Night Vision Symptoms and Progression of Age-related Macular Degeneration in the Complications of Age-related Macular Degeneration Prevention Trial

*Gui-shuang Ying, PhD,[1] Maureen G. Maguire, PhD,[1] Chengcheng Liu, MS,[1] Andrew N. Antoszyk, MD,[2] for the Complications of Age-related Macular Degeneration Prevention Trial Research Group**

Objective: To describe baseline night vision symptoms and their association with ≥3-lines loss in visual acuity (VA), choroidal neovascularization (CNV), and geographic atrophy (GA).

Design: Cohort study within a multicenter randomized clinical trial.

Participants: A total of 1052 participants with ≥10 large (>125 μ) drusen and VA ≥20/40 in each eye.

Methods: At baseline, participants self-administered a 10-item Night Vision Questionnaire (NVQ-10). VA testing was performed at baseline, 6 months, and annually. One eye of each participant was randomly assigned to laser treatment, and the contralateral eye was assigned to observation. During follow-up, trained readers identified CNV on the basis of fluorescein angiograms and end point GA, defined as >1 disc area of new GA, based on color photographs. Evaluation was performed by repeated-measures logistic regression for NVQ-10 score as a risk factor for ≥3-lines loss in VA and by survival analysis for CNV and GA, with and without adjustment for participant and ocular characteristics. Evaluations were based on observed eyes and treated eyes, considered separately and combined.

Main Outcome Measures: A ≥3-lines loss in VA, development of CNV and end point GA.

Results: At baseline, NVQ-10 scores ranged from 3 to 100 with a mean of 70 (100 corresponds to no night vision symptoms). Compared with participants with the best night vision (fourth quartile of scores), participants with the worst night vision (first quartile of scores) were at increased risk of ≥3-lines loss in VA in both observed and treated eyes; odds ratios (95% confidence interval) were 2.85 (1.85–4.39) and 2.00 (1.27–3.14), respectively. The relative risk for the first quartile versus the fourth quartile for development of GA was 4.18 (1.80–9.68) in observed eyes and 2.59 (1.13–5.95) in treated eyes. The relative risk for CNV incidence was 1.99 (1.12–3.54) in observed eyes and 1.33 (0.81–2.19) in treated eyes. These relationships were maintained after adjustment for baseline participant and ocular characteristics.

Conclusions: Participants who perceived the most problems in their night vision at baseline had an increased risk of ≥3-lines loss in VA, CNV, and GA. These associations are independent of established risk factors.

Financial Disclosure(s): The authors have no proprietary or commercial interest in any materials discussed in this article. *Ophthalmology 2008;xx:xxx © 2008 by the American Academy of Ophthalmology.*

Age-related macular degeneration (AMD) is the leading cause of vision loss among older adults in the United States.[1] AMD can be characterized as a progressive regionalized degeneration of the photoreceptors in the macula. The dysfunction and death of photoreceptors, through an atrophic process or a neovascular event, accounts for vision loss associated with the advanced stages of AMD.[2] Patients with early and intermediate AMD can have unimpaired visual acuity (VA) but may report difficulty with activities performed at night and under low illumination (eg, driving, reading at night).[3–10] Impairment of night vision may be due to the slowing of rod-mediated dark adaptation in AMD resulting from the degeneration and loss of rod photoreceptors.[11–13]

Histopathologic studies of human donor retinas with AMD have shown a predilection for parafoveal loss of rods over cones in the nonadvanced AMD. Although both rods and cones in the parafovea degenerated in early AMD, rod loss preceded and was more severe than cone loss in most of the donor retinas evaluated.[14–17] Psychophysical functional studies also have demonstrated preferential vulnerability of rods over cones in early AMD. Photoreceptor degeneration and loss occurs before disease in the retinal pigment epithelium (RPE)/Bruch's membrane complex progresses to late AMD.[2,18–21]

In vivo and in vitro studies of photoreceptors suggest that a significant interdependence exists between rod and cone photoreceptors.[2] Death of rod photoreceptors may contribute to the later degeneration of cones, possibly induced by either excitotoxicity or changes in the structural and biochemical microenvironment.[2] Furthermore, rods are neces-

ISSN 0161-6420/08/$–see front matter
doi:10.1016/j.ophtha.2008.05.023

sary for continued cone survival because rods produce a diffusible substance essential for cone survival.[2,22,23] Thus, dysfunction of rod photoreceptors may serve as an indicator for impending cone dysfunction.[16]

Because of the body of evidence that rod dysfunction and resulting problems with night vision may indicate more advanced age-related maculopathy and higher risk of vision loss from progression to the late stage of the disease, we administered a 10-item questionnaire on night vision to participants enrolling in the Complications of AMD Prevention Trial (CAPT).[24] CAPT was a multicenter clinical trial sponsored by the National Eye Institute to evaluate the efficacy and safety of low-intensity laser treatment in preventing loss of vision in people with bilateral large drusen. Participants were followed longitudinally, VA was measured annually, and development of choroidal neovascularization (CNV) and geographic atrophy (GA) were monitored closely for at least 5 years. The CAPT found that light-intensity laser treatment did not reduce the risk of the development of CNV, GA, or loss of VA.[25] This article seeks to assess whether baseline night vision symptoms predict subsequent vision loss and development of CNV and GA in CAPT participants.

Materials and Methods

Details of the design and methods have been reported elsewhere[9,24,25]; only the major features related to this article are described here. Participants were enrolled through 22 clinical centers. 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 Health Insurance Portability and Accountability Act guidelines. The conduct of the clinical trial adhered to the tenets of the Declaration of Helsinki. A total of 1052 participants were enrolled between May of 1999 and March of 2001. Both eyes of the participants were enrolled in the CAPT; one eye of each participant was randomized to laser treatment, with the contralateral eye assigned to observation. CAPT eligibility criteria specified that each eye have $\geq$10 large drusen ($\geq$125 μm in diameter) and VA $\geq$20/40. Neither eye was to have evidence of CNV, serous pigment epithelial detachment, GA within 500 μm of foveal center or total area $>$1 Macular Photocoagulation Study disc area, or other ocular conditions that were likely to compromise VA or contraindicate application of laser treatment.

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 was measured one time while the participant was seated. During the initial visit and follow-up visits, VA was measured following the procedures developed for the Early Treatment Diabetic Retinopathy Study as adapted for the Age-Related Eye Disease Study.[26,27] Modified Early Treatment Diabetic Retinopathy Study Charts 1 and 2 were used at a distance of 3.2 m. Scoring of the VA test was based on the number of letters read correctly. The range of possible scores was 0 to 95, corresponding to Snellen VA equivalents of $<$20/800 to 20/12.

At the initial visit and annually thereafter, certified photographers adhering to a standardized protocol for field definition and image sequencing took stereoscopic, color fundus photographs on film and a fluorescein angiogram on film, with frames from each eye. Color photographs were also taken at 6 months. All photographic images were graded independently by 2 trained readers in the CAPT Reading Center who later openly discussed their discrepancies to arrive at consensus. At baseline, the fundus features described in the grading included the number of drusen, largest drusen size, percent of area covered by drusen, drusen confluence, focal hyperpigmentation, and RPE depigmentation.

Readers in the CAPT Reading Center also 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. GA was considered present when the color photographs showed an area of atrophy of the RPE with a diameter of at least 250 μ with 2 of the following 3 features: visible choroidal vessels, sharp edges, and a more or less circular shape. "End point GA" was defined as the development of a total of $>$1 Macular Photocoagulation Study disc area of new, additional atrophy when all areas of GA within 3000 μ of the foveal center were combined. Evaluation of GA was not performed after an eye developed CNV because the neovascular complex and subsequent scarring often occupied or obscured the retinal area most likely to develop GA.

Ten-Item Night Vision Questionnaire

CAPT participants completed the 25-item National Eye Institute Visual Functioning Questionnaire at the initial visit. Participants also completed 6 items concerning night vision based on a symptom list designed by Cynthia Owsley, PhD, and Samuel Jacobson, MD, PhD, for patients with AMD. The 4 items concerning night vision from the 25-item National Eye Institute Visual Functioning Questionnaire and the 6 items on night vision symptoms are referred to as the 10-item Night Vision Questionnaire (NVQ-10) (Appendix 2, available at http://aaojournal.org). The first 4 items are on a 5-point scale from "None" to "Stopped doing because of my eyesight" and ask about the difficulty in seeing moving subjects, reading street signs when driving at night, difficulty in seeing street signs as a passenger in the car at night, and difficulty with the oncoming headlights or streetlights when driving at night. The next 6 items are on a 4-point scale from "Not at all" to "Very" and ask about how bothered the participant is by poor vision at night, problem in reading in dim light, a dark spot in the middle of vision in dim light, poor vision in dim lighting, problems adjusting to the dark when entering a theater, and trouble seeing the stars in the sky at night. Each item is scored between 100 (none or not at all) and 0 (stopped doing because of eyesight or very bothered). An item cannot be scored if the participant answered with "not currently driving" or "Stopped doing this for other reasons or not interested in doing this." An overall NVQ-10 score for each participant based on the average score of the items with a score (i.e., excluding items that cannot be scored) is expressed on a scale range from 0 to 100; lower score indicates worse night vision.

The questionnaires were self-administered during the initial visit. The local clinic coordinator reviewed the instructions with the participant and answered any questions that arose for participants self-administering the questionnaires. On completion, the clinic coordinator immediately reviewed the form to ensure that all questions were answered and the responses were legible. If any problems were identified, the clinic coordinator requested that the participant complete or revise missing or illegible responses.

Statistical Analysis

Hypertension was classified according to the blood pressure measured at initial visit and the reported use of antihypertensive medications. Definite hypertension was defined as systolic blood

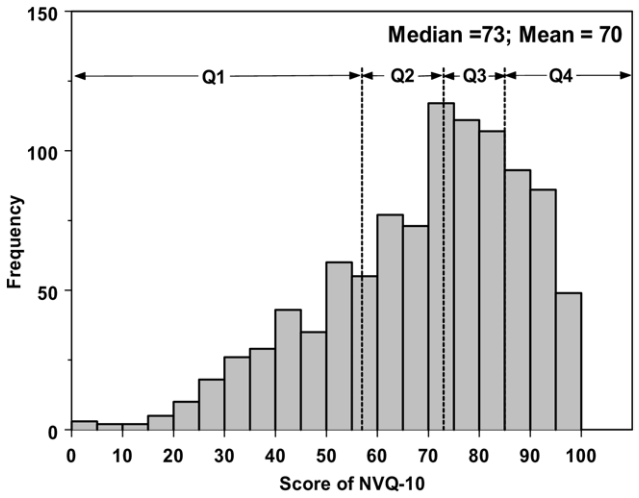

Figure 1. Distribution of night vision scores calculated from the NVQ-10 administered at baseline. Scores were scaled from 0 to 100, with 100 indicating no night vision symptoms. Ranges of the 4 quartiles (Q1, Q2, Q3, and Q4) are shown.

pressure ≥160 mm Hg, diastolic blood pressure ≥95 mm Hg, or current use of antihypertensive medications.

The distribution of night vision scores was summarized by mean, standard deviation, median, and range. For the primary analysis, because of the skewed distribution of night vision score (skewed toward the ceiling of the score with 42 [4.0%] participants scoring 100), we grouped the CAPT participants into 4 groups based on 4 quartiles of NVQ-10 score: The participants with NVQ-10 scores in the first quartile (lowest) have the worst night vision, and the participants with NVQ-10 scores in the fourth quartile (highest) have the best night vision. The prevalence of vision loss ≥3-lines at each follow-up visit and cumulative incidence of CNV and GA over follow-up time were calculated and compared among these 4 groups of participants. The cumulative incidence of CNV over follow-up time was calculated using the Kaplan–Meier method,[28] and the cumulative incidence estimates of GA were calculated using a competing risk model to accommodate the fact that eyes that developed CNV were no longer considered at risk of developing GA.[29]

Eyes with CNV identified by the Reading Center from a 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 allowing assessment of GA during follow-up (N = 28) were excluded from the analysis of development of end point GA.

The association of night vision symptoms with a risk of ≥3-lines loss in VA was evaluated by odds ratios from repeated logistic regression models. The association of night vision symptoms with a risk of CNV and GA was evaluated by the relative risks from proportional hazard models. The group with an NVQ-10 score in the fourth quartile (with the best night vision) was used as the reference group in calculating odds ratios and relative risks. These evaluations were performed with and without the adjustment of significant participant and ocular characteristics as determined from CAPT study.[30] The above analysis was performed for observed eyes and treated eyes, considered separately and combined. For the analysis of the combined data from observed and treated eyes, assigned treatment was included as a covariate, and the correlation between paired eyes of participants was accommodated by using a robust estimator of variance.[31] All the data analysis was performed in SAS 9.1 (SAS Inc, Cary, NC).

Results

NVQ-10 Score at Baseline

At baseline, 1051 of 1052 CAPT participants completed the NVQ-10. The distribution of NVQ-10 scores shows that many CAPT participants reported problems with their night vision (Fig 1). The mean (± standard deviation) NVQ-10 score was 70 (±20), and the median was 73 (range, 3–100). Forty-two participants (4.0%) reported no problems with night vision and attained the maximum NVQ-10 score of 100. The NVQ-10 score ranged from 3 to 57 (mean, 42.1) in the first quartile, 58 to 73 (mean, 66.8) in the second quartile, 74 to 85 (mean, 79.8) in the third quartile, and 86 to 100 in the fourth quartile (mean, 93.1) (Fig 1). The NVQ-10 items showed strong internal consistency and reliability with Cronbach's $\alpha = 0.90$.

Association with Visual Acuity

When participants were compared on the basis of the quartiles of NVQ-10, the participants with the best night vision (in the fourth quartile of NVQ-10) had the lowest proportions of observed eyes with ≥3-lines loss in VA at every visit when VA was measured (Fig 2). Participants with the worst night vision (in the first quartile) generally had the highest proportion of observed eyes with ≥3-lines loss, although the differences among the first 3 quartiles were not large (Fig 2). The association between loss in VA and quartiles of night vision scores followed a similar pattern in treated eyes (data not shown). Compared with participants with the best night vision (in the fourth quartile), participants with worse night vision at baseline (in the first, second, or third quartiles) had at least a 2-fold increased risk of vision loss ≥3-lines in observed eyes. This significant association was maintained after adjustment by the other factors significantly associated with loss of VA (age, current smoking status, hypertension, and focal hyperpigmentation) (Table 1). Weaker associations were seen in the treated eyes and in the combined set of observed and treated eyes

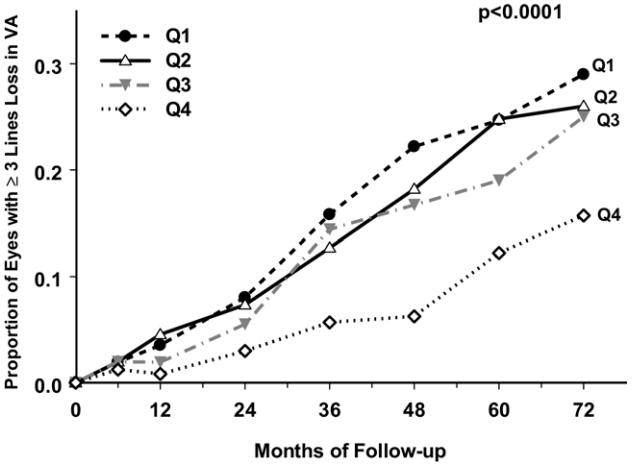

Figure 2. Proportion of observed eyes with ≥3-lines loss in VA across follow-up time by quartiles of the night vision score from the NVQ-10. The proportion of observed eyes with ≥3-lines loss in VA is significantly different among the 4 quartiles of night vision score ($P < 0.0001$).

Table 1. Association of 10-Item Night Vision Questionnaire Score at Baseline with Risk of ≥3-lines Loss in Visual Acuity in Follow-up

NVQ-10 Quartile	Observed Eyes OR† (95% CI)	Treated Eyes OR† (95% CI)	Combined* OR† (95% CI)
Univariate Analysis			
First (lowest)	2.85 (1.85–4.39)	2.00 (1.27–3.14)	2.39 (1.69–3.40)
Second	2.54 (1.62–3.97)	2.04 (1.31–3.17)	2.27 (1.39–3.24)
Third	2.14 (1.39–3.32)	1.78 (1.13–2.81)	1.95 (1.36–2.79)
Fourth (highest)	1.00	1.00	1.00
Overall *P* value	<0.0001	0.0002	<0.0001
Adjusted Analysis‡			
First (lowest)	2.67 (1.69–4.22)	1.50 (0.94–2.39)	2.02 (1.41–2.89)
Second	2.48 (1.55–3.95)	1.75 (1.12–2.74)	2.08 (1.46–2.97)
Third	2.14 (1.36–3.36)	1.69 (1.08–2.65)	1.90 (1.33–2.71)
Fourth (highest)	1.00	1.00	1.00
Overall *P* value	<0.0001	0.04	<0.0001

CI = confidence interval; NVQ-10 = 10-item night vision questionnaire; OR = odds ratio; VA = visual acuity.
*Also adjusted by the assigned treatment.
†Repeated measures logistic regression.
‡Adjusted by age, current smoking status, hypertension, and focal hyperpigmentation.

(Table 1). Interaction between treatment assignment and quartiles of night vision score was not found ($P = 0.63$).

Association with Choroidal Neovascularization

The proportion of participants developing CNV in their observed eye, regardless of the length of follow-up, was lowest for the participants in the fourth quartile of night vision scores (least reported night vision problems) (Table 2). These crude proportions and the Kaplan–Meier estimates of the cumulative proportion of developing CNV (Fig 3) for the other 3 quartiles did not differ consistently over time and did not exhibit a clear dose-response pattern. The relative risk for each of the 3 groups was approximately 2, and adjustment for the other risk factors for CNV in the CAPT participants (age, current smoking status, hypertension, and focal hyperpigmentation) resulted in only minor changes in the estimated relative risks (Table 2). In treated eyes, worse night vision (lower quartile number) was associated with slightly increased risk of CNV (Table 2). Interaction between treatment assignment and night vision score (4 categoric levels) was not found ($P = 0.34$).

Table 2. Association of 10-Item Night Vision Questionnaire Score at Baseline with Risk of Choroidal Neovascularization in Follow-up

NVQ-10 Quartile	Observed Eyes *n*	Observed Eyes CNV (%)	Treated Eyes *n*	Treated Eyes CNV (%)	Combined* *n*	Combined* CNV (%)
First (lowest)	267	35 (13.1)	266	37 (13.9)	533	72 (13.5)
Second	267	45 (16.9)	266	38 (14.3)	533	83 (15.6)
Third	261	43 (16.5)	259	37 (14.3)	520	80 (15.4)
Fourth (highest)	248	18 (7.26)	248	28 (11.3)	496	46 (9.27)
		RR† (95% CI)		**RR† (95% CI)**		**RR† (95% CI)**
Univariate Analysis						
First (lowest)		1.99 (1.12–3.54)		1.33 (0.81–2.19)		1.59 (1.05–2.41)
Second		2.50 (1.44–4.34)		1.34 (0.81–2.19)		1.79 (1.18–2.71)
Third		2.36 (1.36–4.12)		1.27 (0.77–2.09)		1.70 (1.13–2.56)
Fourth (highest)		1.00		1.00		1.00
Overall *P* value		0.008		0.64		0.03
Adjusted Analysis‡						
First (lowest)		1.92 (1.08–3.44)		1.07 (0.64–1.78)		1.41 (0.92–2.16)
Second		2.38 (1.36–4.14)		1.15 (0.69–1.91)		1.63 (1.06–2.48)
Third		2.29 (1.31–4.00)		1.22 (0.74–2.01)		1.64 (1.08–2.49)
Fourth (highest)		1.00		1.00		1.00
Overall *P* value		0.01		0.87		0.09

CI = confidence interval; CNV = choroidal neovascularization; NVQ-10 = 10-item night vision questionnaire; RR = risk ratio.
*Also adjusted by the assigned treatment.
†Cox proportional hazards model.
‡Adjusted by age, current smoking status, hypertension, and focal hyperpigmentation.

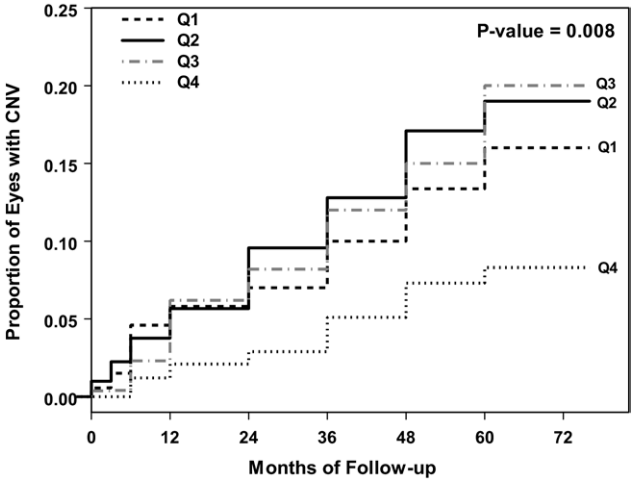

Figure 3. Kaplan–Meier curves for the risk of CNV in observed eyes by quartiles of night vision score from the NVQ-10. The incidence of CNV is significantly different among 4 quartiles of night vision score ($P = 0.008$).

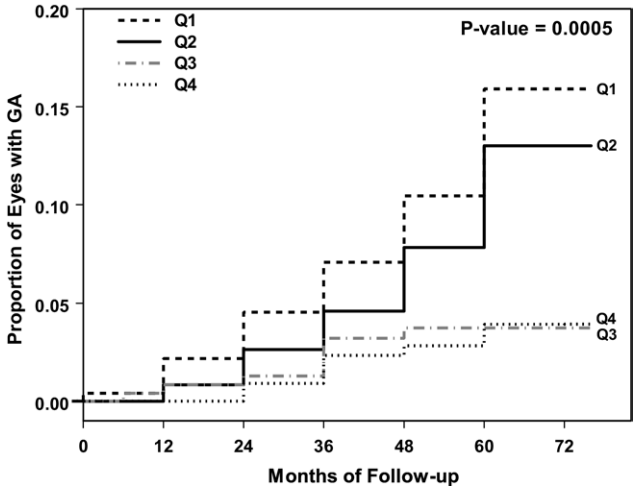

Figure 4. Kaplan–Meier curves for the risk of GA in observed eyes by quartiles of night vision score from the NVQ-10. The incidence of GA is significantly different among 4 quartiles of night vision score ($P = 0.0005$).

Association with Geographic Atrophy

The proportion of participants developing GA in their observed eye, regardless of the length of follow-up, was lower for the participants in the third and fourth quartiles of night vision scores (least reported problems) than for the participants in the first and second quartiles (Table 3). The cumulative incidence estimate of GA from the competing risk model (Fig 4) also showed a large difference between quartiles 1 and 2 versus quartiles 3 and 4. The unadjusted relative risk for each of the first and second quartiles was 4.2 and 3.1, respectively. With adjustment for the other risk factors for GA in the CAPT participants (age, hypertension, larger area of drusen, focal hyperpigmentation, and RPE depigmentation), the estimated relative risks increased to 4.6 and 3.2, respectively. In treated eyes, there was a similar trend for the incidence of GA in quartiles 1 and 2 and within quartiles 3 and 4 (Table 3). Interaction between treatment assignment and quartiles of night vision score was not found ($P = 0.52$).

Discussion

The data from CAPT show that many patients with multiple large drusen bilaterally and good VA (≥20/40) have reported night vision symptoms, and that more night vision symptoms

Table 3. Association of 10-Item Night Vision Questionnaire Score at Baseline with Risk of Geographic Atrophy in Follow-up

	Observed Eyes		Treated Eyes		Combined*	
NVQ-10 Quartile	*n*	GA (%)	*n*	GA (%)	*n*	GA (%)
First (lowest)	247	26 (10.5)	250	19 (7.60)	497	45 (9.05)
Second	250	20 (8.00)	254	21 (8.27)	504	41 (8.13)
Third	251	8 (3.19)	250	10 (4.00)	501	18 (3.59)
Fourth (highest)	240	7 (2.92)	244	8 (3.28)	484	15 (3.10)
	RR† (95% CI)		**RR† (95% CI)**		**RR† (95% CI)**	
Univariate Analysis						
First (lowest)	4.18 (1.80–9.68)		2.59 (1.13–5.95)		3.32 (1.69–6.53)	
Second	3.10 (1.30–7.37)		2.72 (1.20–6.18)		2.90 (1.46–5.76)	
Third	1.16 (0.42–3.22)		1.22 (0.48–3.10)		1.20 (0.55–2.61)	
Fourth (highest)	1.00		1.00		1.00	
Overall *P* value	0.0005		0.02		0.0002	
Adjusted Analysis‡						
First (lowest)	4.60 (1.81–11.6)		2.44 (1.03–5.77)		3.42 (1.69–6.96)	
Second	3.17 (1.23–8.18)		2.97 (1.27–6.93)		3.10 (1.50–6.40)	
Third	1.16 (0.38–3.53)		1.33 (0.51–3.45)		1.22 (0.54–2.79)	
Fourth (highest)	1.00		1.00		1.00	
Overall *P* value	0.001		0.03		0.0008	

CI = confidence interval; GA = geographic atrophy; NVQ-10 = 10-item night vision questionnaire; RR = risk ratio.
*Also adjusted by the assigned treatment.
†Cox proportional hazards model.
‡Adjusted by age, hypertension, global area covered by drusen, focal hyperpigmentation, and RPE depigmentation.

are associated with an increased risk of developing loss in VA, CNV, and GA. Furthermore, the associations are independent of other risk factors, including participant and ocular characteristics. These findings are consistent with the biological and psychophysical findings that rod photoreceptor degeneration precedes cone degeneration in early AMD,[11,15,18,19,21,32–34] and that rod dysfunction may contribute to the later degeneration of cones because of their interdependence.[2,22,23] The predictive value of night vision symptoms on late AMD development is in agreement with the findings from a study by Sunness et al[35] on a small group of patients with drusen, in which the degree of loss of foveal dark-adapted sensitivity at baseline predicted the development of advanced AMD with 100% sensitivity and 92% specificity.

Results from previous studies have established several risk factors for progression to CNV and GA.[1] The risk factors identified within the CAPT data were consistent with previous findings for increased risk with the personal characteristics of advanced age, current cigarette smoking, and hypertension, and the ocular characteristics of drusen area, focal hyperpigmentation, and RPE depigmentation.[30] The results of the analyses presented in this article support night vision symptoms as a novel risk factor of vision loss and development of CNV and GA. It is interesting to note that the association of CNV and GA with night vision symptoms seems different. As shown in Figure 3, the risk of CNV in the fourth quartile is lower than that from the first 3 quartiles, and the risk of CNV in the first 3 quartiles does not show a dose-response pattern, whereas the risk of GA in the third and fourth quartiles is similar, which is much lower than that in the first and second quartiles (Fig 4). These results imply that the CNV and GA may arise from 2 different disease physiologic processes.

The assessment of night vision symptoms provides additional valuable predictive information, because it is independent of the effects of established ocular and other participant risk factors. During the period that CAPT was being performed, Owsley et al[10] developed the 32-item Low-Luminance Questionnaire to characterize the vision problems in low luminance and found that the Low-Luminance Questionnaire scores were related to rod-mediated dark adaptation parameters but not to cone-mediated parameters. Because of the ease of ascertainment compared with testing dark adaptation or rod sensitivity, assessing night vision symptoms may be useful in identifying patients with early or intermediate AMD who are at a relatively high risk of progression. Several agents are currently under evaluation in clinical trials as treatments to prevent the development or progression of GA. Including only patients with night vision symptoms, and therefore higher risk of progression and loss of vision, would be one way to decrease the risk–benefit ratio in these clinical trials and to decrease the total sample size or follow-up period required to attain a specific amount of statistical power.

References

1. Klein R, Peto T, Bird A, Vannewkirk MR. The epidemiology of age-related macular degeneration. Am J Ophthalmol 2004; 137:486–95.
2. Mohand-Said S, Hicks D, Leveillard T, et al. Rod-cone interactions: developmental and clinical significance. Prog Retin Eye Res 2001;20:451–67.
3. Kosnik W, Winslow L, Kline D, et al. Visual changes in daily life throughout adulthood. J Gerontol 1988;43:P63–70.
4. Kuyk T, Elliott JL. Visual factors and mobility in persons with age-related macular degeneration. J Rehabil Res Dev 1999; 36:303–12.
5. Mangione CM, Gutierrez PR, Lowe G, et al. Influence of age-related maculopathy on visual functioning and health-related quality of life. Am J Ophthalmol 1999;128:45–53.
6. Mangione CM, Lee PP, Gutierrez PR, et al, National Eye Institute Visual Function Questionnaire Field Test Investigators. Development of the 25-item National Eye Institute Visual Function Questionnaire. Arch Ophthalmol 2001;119: 1050–8.
7. Scilley K, Jackson GR, Cideciyan AV, et al. Early age-related maculopathy and self-reported visual difficulty in daily life. Ophthalmology 2002;109:1235–42.
8. Clemons TE, Chew EY, Bressler SB, McBee W, AREDS Research Group. National Eye Institute Visual Function Questionnaire in the Age-Related Eye Disease Study (AREDS): AREDS report no. 10. Arch Ophthalmol 2003;121:211–7.
9. Complications of Age-Related Macular Degeneration Prevention Trial Research Group. Baseline characteristics, the 25-item National Eye Institute Visual Functioning Questionnaire, and their associations in the Complications of Age-Related Macular Degeneration Prevention Trial (CAPT). Ophthalmology 2004;111:1307–16.
10. Owsley C, McGwin G Jr, Scilley K, Kallies K. Development of a questionnaire to assess vision problems under low luminance in age-related maculopathy. Invest Ophthalmol Vis Sci 2006;47:528–35.
11. Owsley C, Jackson GR, White MF, et al. Delays in rod-mediated dark adaptation in early age-related maculopathy. Ophthalmology 2001;108:1196–202.
12. Feigl B, Brown B, Lovie-Kitchin J, Swann P. Cone- and rod-mediated multifocal electroretinogram in early age-related maculopathy. Eye 2005;19:431–41.
13. Dimitrov PN, Guymer RH, Zele AJ, et al. Measuring rod and cone dynamics in age-related maculopathy. Invest Ophthalmol Vis Sci 2008;49:55–65.
14. Curcio CA, Millican CL, Allen KA, Kalina RE. Aging of the human photoreceptor mosaic: evidence for selective vulnerability of rods in central retina. Invest Ophthalmol Vis Sci 1993;34:3278–96.
15. Curcio CA, Medeiros NE, Millican CL. Photoreceptor loss in age-related macular degeneration. Invest Ophthalmol Vis Sci 1996;37:1236–49.
16. Curcio CA, Owsley C, Jackson GR. Spare the rods, save the cones in aging and age-related maculopathy. Invest Ophthalmol Vis Sci 2000;41:2015–8.
17. Curcio CA. Photoreceptor topography in ageing and age-related maculopathy. Eye 2001;15:376–83.
18. Steinmetz RL, Haimovici R, Jubb C, et al. Symptomatic abnormalities of dark adaptation in patients with age-related Bruch's membrane change. Br J Ophthalmol 1993;77:549–54.
19. Owsley C, Jackson GR, Cideciyan AV, et al. Psychophysical evidence for rod vulnerability in age-related macular degeneration. Invest Ophthalmol Vis Sci 2000;41:267–73.
20. Jackson GR, Owsley C, Curcio CA. Photoreceptor degeneration and dysfunction in aging and age-related maculopathy. Ageing Res Rev 2002;1:381–96.
21. Chen C, Wu L, Wu D, et al. The local cone and rod system function in early age-related macular degeneration. Doc Ophthalmol 2004;109:1–8.

22. Mohand-Said S, Deudon-Combe A, Hicks D, et al. Normal retina releases a diffusible factor stimulating cone survival in the retinal degeneration mouse. Proc Natl Acad Sci U S A 1998;95:8357–62.
23. Hicks D, Sahel J. The implications of rod-dependent cone survival for basic and clinical research. Invest Ophthalmol Vis Sci 1999;40:3071–4.
24. Complications of Age-Related Macular Degeneration Prevention Trial Research Group. The Complications of Age-Related Macular Degeneration Prevention Trial (CAPT): rationale, design and methodology. Clin Trials 2004;1:91–107.
25. Complications of Age-Related Macular Degeneration Prevention Trial Research Group. Laser treatment in patients with bilateral large drusen: the Complications of Age-Related Macular Degeneration Prevention Trial. Ophthalmology 2006;113: 1974–86.
26. Early Treatment Diabetic Retinopathy Study design and baseline patient characteristics: ETDRS report number 7. Ophthalmology 1991;98(suppl):741–56.
27. Age-Related Eye Disease Study. Manual of Operations (MOP). Examination procedures. Available at: https://web.emmes.com/study/areds/mopfiles/chp7_mop.pdf. Accessed October 29, 2007.
28. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–81.
29. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. Stat Med 1999;18:695–706.
30. Complications of Age-related Macular Degeneration Prevention Trial (CAPT) Research Group. Risk factors for choroidal neovascularization and geographic atrophy: Complications of Age-related Macular Degeneration Prevention Trial. Ophthalmology 2008;115xxx(In press).
31. Wei LJ, Lin DY, Weissfeld L. Regression analysis of multivariate incomplete failure time data by modeling marginal distributions. J Am Stat Assoc 1989;84:1065–73.
32. Medeiros NE, Curcio CA. Preservation of ganglion cell layer neurons in age-related macular degeneration. Invest Ophthalmol Vis Sci 2001;42:795–803.
33. Jackson GR, Curcio CA, Sloan KR, Owsley C. Photoreceptor degeneration in aging and age-related maculopathy. In: Penfold PL, Provis JM, eds. Macular Degeneration. New York: Springer; 2004:45–62.
34. Haimovici R, Owens SL, Fitzke FW, Bird AC. Dark adaptation in age-related macular degeneration: relationship to the fellow eye. Graefes Arch Clin Exp Ophthalmol 2002;240: 90–5.
35. Sunness JS, Massof RW, Johnson MA, et al. Diminished foveal sensitivity may predict the development of advanced age-related macular degeneration. Ophthalmology 1989;96: 375–81.

Footnotes and Financial Disclosures

Originally received: February 20, 2008.
Final revision: May 12, 2008.
Accepted: May 13, 2008.
Available online: ●●●. Manuscript no. 2008-231.

[1] Department of Ophthalmology, School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania.

[2] Charlotte Eye, Ear, Nose and Throat Associates, Charlotte, North Carolina.

Presented in part at the meetings of the Association for Research and Vision in Ophthalmology in Fort Lauderdale, Florida, on May 1, 2005, and the Fourth US Symposium on Ocular Epidemiology on January 31, 2007.

Financial Disclosure(s):
The Writing Committee has no conflict of interest with regard to the material presented in the article.

Supported by grants EY012211, EY012261, and EY012279 from the National Eye Institute, National Institutes of Health, and Department of Health and Human Services.

Correspondence:
Gui-shuang Ying, PhD, University of Pennsylvania, 3535 Market Street, Suite 700, Philadelphia, PA 19104-3309.

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

Appendix 1: Complications of Age-related Macular Degeneration Prevention Trial Research Group

Retinal Consultants of Arizona
Mesa and Sun City, AZ
Donald W. Park, MD
Pravin V. Dugel, MD
Allen B. Thach, MD
Siru Adhikari
Christina Alvarado
Jennifer Blaisdell
Jennifer Cavanagh
Jennifer Cornelius
Elena Marcos
Kaz Tysiac
Norma Jimenez
Adriana Falcon
Sharon Kosecki
Elena Marcos
Carol Slagle
Cheri Tuttle
Scott E. Bohnen
Brian M Manor
John Martin
Anne C. Monday

West Coast Retina
San Francisco, CA
Robert N. Johnson, MD
Everett Ai, MD
H. Richard McDonald, MD
Irina Rozenfeld, MD
Margaret Stolarczuk, OD
Pat Wood, LVN, CCRS
Kevan Curren, COA
Irina Rozenfeld, MD
Brandi Teske, COA
Marsha Apushkin
Silvia Linares
Kelly DeBoer
Sarah Huggans
Jeremy Miller
John Uy

Northwestern University
Chicago, IL
Alice Lyon, MD
Susan Anderson-Nelson, MD
Lee M. Jampol, MD
David V. Weinberg, MD
Annie Muñana, RN
Zuzanna Rozenbajgier, MA
Lori Kaminski, RN
Jill Koecher
Laima O'Donnell
Renata Swigost
Lisa Volland, RN
Marsha Apushkin
Alexander Habib
Pamela Hulvey
Jonathan Shankle
James Yuhr

Illinois Retina Associates
Harvey and Skokie, IL
University of South Florida Eye Institute
Tampa, FL
Peter Reed Pavan, MD
Karina K. Billiris, MD
Burton Goldstein, MD
Mohan Iyer, MD
Matthew M. Menosky, MD
Jonathan Mines, MD
Scott E. Pautler, MD
Sharon M. Millard, RN, COT
Susan Sherouse, COT
Michelle D. West, COT
Steve Carlton
Wyatt Saxon

Emory Eye Center
Atlanta, GA
Paul Sternberg Jr, MD
Thomas Aaberg Sr, MD
Baker Hubbard III, MD
David Saperstein, MD
Lindy DuBois, MEd, MMSC, CO, COMT
Ann Ervin, MPH
Judy Brower, MMSC, CO, COMT
Jayne Brown
Gail Browne
Gabriela Burian
Natalie Schmitz
Rhonda Waldron, MMSc, COMT
James Gilman, CRA
Bob A. Myles

Ophthalmology and Visual Sciences at the University of Lousiville
Louisville, KY
Charles C. Barr, MD
Steve Bloom, MD
Brian Kritchman, MD
Greg Whittington, PsyS
Rhonda Bowyer
Dee Denning, COT
Janice Goatley
Janet Nutting
Judy Swartz
Evelyn Temple
Wendy Wilson, COT

Ophthalmic Consultants of Boston
Boston, MA
Jeffrey Heier, MD
Albert R. Frederick Jr, MD
Michael G. Morley, MD
Trexler Topping, MD
Tammy Hanner, COA
Molly Doherty
Heather L. Davis
Linda Beal, COA
Sean Mahoney, COA
Robin A. Ty
Cullen Mike Jones, COA
Elna Rapp, RN, COT, CRA
David Orth, MD
Jack Cohen, MD
Matthew MacCumber, MD
Pauline Merrill, MD
Celeste Figliulo
Liz Porcz
Carrie L. Violetto, CMA
Tana N. Drefcinski
Hope P Nenadov
Laurie Rago
Donald Doherty
Marian McVicker
David Nash

University of Iowa Hospitals and Clinic
Iowa City, IA
James C. Folk, MD
H. Culver Boldt, MD
Karen M. Gehrs, MD
Stephen R. Russell, MD
Rachael Ivins, CCRC
Steven A. Wallace
Connie Hinz, COT
Michael Harker
Ed Heffron
Stefani Karakas
Jacquelyn M. McDonald
Jon Dahl
Timothy Holle
Matt Raeber
John Mark Rogers

Southeast Clinical Research Associates
Charlotte, NC
Andrew N. Antoszyk, MD
David J. Browning, MD, PhD
Tonia Ellsmore, CRC
Jennifer V. Helms, CCRC
Lori Lundy, COMT
Alison H Stallings
Loraine Clark
Sandy Efird, COT
Mark Evans
Fereshteh Jarrahi
Kara Mundy
Heather Murphy
Tisha L O'Marah
Jennifer Wike, COA
Patricia Woodland
Linda Davis
Mike McOwen

Retina-Vitreous Center
Edison and Lakewood, NJ
Steven R. Leff, MD
Eric Friedman, MD
Stuart N. Green, MD
Bruce Keyser, MD
Miriam Kushner, MD
David L. Yarian, MD
Cheryl Hambrock, RN

Wilmer Ophthalmological Institute
Johns Hopkins University
Baltimore, MD
Susan B. Bressler, MD
Andrew P. Schachat, MD
Dante Pieramici, MD
Neil M. Bressler, MD
Warren Doll, COA
Ellen Greenberg, COT
Robert A. Jurao, COA
Deborah F. Donohue, COA
Mary Frey
Siobhan Sheehan
Tracey Porter
Judith E. Belt
Dennis R. Cain, CRA
Rachel Falk
Charles M. Herring

Associated Retinal Consultants
Royal Oak, MI
Michael Trese, MD
Antonio Capone, MD
Bruce R. Garretson, MD
Tarek S. Hassan, MD
Alan J. Ruby, MD
Michelle M. Kulak, RN
Pat Manatrey, RN
Tammy Osentoski, RN
Linda Vandell, RN
Kristi Cumming, RN, MSN
Beth Mitchell, RN
Mary Zajechowski, COT
Craig Bridges
Patricia Siedlak
Patricia Streasick
Lynette Szydlowski

Mayo Clinic
Rochester, MN
Colin A. McCannel, MD
Helmut Buettner, MD
John M. Pach, MD
Dennis M. Robertson, MD
Margaret J. Ruszczyk, CCRA
Jean Burrington
Kathleen LeBarron, COA
Cindy A. Stephan, COA
Thomas Link
Jay A. Rostvold

Barnes Retina Institute
St. Louis, MO
Gilbert Grand, MD
Kevin Blinder, MD
Nancy M. Holekamp, MD
Daniel P. Joseph, MD, PhD
Travis A. Meredith, MD
Gaurav Shah, MD
Julie A. Binning, COT, CCRS
Linda Wagner, COT
Marge Lucido
Donna Coffey, RN
Melinda Geddes
Thea Tantum, COT
Finn Andersen
Alex Schlosser
Howard "Dan" Daniel
Milt Johnson
R. Joseph Logan
Harry J. Wohlsein Jr

Casey Eye Institute
Portland, OR
Michael L. Klein, MD
David J. Wilson, MD
Susan K. Nolte
Patricia D. Lindstrom, COT
Susan Pope, COT
Debora R. Vahrenwald, COT
Jessica Gaultney
Ellen Redenbo
Patrick Rice
Peter Steinkamp
Patrick Wallace

University of Pennsylvania
Philadelphia, PA
Juan E. Grunwald, MD
Jeffrey W. Berger, MD, PhD
Alexander J. Brucker, MD
Josh Dunaief, MD, PhD
Stuart L. Fine, MD
Allen Ho, MD
Albert M. Maguire, MD
Michael Tolentino, MD
Sharon Decker
Emily Hall
Jennifer Levin, MD
Monique N. McRay
Gretchen Warley, MSW
Stacey Boxley
Joan DuPont, CCRC
Claudette Geist, CRA, COT
Tatyana Metelitsina, MD
Michele Sheehan, COMT
Cheryl Devine, CRA
Deborah Elkins
William Nyberg, RBP, CRA
Laurel Weeney, CRA

CAPT Coordinating Center
University of Pennsylvania Philadelphia, PA
Maureen G. Maguire, PhD
Ginny S. Nobel, COT
Cindy M Wright
Linda Boyd, COA
Janel Gualdoni, COT
Pam Light, CCRC
Nancy Soueidan, RN
Bryan Barts

Retina Associates of Cleveland
Cleveland and Lakewood, OH
Lawrence J. Singerman, MD
David Miller, MD
Robert Mittra, MD
Michael Novak, MD
Scott Pendergast, MD
Jeffrey H. Stockfish, MD
Hernando Zegarra, MD
Scott D. Marella, CCRP, COA
Stephanie A. Schura, COT
Sheila Smith-Brewer, CRA, COMT, FOPS
Kimberly DuBois, CCRP, COA
Jacqueline L. Hursky, COA
Mary Ilc, COT
Sheri L. Joyce, COA
Vivian Tanner, COT
John DuBois, CRA
Gregg Greanoff, CRA
David S. Lehnhardt, COA

The Ohio State University
Columbus, OH
Frederick H. Davidorf, MD
Robert Chambers, DO
Louis Chorich, MD
Cynthia S. Taylor, CCRC
Jill Salerno, COA
Mary T. Deringer, COA
Jill Milliron, COA
Jerilyn Perry, COT, ABO
Scott Savage, EMT-A

Retina Northwest
Portland, OR
Richard F. Dreyer, MD
Colin Ma, MD
Patricia Bartholomew, CCRC
Harold L. Crider, COT
Marcia R. Kopfer, COT
Jeanette R. Larson, COMT
Cindy Armstrong
Debra DeShazer
Steve Hobbs
Wendy Raunig, COT
Katie Reichenberger
Stephanie Schmidt
Don Sitts

Kate Atkins
Mary Brightwell-Arnold
Sandra Harkins
Christine D. Holmes
Andrew James, MS
Margaret Jewell
Alexander Khvatov
Chengcheng Liu, MS
Lori O'Brien
Kathy McWilliams, CCRP
Ellen Peskin, MA, CCRP
Renee Rees, PhD
Susan Ryan
N. Nefertiti Stanford
Karen Taylor
Claressa Whearry
Gui-Shuang Ying, PhD

Texas Retina Associates
Dallas and Arlington, TX
Gary Edd Fish, MD
Rajiv Anand, MD
Rand Spencer, MD
Jean Arnwine
Jeff Harris
Nancy Resmini
Marilyn Andrews
Sally Arceneaux, COA
Barbara McCarty
Dustin Pierce
Rubye Rollins
Brenda Sanchez
Hank A. Aguado
Bob Boleman
Penny B. Ellenich
John G. King

University of Wisconsin, Madison
Madison, WI
Suresh R. Chandra, MD
Michael Altaweel, MD
Barbara Blodi, MD
Justin Gottlieb, MD
Michael Ip, MD
T. Michael Nork, MD
Erika D. Soderling
Wendy Walker, COA
Jennie Perry-Raymond
Margo Blatz
Jennifer M. Buechner
Shelly Olson
Alyson Pohlman
Barb Soderling
Gene Knutson
Denise Krolnik
John Peterson

CAPT Chairman's Office
University of Pennsylvania, Philadelphia, PA
Stuart L. Fine, MD
Marilyn Katz

CAPT Reading Center
University of Pennsylvania, Philadelphia, PA
Judith Alexander
Jeffrey Berger, MD, PhD
Robert Stoltz, MD, PhD
Steven Begley
Keith Elsner
Allen Ho, MD
Noreen Javornik, MS
Kristin Mathias, MS
Bojidar Majarov, MD
E. Revell Martin
Renee Zawacki

National Eye Institute
Natalie Kurinij, PhD

Appendix 2: Ten-Item Night Vision Related Questionnaire

1. How difficult is it for you to see moving objects, such as people or other cars when *driving at night*? Would you say you have:

   No difficulty at all……1
   A little difficulty ……..2
   Moderate difficulty ……..3
   Extreme difficulty…….....4
   Stopped doing this because of your eyesight …….....5
   Stopped doing this for other reasons
   or not interested in doing this ……....6
   Not currently driving ……...7

2. How difficult do oncoming headlights or streetlights make it for you to *drive at night*? Would you say you have:

   No difficulty at all…….....1
   A little difficulty ……..….2
   Moderate difficulty ……...3
   Extreme difficulty…….....4
   Stopped doing this because of your eyesight …….....5
   Stopped doing this for other reasons
   or not interested in doing this …….....6
   Not currently driving ……..…7

3. How difficult is it for you to read street signs when *driving at night*? Would you say you have:

   No difficulty at all…….....1
   A little difficulty …….....2
   Moderate difficulty ……..…...3
   Extreme difficulty…….…….....4
   Stopped doing this because of your eyesight ….....….5
   Stopped doing this for other reasons
   or not interested in doing this…….....……6
   Not currently driving ……7

4. How difficult is it for you to see street signs when you are a passenger in the car at night? Would you say you have:

   No difficulty at all……..1
   A little difficulty……...…….2
   Moderate difficulty……3
   Extreme difficulty...…….....4

Following are some additional characteristics of vision. Tell us how bothered you are by these items:

	(Circle one on each line)			
	Not at all bothered	A little bothered	Somewhat bothered	Very bothered
5. Poor vision at night	1	2	3	4
6. Problem in reading in dim light	1	2	3	4
7. A dark spot in the middle of my vision in dim light	1	2	3	4
8. Poor vision in dim lighting	1	2	3	4
9. Problems adjusting to the dark when entering a theater	1	2	3	4
10. Trouble seeing the stars in the sky at night	1	2	3	4