

Description of the Age-Related Eye Disease Study 9-Step Severity Scale Applied to Participants in the Complications of Age-related Macular Degeneration Prevention Trial

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Objective: To describe characteristics of the Age-Related Eye Disease Study (AREDS) 9-step severity scale applied to participants in the Complications of Age-related Macular Degeneration Prevention Trial (CAPT).

Methods: Eligibility criteria for CAPT required 10 or more large ($\geq 125 \mu\text{m}$) drusen in each eye. Readers graded baseline photographs from all participants and all follow-up photographs from 402 untreated eyes. Drusen and pigment characteristics were used to assign the AREDS scale score. Choroidal neovascularization was identified from fluorescein angiograms. Geographic atrophy involving the macular center was identified from color photographs.

Results: Among 1001 untreated eyes, 90% were at steps 5 to 7 at baseline. The 5-year incidence of advanced age-

related macular degeneration (AMD) increased with each step from 8% (step 4) to 40% (steps 8 and 9 combined). These rates were similar to those reported in AREDS. Among 261 eyes with all 5 annual photograph gradings available and without progression to advanced AMD, 55% of eyes had scores that indicated improvement at least once. Before progression to advanced AMD, only 32% of 141 eyes either went through step 8 or 9 or had an increase of 2 or more steps from baseline.

Conclusions: The AREDS 9-step severity scale was predictive of development of advanced AMD. The AREDS scale has deficiencies as a surrogate outcome for progression to advanced AMD.

Arch Ophthalmol. 2009;127(9):1147-1151

POPULATION-BASED EPIDEMIOLOGICAL studies^{1,2} and cohort studies involving clinical trial participants³⁻⁵ have demonstrated that the characteristics of early and intermediate age-related macular degeneration (AMD), including drusen size, area, and pigment abnormalities, are strong risk factors for the progression to advanced AMD. The Age-Related Eye Disease Study (AREDS) recently developed a complicated 9-step AMD severity scale for eyes⁶ and a simplified 5-step severity scale for persons⁷ based on gradings of stereoscopic color photographs for drusen features and pigment abnormalities. The AREDS 9-step severity scale, which will be referred to as the AREDS scale, was developed with the intention

to provide baseline risk categories, to allow tracking of progression along the scale, and to define surrogate outcomes for progression to advanced AMD.^{6(p1484)}

The AREDS scale was found to be highly associated with progression to advanced AMD in AREDS participants, with eyes classified in the lowest category at baseline hav-

ing a 5-year risk of progression of less than 1% and eyes in the highest category having a risk of approximately 50%. The AREDS investigators performed an initial assessment of longitudinal changes in the AREDS scale score by examining the pattern of 4 scale steps ordered in time (baseline and 2, 4, and 5 years of follow-up) in a subgroup of 366 eyes that had changed between baseline and 5 years by at least 3 steps. In 334 eyes (91%), the AREDS scale step at 5 years was higher than at baseline and in 259 (78%) of these eyes there were no reversals toward improvement at 2 and 4 years. On the basis of these analyses, the AREDS investigators concluded that progression on the AREDS scale may prove to be useful as a surrogate for progression to advanced AMD.

Before any severity scale is adopted for clinical or research purposes, the risk estimates should be validated in an independent sample.⁸ However, to our knowledge, the AREDS scale has not been validated in any population-based cohorts or in other large groups of people with early or intermediate AMD. In addition, much additional infor-

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mation is needed about the characteristics of the changes in scale step over time in eyes with and without progression to advanced AMD before changes in the AREDS scale score can be considered as a surrogate outcome measure.

The Complications of Age-related Macular Degeneration Prevention Trial (CAPT) was a multicenter randomized clinical trial in a large cohort of participants ($n=1052$). Each participant was followed up for at least 5 years to observe the development of advanced AMD (about 20% of eyes developed advanced AMD within 5 years), and color photographs and fluorescein angiograms were obtained at least yearly and graded following a protocol similar to AREDS. Thus, the CAPT data provide a unique opportunity to validate risk estimates associated with the AREDS scale and to assess patterns of severity scale score changes over time in eyes with and without subsequent progression to advanced AMD.

METHODS

Details of the design and methods have been reported elsewhere^{5,9,10}; only major features related to this article are described herein. A total of 1052 participants were enrolled into CAPT between May 1999 and March 2001. One eye of each participant was randomized to laser treatment, with the contralateral eye assigned to observation. CAPT eligibility criteria specified that each eye had 10 or more large drusen ($\geq 125 \mu\text{m}$ in diameter). Neither eye was to have evidence of choroidal neovascularization (CNV), serous pigment epithelial detachment, geographic atrophy (GA) within 500 μm of foveal center or total area more than 1 Macular Photocoagulation Study disc area (DA), or other ocular conditions that were likely to compromise visual acuity or contraindicate application of laser treatment.

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 taken also at 6 months. Fluorescein angiograms were taken also when there were signs or symptoms of CNV. 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 grading included number of drusen, largest drusen size, drusen area, drusen confluence, GA, focal hyperpigmentation, and retinal pigment epithelium depigmentation. Because the initial grading of fundus photographs was slightly different from the AREDS grading with respect to categorization of drusen size, drusen area, GA, and pigmentation abnormalities, we regraded the photographs for AMD characteristics needed for determination of the AREDS scale step, following the AREDS grading protocol.¹¹ The regrading involved all the baseline photographs of treated and untreated eyes, all follow-up photographs of a random sample of 261 untreated eyes without progression to advanced AMD, and 141 untreated eyes with progression to advanced AMD after 12 months' follow-up.

Readers in the CAPT Reading Center also evaluated the follow-up images for the presence of CNV and GA involving the center of the macula (CGA). 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 retinal pigment epithelium 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. Geographic atrophy involving the center of the macula was defined as development of GA involving the center of the macula. Evaluation of CGA 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.

The institutional review board associated with each clinical 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.

Statistical analyses were restricted to the data from the untreated eye of each CAPT participant. A computer algorithm was used to assign an AREDS scale step to each eye derived from the gradings of the photograph, following the definition of the AREDS scale.⁶ A descriptive analysis was performed to examine the distribution of the AREDS severity scale steps at baseline. Crude 5-year incidence rates and their 95% confidence intervals (CIs) of advanced AMD (CNV or CGA separately and combined) by baseline AREDS scale step were calculated. These rates were compared with those reported by the AREDS investigators using χ^2 tests or Fisher exact tests (when an expected number in a cell was <5) of proportions. These tests did not account for the intereye correlation between the outcomes of the 2 eyes of the same participant used in the AREDS estimates. Accounting for the positive correlation requires the use of raw data from each eye from AREDS and would increase the P values. Longitudinal patterns of the AREDS scale steps were examined with descriptive statistics. All data analyses were performed in SAS 9.1 (SAS Institute Inc, Cary, North Carolina).

RESULTS

AREDS 9-STEP SCALE SCORE AT BASELINE

At baseline, the drusen area and pigmentation abnormalities necessary for application of the AREDS scale could be determined from fundus photographs in 1018 untreated eyes (96.8%) of 1052 CAPT participants. Among these, 1001 eyes (98.3%) met the drusen eligibility criteria (at least 10 large drusen $>125 \mu\text{m}$) and were free of advanced AMD (CNV or CGA) at baseline. The distribution of baseline AREDS scale steps from 1001 eyes is shown in **Figure 1**. About half (52%) of the eyes had a severity step of 7 and more than a quarter (28%) of eyes had a step of 6, indicating that the majority of eyes had drusen area more than 0.5 DA or drusen area more than 0.028 DA with the definite presence of increased pigment or depigmentation. The steps 8 (ie, drusen area >0.5 DA and depigmentation area of 0.056-0.5 DA or depigmentation area >0.5 DA) and 9 (ie, presence of noncentral GA) were uncommon ($<5\%$) among the CAPT eyes.

ASSOCIATION WITH 5-YEAR INCIDENCE OF ADVANCED AMD

Among 1001 participants with an eligible untreated eye at baseline, 866 (87%) survived and completed 5-year follow-up. Within 5 years of follow-up, 178 eyes (20.5%) developed advanced AMD, either CNV (12.6%) or CGA (8.4%). Four eyes (0.5%) developed CNV after developing CGA. The crude 5-year incidence of advanced AMD increased with the AREDS 9-step scale score, 8% (95%

CI, 3%-21%) for step 4, 9% (95% CI, 5%-16%) for step 5, 19% (95% CI, 15%-25%) for step 6, 23% (95% CI, 20%-27%) for step 7, and 40% (95% CI, 26%-55%) for steps 8 and 9 combined. The CAPT estimated 5-year incidence rates were higher than the AREDS estimates for eyes with baseline steps of 4 to 6 and lower for eyes with baseline steps of 7 to 9 (**Table 1**) (**Figure 2**); however, none of these differences were statistically significant ($P > .05$). The 5-year incidence of CNV and incidence of CGA each also increased with higher steps on the AREDS scale. In both CAPT and AREDS eyes, the incidence of CGA was very low ($<1\%$) for baseline steps 4 or 5 and increased sharply at steps 7 and higher. Those with baseline steps 4 to 6 were more likely to develop CNV than CGA, those with step 7 were approximately equally likely to develop CNV as CGA, and those with steps 8 or 9 were more likely to develop CGA than CNV.

AREDS 9-STEP SCALE SCORE CHANGE OVER TIME

The progression of the AREDS scale step over 5 years was assessed among a randomly selected subset of 261 of 644 untreated eyes (41%) without the development of advanced AMD during 5-year follow-up and with all 5 annual gradings available. Among these 261 eyes, 47 eyes

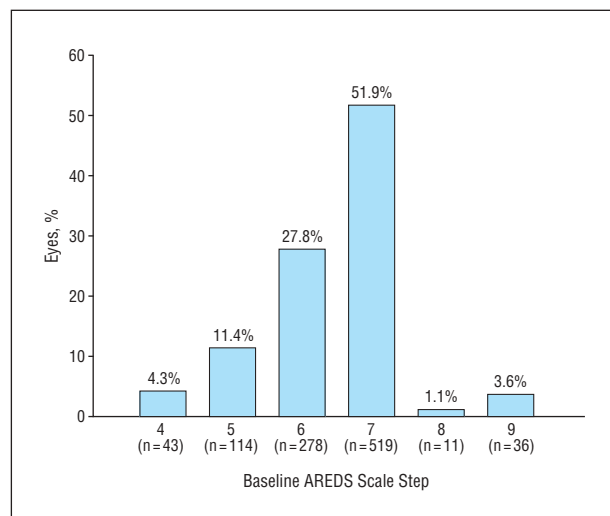


Figure 1. The distribution of Age-Related Eye Disease Study (AREDS) 9-step severity scale scores among Complications of Age-related Macular Degeneration Prevention Trial untreated eyes at baseline (N=1001 eyes).

(18%) maintained the same scale step through 5 years and 71 eyes (27%) increased 1 or more steps without reversals (**Table 2**), including 12 eyes (5%) with scale steps that increased more than 2 steps within 5 years. The scale step decreased at least once between 2 annual photographs during the 5 years of follow-up in the remaining 143 eyes (55%). Among these eyes, 13 eyes (5%) decreased 1 or more steps without reversals, including 1 eye that decreased more than 2 steps; 107 eyes (41%) fluctuated within 1 or 2 steps, and 23 eyes (9%) fluctuated more than 2 steps. At baseline or during the 5-year course of follow-up, 73 eyes (28%) reached the scale steps of 8 or 9, and 82 of 249 eyes (33%) ever had at least a 2-step increase from baseline scale step of 7 or less.

To assess the pattern of scale steps before an eye developed advanced AMD, baseline and annual follow-up AREDS scale steps were analyzed in 141 untreated eyes that developed advanced AMD (CNV or CGA) within 5 years and had at least 1 annual grading available. The median number of annual gradings available before the development of advanced AMD was 3, with 24 eyes (17%) having only 1 annual grading. Of these 141 eyes, 52 eyes (37%) maintained the baseline scale step until development of advanced AMD (Table 2); however, 17 of these eyes had only 1 annual grading. Thirty-six eyes (26%) showed a stepwise increase, including 23 eyes (16%) that increased by 2 or more steps. The scale step decreased at least once between 2 annual photographs before development of advanced AMD in the remaining 53 eyes (38%). Among these eyes, 16 eyes (11%) showed a stepwise decrease in scale steps, while 37 eyes (26%) fluctuated over time, including 9 eyes (6%) that changed more than 2 steps. Prior to progression to advanced AMD, 41 eyes (29%) reached the highest AREDS scale steps of 8 or 9, and 33 eyes (26%) had a 2-step increase or greater from baseline among 129 eyes that had a baseline scale step of 7 or less.

The pattern of AREDS scale steps over time was also examined within type of advanced AMD (Table 2). The median number of annual gradings available before development of advanced AMD was 3 for both those developing CNV and those developing CGA. A higher proportion of eyes developing CGA went through steps 8 or 9 than eyes developing CNV (56% vs 14%; $P < .001$) (Table 2). Also, increases of 2 or more steps from baseline were more common in eyes that later developed CGA than eyes that later developed CNV (44% vs 17%; $P = .002$).

Table 1. Crude 5-Year Rates of Advanced AMD by Baseline AREDS Scale Step in CAPT Untreated Eyes and AREDS Eyes

Step	No. at Risk		CNV		CGA		CNV or CGA	
	CAPT (n=866)	AREDS ^a (n=2256)	CAPT, No. (%) (n=109)	AREDS, % ^a (n=240)	CAPT, No. (%) (n=73)	AREDS, % ^a (n=173)	CAPT, No. (%) (n=178)	AREDS, % ^a (n=382)
4	38	653	3 (7.89)	4.44	0	0.60	3 (7.89)	4.90
5	92	380	8 (8.70)	5.53	0	0.79	8 (8.70)	6.05
6	241	483	38 (15.8)	11.8	9 (3.73)	2.69	36 (19.1)	13.9
7	457	488	57 (12.5)	15.6	51 (11.2)	15.0	106 (23.2)	28.1
8 and 9	38	252	3 (7.89)	22.6	13 (34.2)	31.7	15 (39.5)	48.8

Abbreviations: AMD, age-related macular degeneration; AREDS, Age-Related Eye Disease Study; CAPT, Complications of Age-related Macular Degeneration Prevention Trial; CGA, geographic atrophy involving the center of the macula; CNV, choroidal neovascularization.

^aDetermined based on Table 7 of AREDS report No. 17.⁶

The large number and long-term follow-up of CAPT participants along with the similarity of the CAPT photograph grading protocol to the AREDS protocol provided an excellent opportunity to validate the AREDS 9-step AMD severity scale in an independent sample. As in AREDS, the risk of advanced AMD among CAPT participants increased with each successive step of the AREDS scale. Furthermore, the estimates of the level of risk for each of the steps among CAPT participants were relatively close to the AREDS estimates (Figure 2). Thus, the CAPT data validate the predictive power of the AREDS 9-step severity scale for the progression to advanced AMD for the range of steps present in CAPT patients at base-

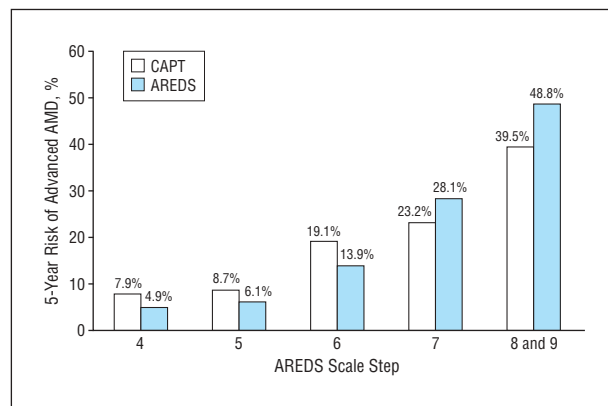


Figure 2. The crude 5-year incidence of advanced age-related macular degeneration (AMD) by Age-Related Eye Disease Study (AREDS) scale step in Complications of Age-related Macular Degeneration Prevention Trial (CAPT) eyes and AREDS eyes.

line (4-9). Although the AREDS simplified 5-step severity scale for persons has been recently validated in a population-based Blue Mountains cohort,² to our knowledge, ours is the first study to validate the AREDS complicated 9-step scale for eyes in a large, independent cohort.

Decreases in the AREDS scale step over time were common in CAPT participants (Table 2). Among eyes that did not progress to advanced AMD and had all 5 follow-up annual photographs, the AREDS scale step for 55% of eyes either decreased from baseline and did not later increase (5%) or decreased and later increased (50%). Some fluctuation in steps may be due to grading variation, because the grading-regrading agreement for drusen and pigmentary characteristics was moderate to substantial in both CAPT and AREDS, with the percentage of exact agreement ranging from 78% to 94% in CAPT⁵ and 63% to 78% in AREDS.¹¹ However, fluctuation greater than 2 steps is less likely due to grading variation, as grading-regrading agreement within 2 steps of the AREDS scale was 94% in the AREDS study⁶; instead, it is more likely due to the true disappearance of drusen or pigment. In 1973, Gass¹² noted that drusen appear and disappear naturally, a finding that has been confirmed by others.^{13,14} Sarks et al^{15,16} have described the natural progression of soft drusen as growth to confluence, leading to a small retinal pigment epithelial detachment, then fading to leave behind pigment mottling and/or atrophy in some, but not all, cases. A recent report based on 95 AREDS eyes that developed GA during AREDS follow-up provided results consistent with the Sarks et al description. Klein et al¹⁷ noted that the development of GA was nearly always preceded by regression of drusen and pigment followed by the appearance of hypopigmentation. On the AREDS scale, smaller drusen area and disappearance of pigment results in a lower step un-

Table 2. Transition of the AREDS 9-Step Severity Scale Score Over 5 Years in Eyes With and Without Development of Advanced AMD Within 5 Years

Type of Transition	No. (%)			
	Eyes Did Not Develop Advanced AMD (n=261)	Eyes Developed Advanced AMD (n=141)	Eyes Developed CNV (n=89) ^a	Eyes Developed CGA (n=52)
Stable ^b	47 (18.0)	52 (36.9)	33 (37.1)	19 (36.5)
Stepwise ^c				
Increase	71 (27.2)	36 (25.5)	21 (23.6)	15 (28.9)
Decrease	13 (4.98)	16 (11.4)	11 (12.4)	5 (9.62)
Variable ^d				
Fluctuation ≤2 steps	107 (41.0)	28 (19.9)	21 (23.6)	7 (13.5)
Fluctuation >2 steps	23 (8.81)	9 (6.38)	3 (3.37)	6 (11.5)
Ever reached step 9	71 (27.2)	38 (27.0)	11 (12.4)	27 (51.9)
Ever reached step 8 or 9	73 (28.0)	41 (29.1)	12 (13.5)	29 (55.8)
Ever had ≥2-step increase in scale step from baseline ^e	82 (32.9)	33 (25.6)	15 (17.1)	18 (43.9)
Ever reached steps 8 or 9 or had ≥2-step increase in scale step from baseline	95 (36.4)	45 (31.9)	16 (18.0)	29 (55.8)

Abbreviations: AMD, age-related macular degeneration; AREDS, Age-Related Eye Disease Study; CGA, geographic atrophy involving the center of the macula; CNV, choroidal neovascularization.

^aFour eyes that developed CNV after developing CGA were not included.

^bScale step constant throughout 5-year follow-up (eg, 7, 7, 7, 7, 7, and 7).

^cScale steps from any pair of 2 visits next to each other are tied or in increasing (decreasing) order, with at least 1 scale step different from others (eg, 5, 5, 5, 6, 7, and 9 [stepwise increase] or 7, 7, 7, 6, 5, and 4 [stepwise decrease]).

^dScale steps from some pairs of 2 visits next to each other are in increasing order while steps from some pairs are in decreasing order (eg, 6, 4, 5, 5, and 6 [within 2 steps] or 6, 7, 4, 5, 5, and 6 [more than 2 steps]).

^eEyes at step 8 or 9 at baseline were excluded because they had no chance to increase 2 steps on the severity scale. This excluded 11 eyes that developed CGA, 1 eye that developed CNV, and 12 eyes that did not develop advanced AMD.

less there is a simultaneous increase in the area of hypopigmentation.

In their report on the construction of the 9-step severity scale, AREDS investigators concluded that the AREDS scale might prove useful as a surrogate outcome. This conclusion was based on the assessment of changes in scale steps over time (baseline, years 2, 4, and 5) in 366 eyes that had changed by at least 3 steps between baseline and 5 years.⁶ One possible candidate for a surrogate outcome measure would be a change in step greater than the variation attributable to grading error (ie, ≥ 2 steps). Our detailed path analyses of CAPT eyes showed that 33% of eyes that did not progress to advanced AMD within 5 years had such a change, while such a change occurred in 26% of eyes that did progress to advanced AMD. To accommodate the eyes with severity scale steps of 8 or 9 that did not have the opportunity to increase 2 or more steps, another possible candidate for a surrogate outcome is the change to steps 8 or 9 or an increase of 2 or more steps from baseline. We found that about 36% of eyes reached scale steps 8 or 9 or ever had increases of 2 or more steps from baseline, yet did not progress to advanced AMD within 5 years. More than two-thirds of eyes neither reached the most severe scale steps (steps 8 or 9) nor had a substantial increase in scale step (≥ 2 steps) from baseline before eyes progressed to advanced AMD. Thus, using change in the AREDS scale step as a surrogate outcome would not decrease the time to observing an outcome relative to development of advanced AMD in the majority of eyes. This, along with the fact that fluctuations in scale step often occur over time, compromises the usefulness of change in step on the severity scale as a surrogate outcome for progression of AMD.¹⁸

The pattern of scale steps over time was different between eyes that later developed CNV and those that developed CGA. Before progression to CGA, about 50% of eyes ever had reached the steps 8 or 9 or had experienced an increase of 2 or more steps from baseline; this occurred in less than 20% of eyes that later progressed to CNV. This may be because the AREDS 9-step scale algorithm assigns step 9 to eyes with noncentral GA and step 8 to eyes whose predominant feature is hypopigmentation. This suggests that the AREDS 9-step severity scale is better used to monitor the development of CGA than of CNV.

The CAPT study is limited by the homogeneity of CAPT participants. The eligibility criteria of CAPT required each eye to have at least 10 large drusen (≥ 125 μm in diameter, 0.0069 DA in area); thus, at baseline the majority of eyes ($>80\%$) in CAPT participants were at steps 6 or 7, and no eyes were at steps 1, 2, or 3 (drusen area <0.056 DA). This fact prevents us from assessing and validating the 5-year incidence rate for steps 1, 2, and 3. Also, because steps 8 and 9 were uncommon ($<5\%$) in both CAPT and AREDS participants, we lack power to reliably validate the incidence rate of advanced AMD for these steps.

In conclusion, we validated the predictive power of the AREDS 9-step severity scale for advanced AMD in CAPT participants. The severity scale provides convenient risk categories for patients with AMD. However, our longitudinal path analyses show that change in the

AREDS scale step has deficiencies in serving as a surrogate outcome for progression to advanced AMD.

Submitted for Publication: December 3, 2008; final revision received February 3, 2009; accepted February 9, 2009.

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Financial Disclosure: None reported.

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

Previous Presentation: Presented in part at the meeting of the Association for Research and Vision in Ophthalmology; April 28, 2008; Fort Lauderdale, Florida.

Additional Information: The eAppendix is available at <http://www.archophthalmol.com>.

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