Development of a Risk Score for Geographic Atrophy in Complications of the Age-related Macular Degeneration Prevention Trial

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Objective: To develop a risk score for developing geographic atrophy (GA) involving easily obtainable information among patients with bilateral large drusen.

Design: Cohort study within a multicenter randomized clinical trial.

Participants: We included 1052 participants with ≥10 large (>125 μm) drusen and visual acuity ≥20/40 in each eye.

Methods: In the Complications of Age-related Macular Degeneration (AMD) Prevention Trial (CAPT), 1 eye of each participant was randomly assigned to laser treatment and the contralateral eye was assigned to observation to evaluate whether laser treatment of drusen could prevent vision loss. Gradings by a reading center were used to identify: CAPT end point GA (total area of GA [>250 μm] > 1 disc area), GA (>175 μm) involving the foveal center (CGA), and GA of any size and location (any GA). Established risk factors (age, smoking status, hypertension, Age-related Eye Disease Study simple severity scale score), both with and without a novel risk factor (night vision score), were used in assigning risk points. The risk scores were evaluated for the ability to discriminate and calibrate GA risk.

Main Outcome Measures: Development of end point GA, CGA, and any GA.

Results: Among 942 CAPT participants who completed 5 years of follow-up and did not have any GA at baseline, 6.8% participants developed CAPT end point GA, 9.6% developed CGA, and 34.4% developed any GA. The 5-year incidence of end point GA in 1 or both eyes of a participant increased with the 15-point GA risk score, from 0.6% for <7 points to 15% for ≥12 points. The 5-factor risk score predicted development of GA moderately well with the area under the receiver operating characteristic curve (AUC) 0.76 (95% confidence interval [CI], 0.71–0.81) for end point GA; 0.76 (95% CI, 0.71–0.80) for CGA, and 0.68 (95% CI, 0.65–0.72) for any GA. Prediction from the risk score without the night vision score had lower AUCs (range, 0.67–0.72).

Conclusions: If validated in other patients, the GA risk score will be useful for identifying high-risk patients for clinical trials of prevention of GA and for clinical assessment of GA risk in early AMD patients.

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Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in the developed world. Choroidal neovascularization (CNV) and geographic atrophy (GA) are 2 forms of end-stage AMD. Geographic atrophy is responsible for about 10% of the severe vision loss attributed to the AMD,[1] and affects approximately 900 000 persons in the United States.[2] Anti-vascular endothelial growth factor therapy has been proven to be highly effective in reducing the vision loss in patients with CNV.[3,4] Although several agents to prevent the development or arrest the progression of GA are currently under investigation in clinical trials, none have yet been shown to be effective.

Geographic atrophy progresses gradually over time, and the causes are largely unknown. However, data from large, observational studies and clinical trial cohorts have consistently identified age, current smoking status, hypertension, drusen size or area, and pigmentary changes as risk factors.[5–15] Recent investigations have identified genes associated with GA, including complement factor H, complement factor B, LOC387715, and complement C3 variant.[16–18] More recently, night vision as assessed by a 10-item questionnaire was found to be highly predictive of the development of GA, independent of other established risk factors.[19]

In this article, we describe the development and evaluation of risk scores for the development of GA within 5 years based only on readily available risk factors. Risk scores are useful for both clinical research studies and individual patient care. Predictive summary scores were first introduced by the Framingham Heart Study Group for the 10-year risk of coronary heart disease[20] and have been applied to many disease areas, including the development of glaucoma for

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patients with ocular hypertension.[21–23] Although a prediction model including ocular, environmental, and genetic risk factors for advanced AMD (GA and CNV combined) has been developed recently,[18] a risk score for GA alone has not been developed.

Methods

Details of the design and methods of the clinical trial have been reported elsewhere[24,25]; only major features related to this paper are described here. The Complications of Age-related Macular Degeneration Prevention Trial (CAPT) was a multicenter, randomized clinical trial to evaluate low-intensity laser treatment of eyes with drusen for the prevention of vision loss from AMD in participants with bilateral large drusen. For each participant, 1 eye was randomized to laser treatment with the contralateral eye assigned to observation. The CAPT results showed that there was no statistical difference between treated and observed eyes on visual acuity loss, incidence of CNV, or incidence of end point GA.[25]

A total of 1052 participants were enrolled into CAPT between May 1999 and March 2001 from 22 participating 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. The CAPT eligibility criteria specified that each eye have ≥10 large drusen (≥125 μm in diameter). Neither eye was to have evidence of CNV, serous pigment epithelial detachment, GA within 500 microns of the foveal center or total area >1 Macular Photocoagulation Study disc area (DA).

At the initial visit and annual visits 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. The fundus features described in the baseline grading included number of drusen, largest drusen size, drusen area, drusen confluence, GA, focal hyperpigmentation, and retinal pigment epithelium depigmentation.

Risk Factor Assessment

At initial visit, information regarding age, cigarette smoking status, and current use of medication for hypertension was collected through questioning participants by use of a standardized questionnaire. Blood pressure was measured once while the participant was sitting. Hypertension was defined as reported current use of antihypertensive medications, or systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg in participants not taking antihypertensive medications.

The score on the Age-related Eye Disease Study (AREDS) simple severity scale at study enrollment was determined using the following definition.[26] For each eye, 1 point was assigned for presence of large drusen and 1 point for presence of pigmentary changes. The points from the 2 eyes are added together to provide the score, which can range from 0 to 4.

At baseline, a 10-item night vision symptoms questionnaire (NVQ-10) was self-administered.[19] 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, problems 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. For the night vision score, each item is scored between 100 (none or not at all) and 0 (stop doing because of eyesight, or very bothered). An overall NVQ-10 score for each participant was calculated based on the average score of 10 items. The score ranges from 0 to 100, with lower scores indicating worse night vision.

Geographic Atrophy Definitions

Readers in the CAPT Reading Center evaluated the annual follow-up fundus color photographs for the presence of GA, amount of GA (<0.028 DA [i.e., 250 μm in diameter], 0.028–1 DA, 1–2 DA, and >2 DA), presence of a new area of GA, considering only the central area within 500 μm of foveal center, only the annulus from 500 to 1500 μm, and only the annulus from 1500 to 3000 μm, and whether the total area of GA within 3000 μm of foveal center was >1 DA. Geographic atrophy was considered to be present when the color photographs showed an area of atrophy of the retinal pigment epithelium with 2 of the following 3 features: visible choroidal vessels, sharp edges, and a more or less circular shape. We defined "CAPT end point GA" as development of a total of >1 DA of new, additional atrophy when all areas of GA (>250 μm in diameter) within 3000 μm of the foveal center were combined. End point GA was used in CAPT to identify eyes that had progressed. We defined CGA as development of GA (>175 μm in diameter) involving the center of macula. In AREDS, CGA was used to identify eyes that had progressed. Any GA was defined as the presence of any size GA (i.e., including areas <0.028 DA) within 3000 μm of the foveal center. 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.

Statistical Analysis

Analyses were restricted to 942 CAPT participants who completed 5-year follow-up, did not have any GA at baseline, and had information available on all the baseline risk factors. The development of the risk score followed the approach used for the Framingham Study risk score.[27] Specifically, a multivariate logistic regression model was fit to the data and included 5 risk factors as predictors: Age (50–59, 60–69, 70–79, and ≥80 years), smoking status (never or former vs current), hypertension status (no vs yes), AREDS simple severity score (2, 3, or 4), and night vision score (<60, 60–75, 75–85, and >85). The outcome was the development of CAPT end point GA in 1 or both eyes (person-specific GA yes/no) during a 5-year follow-up period. Estimates of the regression coefficients corresponding to each level of a risk factor were obtained, and risk points were assigned for each level of a risk factor based on the value of the associated regression coefficient and the reference regression coefficient corresponding to 1 risk point. The risk score for a participant was determined as the total of risk points based on a participant's risk factor profile. Because the night vision questionnaire is not commonly administered in clinical practice, another risk points system was developed by using the same methodology described, but without the inclusion of the night vision score (i.e., only including age, smoking, hypertension, and AREDS simple scale score).