Drusen ≥125 μm within 500 μm of the foveal center							
None	87	(16.1)	1.00	78	(10.3)	1.00	1.00
<10	899	(13.5)	0.85 (0.49–1.49)	893	(13.8)	1.42 (0.69–2.94)	1.06 (0.66–1.69)
≥10	37	(10.8)	0.68 (0.22–2.09)	49	(10.2)	1.00 (0.32–3.10)	0.79 (0.32–1.92)

RPE = retinal pigment epithelium.
*From the Cox model of time to development of CNV with the correlation from paired eyes accounted for. The model was not adjusted by any other covariates.

Table 4. Association of Baseline Participant Characteristics with the Risk of Geographic Atrophy: Univariate Analysis by Treatment Group and Combined

	Observed			Treated			Combined*
Baseline Characteristic	*No.*	*Geographic Atrophy (%)*	*Relative Risk (95% Confidence Interval)*	*No.*	*Geographic Atrophy (%)*	*Relative Risk (95% Confidence Interval)*	*Relative Risk (95% Confidence Interval)*
Age (yrs)							
As continuous (10-yr increase)	989	(6.2)	1.21 (0.86–1.71)	999	(5.8)	1.22 (0.86–1.74)	1.22 (0.94–1.58)
As categorical							
50–59	89	(1.1)	1.00	88	(3.4)	1.00	1.00
60–69	284	(8.5)	8.37 (1.13–62.0)	285	(7.4)	2.50 (0.74–8.43)	3.98 (1.14–13.8)
70–79	513	(5.5)	6.00 (0.82–44.2)	516	(5.2)	1.88 (0.57–6.23)	2.91 (0.85–9.99)
>79	103	(7.8)	9.43 (1.17–75.7)	110	(6.4)	2.70 (0.69–10.5)	4.39 (1.17–16.4)
Gender							
Male	385	(4.9)	1.00	396	(3.8)	1.00	1.00
Female	604	(7.0)	1.36 (0.79–2.35)	603	(7.1)	1.80 (0.99–3.24)	1.55 (0.98–2.46)
Hypertension							
Normal	350	(3.7)	1.00	348	(4.3)	1.00	1.00
Suspect	172	(5.8)	1.57 (0.68–3.59)	183	(9.8)	2.31 (1.16–4.62)	1.98 (1.06–3.70)
Definite	460	(8.0)	2.39 (1.26–4.51)	463	(5.2)	1.25 (0.66–2.40)	1.76 (1.04–3.01)
Cigarette smoking							
Never	448	(6.5)	1.00	453	(6.0)	1.00	1.00
Quit	489	(5.7)	0.90 (0.54–1.53)	491	(5.3)	0.91 (0.53–1.57)	0.91 (0.58–1.43)
Current	52	(7.7)	1.37 (0.47–3.93)	55	(9.1)	1.76 (0.67–4.62)	1.56 (0.62–3.89)
Aspirin use							
Never	352	(6.3)	1.00	355	(5.9)	1.00	1.00
Occasionally	235	(7.2)	1.13 (0.60–2.14)	237	(7.6)	1.22 (0.65–2.30)	1.17 (0.67–2.04)
Regularly	402	(5.5)	0.87 (0.48–1.58)	407	(4.7)	0.80 (0.43–1.50)	0.84 (0.50–1.39)
Diabetes							
No	904	(6.2)	1.00	912	(5.7)	1.00	1.00
Yes	80	(5.0)	0.86 (0.31–2.40)	82	(6.1)	1.15 (0.46–2.91)	1.00 (0.44–2.31)

*From the Cox model for time to development of geographic atrophy with the correlation from paired eyes accounted for. The model was not adjusted by any other covariates.

Table 5. Association of Baseline Ocular Characteristics with the Risk of Geographic Atrophy: Univariate Analysis by Treatment Group and Combined

	Observed			Treated			Combined*
Baseline Ocular Characteristic	*No.*	*Geographic Atrophy (%)*	*Relative Risk (95% Confidence Interval)*	*No.*	*Geographic Atrophy (%)*	*Relative Risk (95% Confidence Interval)*	*Relative Risk (95% Confidence Interval)*
Largest drusen (μm)							
<250	286	(4.6)	1.00	266	(3.0)	1.00	1.00
≥250	689	(6.8)	1.54 (0.82–2.88)	719	(7.0)	2.40 (1.13–5.06)	1.86 (1.10–3.17)
Predominant drusen size (μm)							
<125	517	(4.3)	1.00	493	(4.9)	1.00	1.00
≥125	454	(8.4)	2.18 (1.29–3.70)	484	(7.0)	1.60 (0.94–2.70)	1.87 (1.24–2.81)
Percent of area covered by drusen							
<10%	658	(2.7)	1.00	665	(3.2)	1.00	1.00
10%–24%	266	(10.2)	3.81 (2.09–6.94)	263	(11.4)	3.86 (2.20–6.77)	3.83 (2.41–6.09)
≥25%	50	(30.0)	12.1 (6.03–24.3)	56	(12.5)	3.98 (1.67–9.50)	7.41 (4.04–13.6)
Confluent drusen							
<10 pairs	464	(3.0)	1.00	453	(3.1)	1.00	1.00
≥10 pairs	492	(9.2)	3.08 (1.68–5.63)	506	(8.5)	2.81 (1.53–5.15)	2.94 (1.79–4.84)
Focal hyperpigmentation (μm)							
None/questionable	294	(1.0)	1.00	315	(1.9)	1.00	1.00
<250	550	(4.7)	4.93 (1.50–16.3)	531	(5.1)	2.92 (1.20–7.10)	3.58 (1.66–7.71)
≥250	130	(23.9)	30.2 (9.20–98.9)	132	(18.9)	12.4 (5.07–30.2)	18.3 (8.37–40.2)
RPE depigmentation							
No	931	(5.6)	1.00	934	(5.4)	1.00	1.00
Yes	45	(17.8)	3.48 (1.56–7.78)	49	(14.3)	2.84 (1.24–6.50)	3.14 (1.61–6.12)
Drusen ≥125 μm within 500 μm of the foveal center							
None	78	(6.4)	1.00	76	(7.9)	1.00	1.00
<10	856	(6.3)	0.99 (0.39–2.50)	855	(5.7)	0.79 (0.34–1.87)	0.88 (0.43–1.83)
≥10	37	(2.7)	0.43 (0.05–3.71)	48	(4.2)	0.53 (0.11–2.65)	0.50 (0.13–1.86)

RPE = retinal pigment epithelium.
*From the Cox model of time to development of geographic atrophy with the correlation from paired eyes accounted for. The model was not adjusted by any other covariates.