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The Age-Related Eye Disease Study Severity Scale for Age-Related Macular Degeneration:

AREDS Report No. 17

Age-Related Eye Disease Study Research Group[*]

Abstract

Objective—To develop a fundus photographic severity scale for age-related macular degeneration (AMD).

Methods—In the Age-Related Eye Disease Study, stereoscopic color fundus photographs were taken at baseline, at the 2-year follow-up visit, and annually thereafter. Photographs were graded for drusen characteristics (size, type, area), pigmentary abnormalities (increased pigment, depigmentation, geographic atrophy), and presence of abnormalities characteristic of neovascular AMD (retinal pigment epithelial detachment, serous or hemorrhagic sensory retinal detachment, subretinal or sub-retinal pigment epithelial hemorrhage, subretinal fibrous tissue). Advanced AMD was defined as presence of 1 or more neovascular AMD abnormalities, photocoagulation for AMD, or geographic atrophy involving the center of the macula. We explored associations among right eyes of 3212 participants between severity of drusen characteristics and pigmentary abnormalities at baseline and development of advanced AMD within 5 years of follow-up.

Results—A 9-step severity scale that combines a 6-step drusen area scale with a 5-step pigmentary abnormality scale was developed, on which the 5-year risk of advanced AMD increased progressively from less than 1% in step 1 to about 50% in step 9. Among the 334 eyes that had at least a 3-step progression on the scale between the baseline and 5-year visits, almost half showed stepwise progression through intervening severity levels at intervening visits. Replicate gradings showed agreement within 1 step on the scale in 87% of eyes.

Conclusions—The scale provides convenient risk categories and has acceptable reproducibility. Progression along it may prove to be useful as a surrogate for progression to advanced AMD.

THE AGE-RELATED EYE DISEASE Study (AREDS) is a multicenter prospective cohort study of the clinical course, prognosis, and risk factors for age-related macular degeneration (AMD) and cataract. Between 1992 and 1998, 11 retina clinics enrolled 4757 people aged 55 to 80 years in AREDS. Fifty-six percent of participants were women, 96% were white, and median age was 68 years.[1] The study also included a randomized, placebo-controlled clinical trial of treatment with high-dose antioxidant vitamins and/or zinc on the incidence of advanced AMD and vision loss. A 25% reduction in the risk of developing advanced AMD was observed with the combination treatment.[2]

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See also pages 1570 and 1598

An important goal of AREDS has been the development of a severity scale for AMD, to provide baseline risk categories, to allow tracking of progression along the scale, and to define surrogate outcomes for progression to advanced AMD. This report describes the scale as it has been developed to date, using neovascular AMD and geographic atrophy (GA) involving the center of the macula (CGA) as the principal outcome measures.

METHODS

GRADING OF PHOTOGRAPHS

Methods for taking and grading stereoscopic color fundus photographs in AREDS have been described previously.[3] Photographs were scheduled at baseline, at the 2-year visit, and annually thereafter. Briefly, stereoscopic pairs of fields 1 (disc) and 2 (macula) and a single photograph of field 3 (temporal to the macula) were taken with 30° cameras and mounted in plastic sheets, which were viewed on light boxes with ×5 Donaldson stereo viewers. Graders assessed the photographs for presence, extent, and other features of the abnormalities characteristic of AMD by using a standard grid template adapted from the Early Treatment Diabetic Retinopathy Study and standard circles consisting of opaque black lines printed on transparent stock that could be placed over or under the transparency being evaluated (Figure 1). Photographs from each visit were graded independently of those from all other visits.[3]

BASELINE CHARACTERISTICS ASSESSED

In the AREDS classification, the area occupied by drusen (all sizes and types combined) and the areas of increased pigment thought to be related to AMD, retinal pigment epithelial (RPE) depigmentation, and GA are estimated on ordinal scales in each of 3 nested zones: within one-third disc diameter (DD) of the center of the macula (the central subfield of the grid), within 1 DD of the center (the central plus 4 inner subfields of the grid, referred to as the *inner zone*), and within 2 DD of the center, ie, the grid as a whole (see Figure 1). Largest drusen size present is assessed only for the grid as a whole. In developing the scale, the grade for the grid as a whole was used for the areas of drusen and GA. The grade for the inner zone was used for increased pigment and depigmentation, because we anticipated that occurrence of these abnormalities in 1 or more of the 4 outer subfields only might frequently represent a disorder other than AMD. Predominance of soft indistinct drusen was assessed separately in each of 3 zones: the central subfield alone, the 4 inner subfields combined, and the 4 outer subfields combined. The grading scales are given in Table 1.

Geographic atrophy was defined as an area of partial or complete depigmentation of the RPE in the fundus photographs that had at least 2 of the following 3 characteristics: roughly round or oval shape, sharp margins, and visibility of underlying large choroidal vessels. Depigmentation adjacent to disciform scars was not classified as GA, even if these criteria were met. Only 35 of the 3212 right eyes initially used in scale building had noncentral GA at baseline. Preliminary analyses showed that development of CGA was more frequent in these eyes than in eyes with depigmentation not meeting the GA definition and was as frequent in eyes with noncentral GA graded questionable (probable) as in those placed in a higher category. Consequently, presence of questionable or definite noncentral GA (within the grid) was added as the highest step of a combined depigmentation (within the inner zone)–GA scale (shown in the “Results” section).

OUTCOME MEASURES

The principal outcomes analyzed were neovascular AMD and CGA. Neovascular AMD was defined as the definite presence in the fundus photographs of 1 or more of 4 characteristics:

serous sensory retinal detachment, RPE detachment, subretinal hemorrhage, or subretinal fibrous tissue; or of a report from the clinic of the application of photocoagulation for choroidal new vessels at any previous visit. The presence of CGA was defined as questionable or definite involvement of the center of the macula by definite GA. Advanced AMD was defined as neovascular AMD or CGA. Initially, advanced AMD was the only outcome used in scale building; later, progression from lower steps on the scale to higher steps was also used.

DATA SETS AND ANALYSES

As of May 2001, baseline and 5-year follow-up gradings were available for the right eyes of 3212 participants without advanced AMD in either eye at baseline (all treatment groups combined). We tabulated the frequency of development of each of the 2 types of advanced AMD within 5 years in these eyes by the baseline grade for each characteristic and examined cross-tabulations for pairs of characteristics. Concurrently, associations between the non-advanced AMD characteristics at baseline and development of advanced AMD at or before the 5-year follow-up visit were explored by means of tree-structured models.[4] With the statistical software package S-PLUS (Insightful Corp, Seattle, Wash), the tree-structured models were fit[5] and pruned on the basis of the average deviance from 10 replications of 10-fold cross-validation.[6] Models were run separately for the predictiveness of drusen characteristics alone, pigment abnormalities alone, and the 2 sets of variables together. After the scale was developed, we examined its performance in the left eyes of these same participants and then in the eye with nonadvanced AMD of other participants who had advanced AMD in one eye at baseline (543 with neovascular AMD and 57 with CGA).

REPRODUCIBILITY

Reproducibility of the scale was assessed by applying it to duplicate gradings carried out periodically throughout the course of the study as part of ongoing quality control exercises (total number of eyes, 1225).[3]

RESULTS

DRUSEN SIZE AND AREA

Table 2 gives the number and percentage of right eyes of participants free of advanced AMD in both eyes at baseline that developed advanced AMD within 5 years, by drusen area and maximum drusen size at baseline. The association between drusen size and area is apparent. Among 401 eyes with very large drusen, 309 (77%) had drusen area of 0.5 standard disc area (DA) or greater, while among 1249 eyes with only small drusen, 1096 (88%) had area less than C-1. The *P* values at the bottom of each column are from a test for trend in risk of advanced AMD with increasing drusen area within each drusen size category, while those at the end of each row are for this trend across drusen size within area. Within drusen size categories, the risk of developing advanced AMD generally increases with increasing drusen area, although there is little or no increase between the 2 largest area categories (≥0.5 DA, <1.0 DA; and ≥ 1.0 DA). The increase in risk of advanced AMD with increasing drusen size is less consistent. Because drusen area appeared to be the stronger and more consistent risk factor and because the drusen size grade indicates only the largest druse present, whereas drusen area provides a measure of total drusen, subsequent development of the severity scale focused on drusen area rather than size.

SOFT INDISTINCT DRUSEN

A similar analysis comparing drusen area and predominance of soft indistinct drusen demonstrated the association between these characteristics (Table 3). Among 467 eyes with drusen area of 0.5 DA or greater, in 211 (45%) soft indistinct drusen were predominant in all

3 zones and in 410 (88%) they were present to some degree. The predictive power of drusen area was stronger and more consistent than that of predominance of soft indistinct drusen. In view of the complexity that would be added to the scale by inclusion of a second drusen characteristic, and the limited additional predictive power to be gained, further scale building used only drusen area.

PIGMENTARY ABNORMALITIES

Table 4 gives 5-year rates of advanced AMD by baseline gradings for area of increased pigmentation and for area of depigmentation or presence of noncentral GA (the combined depigmentation-GA scale; see the "Methods" section). Of the 3212 eyes, 2412 (75%) had no pigmentary abnormalities (column 1, row 1); among them, 38 (1.6%) developed neovascular AMD and none developed CGA. Among the remaining 381 eyes in column 1, which had any degree of increased pigmentation but no depigmentation, 67 (18%) developed advanced AMD. This rate appeared to change little with increasing amounts of pigment except for an increase in the 2 highest categories. Only 52 eyes had depigmentation without accompanying increased pigment (row 1, columns 2–7). Although the numbers in each cell of columns 2 through 7 are small, the rates shown in the column totals show a steady increase from 8.5% when depigmentation was questionable to about 50% when depigmentation was 0.5 DA or greater or noncentral GA was present.

Table 5 gives a pigment abnormality scale created by collapsing Table 4. Step 1 represents the upper left cell of Table 4. Step 2 combines the remainder of column 1 with columns 2 and 3. Step 3 combines columns 4 and 5. Steps 4 and 5 represent columns 5 and 6, respectively. For both neovascular AMD and CGA, risk increased progressively except for the decrease in risk of neovascular AMD in eyes that had previously developed noncentral GA (step 5).

TREE-STRUCTURED REGRESSION ANALYSES

Figure 2 shows the results of tree-structured regression analyses of progression to neovascular AMD or CGA within 5 years. In Figure 2A, baseline variables were limited to drusen area, increased pigmentation, and depigmentation-GA in the subfields chosen a priori (see the "Methods" section). The branchings helped in the selection of cutoff points for collapsing Table 4 to create Table 5 and in collapsing the drusen area axis of Table 2 to that used in Table 6. In Figure 2B, baseline variables included drusen size and predominance of soft indistinct drusen, as well as assessments of drusen area, increased pigment, and depigmentation in each of 3 nested zones (see the "Methods" section). The principal differences between parts A and B of Figure 2 are (1) selection of drusen size, rather than area, at the second branching of the drusen area less than O-2 limb, and (2) selection of drusen area in the central subfield, rather than depigmentation, at the pigment present branching of the limb for drusen area greater than or equal to O-2. These differences were not considered substantial enough to warrant increasing the complexity of the scale.

DRUSEN AREA AND PIGMENT ABNORMALITIES CROSS-CLASSIFIED

The 2 smallest steps on the drusen area scale (Table 2) were combined, as were the 2 largest, and eyes were cross-classified by this collapsed drusen area scale and by the pigment abnormality scale shown in Table 5 to produce the entries shown in the cells of Table 6 for right eyes. This table also provides comparable information for the left eyes of the same participants, ie, participants in whom both eyes were free of advanced AMD at baseline. Development of the scale was based on results for right eyes; left eyes are shown for comparison. The cells in Table 6 were combined to create a 9-step overall severity scale (the cells assigned to each of the 9 steps are indicated by shading). For each drusen area category in Table 6, the number at risk and the percentage of eyes (right and left separately) that developed advanced AMD within 5 years are provided. The cells that make up parts of steps

1 to 6 of the overall severity scale also provide percentages of eyes progressing to steps 7, 8, or 9, but not to advanced AMD. The assignment of cells to steps in the scale was based primarily on similarity of these 2 outcomes between cells. Secondarily, preference was given to the diagonal connection between cells that would be expected when 2 predictive characteristics are cross-classified.

Results for right and left eyes were similar, but if the grouping of cells into the 9 steps of the scale had been based on left eyes, there could have been several differences, for example: (1) step 3 might have been combined with 2; (2) the smallest cell in step 5 (11 left eyes) might have been combined with the cell below it in step 6 (16 left eyes); and (3) pooling all eyes with depigmentation of 0.5 DA or greater as step 8 might have seemed less appropriate.

The data for the first and last drusen area categories of Table 6 demonstrate the close association of pigmentary abnormalities with large drusen area; 6% of eyes with drusen area less than C-1 had pigmentary abnormalities, compared with 67% of eyes with drusen area of 0.5 DA or greater.

Table 7 combines the same-step cells of Table 6 for right and left eyes combined, and presents the proportions of eyes progressing to the specified outcomes. These findings are summarized in Figure 3. Progression to advanced AMD increased across all 9 steps of the scale, although there was little change between steps 4 and 5, and progression to steps 7 to 9 increased across steps 1 to 6, although there was little difference between steps 2 and 3 (Figure 3A). The risk of neovascular AMD increased from steps 1 through 8 and then decreased in step 9 (Figure 3B). The risk of CGA was low in steps 1 to 5 and then increased across the remaining steps (Figure 3C). The bar representing step 9 is offset to emphasize that the increase in outcome in this step is due exclusively to CGA. This step can be included in or excluded from the scale depending on the goals of the study in which it is used. Inclusion would seem appropriate when CGA alone or the AREDS definition of advanced AMD is the outcome of interest, but would be problematic for neovascular AMD. Table 8 defines the steps in the scale.

EYES FREE OF ADVANCED AMD IN PARTICIPANTS WITH NEOVASCULAR AMD IN ONE EYE AT BASELINE

Table 9 corresponds to Table 6 but considers the eye with nonadvanced AMD of the 543 participants whose other eye had neovascular AMD at baseline, and Table 10 provides information for these eyes comparable to that in Table 7. Comparison of Table 10 with Table 7 (Figure 4) shows that presence of neovascular AMD in one eye of an individual increases the risk of its development in the fellow eye by a factor that ranges from 2 for eyes in step 8 to about 20 for eyes in steps 1 and 2, as compared with an eye in an individual free of neovascular AMD in both eyes.

EYES FREE OF ADVANCED AMD IN PARTICIPANTS WITH CGA IN ONE EYE AT BASELINE

There were only 57 participants who had CGA in one eye at baseline; in 16 of them the fellow eye was in steps 1 to 6 combined at baseline and in 41 it was in steps 7 to 9. In the former group, 1 eye developed neovascular AMD and 1 developed CGA (total, 12.5%), while in the latter group, 7 developed neovascular AMD, 13 developed CGA, and 2 developed both (total, 53.7%).

TRANSITIONS ALONG THE SCALE

Table 11 classifies the 334 right eyes of participants free of advanced AMD in both eyes at baseline that progressed (and 32 right eyes that improved) by 3 or more steps on the scale between the baseline and 5-year visits by the course followed at the 2- and 4-year visits. Progression was “abrupt” in 31% of the 334 eyes (the steps at 2 and 4 years were the same as

those at baseline and/or 5 years and never had a reversal of direction) and was "stepwise" in 47% (at least 1 of the steps at 2 and 4 years was intermediate between baseline and 5 years and there was never a reversal). The remainder had reversals of some degree. For example, progressions in the sequence 3-3-3-6 or 3-6-6-6 would be classified as abrupt, 2-4-4-5 or 2-3-4-5 as stepwise, and 2-4-3-4 as "variable 1" (because changing 1 visit 1 step would be sufficient to move the eye to either the stepwise category, 2-3-3-4, or the abrupt category, 2-4-4-4). Variable 2 and variable 3 have corresponding definitions of the number of steps of change required in the 2- and/or 4-year gradings to remove reversals. Similar tables for each baseline severity level showed similar results (data not shown).

REPRODUCIBILITY OF THE SCALE

Table 12 examines the reproducibility of the scale, expanded to include CGA and neovascular AMD as additional steps, by comparing the original grading with a replicate grading (see the "Methods" section). There was complete agreement in 63.4% of eyes, agreement within 1 step in 86.6%, and agreement within 2 steps in 93.6%. An unweighted κ statistic (SE) was 0.58 (0.015), and κ weighted to give 75% credit for 1-step disagreement was 0.73(0.013).

INFLUENCE OF AREDS TREATMENT

The scale-building data set was selected before publication of AREDS results, and analyses were carried out without knowledge of treatment assignment. After completion of all analyses, 5-year rates of advanced AMD in the placebo group were compared with those in the antioxidants plus zinc group and in the 3 active treatment groups combined (Table 13). Events were few, and there was no suggestion of a treatment effect through step 4. As events and rates increased thereafter, trends consistent with the beneficial treatment effect previously reported were seen in steps 5 through 9 and when steps 2 through 9 were pooled. Inspection of Table 13, and of the underlying cross-tabulations of drusen area by pigment abnormalities from which individual cells were combined to create Table 13 (data not shown), does not suggest any change in the definitions of scale steps. Although based on small numbers, comparison of the placebo and all groups combined columns for scale steps 8 and 9 suggests that 5-year risks of advanced AMD for untreated eyes in these steps are somewhat higher than those given by the scale.

A similar analysis for the eye at risk in participants with neovascular AMD in the fellow eye at baseline demonstrated treatment effect more clearly and suggested that risks for untreated eyes in steps 1 to 7 were somewhat higher than those given by the scale (Table 14).

COMMENT

The large size and long follow-up of the AREDS cohort, together with the broad severity range of drusen characteristics and pigmentary abnormalities present at baseline, provide a unique opportunity for development of an AMD severity scale. Using gradings of stereoscopic color fundus photographs that were taken at baseline, 2 years later, and annually thereafter through 5 years, we developed a 9-step severity scale that combines a 6-step drusen area scale with a 5-step pigmentary abnormality scale (Tables 6, 7, and 8). The scale is based primarily on the 5-year risk of progression to advanced AMD in individual eyes of patients free of advanced AMD in both eyes at baseline. Five-year rates of this outcome range from less than 1% in step 1 to about 50% in step 9 of the scale (Figure 3A, Table 13).

The scale provides convenient risk categories, and progression along it may prove to be useful as a surrogate for progression to advanced AMD. Replicate gradings showed agreement within 2 steps in 94% of eyes (Table 12), reproducibility similar to that reported for the Early Treatment Diabetic Retinopathy Study retinopathy severity scale, on which progression by 3

or more steps served as the primary outcome in the Diabetes Control and Complications Trial.[7] Among 334 eyes in which progression of 3 or more steps on the scale occurred between the baseline and 5-year visits, almost half showed stepwise progression through intervening severity levels at intervening visits (Table 11).

Large drusen size, extensive drusen area, soft indistinct drusen, and pigmentary abnormalities have all been recognized previously as risk factors for progression to advanced AMD, both in persons free of advanced AMD in both eyes and in the second eye of individuals in whom advanced AMD has already developed in the first eye.[8] Table 15 compares 5-year rates of progression to GA or neovascular AMD in 3 population-based studies (the Beaver Dam Eye Study,[10,11] the Blue Mountains Eye Study,[12] and the Rotterdam Study[9]) with rates of CGA or neovascular AMD in AREDS. In both the Beaver Dam study and AREDS, drusen size was reported in 4 categories; progression rates were somewhat higher in AREDS in all categories. In the Blue Mountains study, the largest category was 125 μm or greater, in which the progression rate was 14%, very similar to the 17% rate for AREDS when the categories for 125 μm or greater and 250 μm or greater are pooled, but greater than the 6% rate in the Beaver Dam study with corresponding pooling. Progression rates for eyes with soft indistinct drusen in the Blue Mountains and Rotterdam studies (23% and 18%, respectively) were somewhat higher than the AREDS rate (14%), while the Beaver Dam rate (6%) was somewhat lower. Drusen area was reported for all types and sizes combined in the Rotterdam study and in AREDS; progression rates in the largest category were 26% in both. In the Beaver Dam and Blue Mountains studies, drusen area was reported only within drusen type (Beaver Dam) or drusen size (Blue Mountains); rates in the largest categories were 18% and 31%, respectively. Corresponding rates in AREDS were 24% and 26%, respectively. Increased pigment and depigmentation were strong risk factors in all the studies, with rates in the highest categories for each ranging from 3-fold to more than 10-fold higher than those for eyes in which the abnormalities were absent.

The Rotterdam study combined drusen type and presence or absence of pigmentary abnormalities to create a 4-step scale based on 5-year risk of GA or neovascular AMD. Rates ranged from less than 0.2% for persons with no abnormalities other than hard drusen to 30% in persons with soft indistinct drusen and pigmentary abnormalities. A similar analysis in the Beaver Dam cohort that was limited to eyes with soft indistinct drusen gave similar results. Five-year rates ranged from 0% of 140 eyes with drusen area less than 0.1 DA (with or without pigmentary abnormalities) to 30% of 50 eyes with drusen area of 0.1 DA or greater and pigmentary abnormalities; the 10-year rate in the latter category approached 60%. Corresponding 5-year rates for the AREDS scale (when progression to noncentral GA is included in the outcome, to be consistent with these other studies) ranged from 0.4% in step 1 to 47% in step 7 and 67% in step 8 (Table 7).

The outcome of fellow eyes without neovascular AMD at baseline in individuals with choroidal neovascularization in one eye who were enrolled in the Macular Photocoagulation Study provides the best comparison for our results in similar eyes. In an earlier study of 127 fellow eyes of participants with extrafoveal choroidal neovascularization, 5-year rates of neovascular AMD ranged from 10% for eyes with neither large drusen nor pigmentary abnormalities to 58% for eyes with both.[13] More recently, in a study of 485 fellow eyes free of neovascular AMD at entry in participants with new juxtafoveal or new or recurrent subfoveal choroidal neovascularization in one eye, corresponding rates were 26% and 73%.[14] Corresponding rates for the AREDS scale were from about 10% in steps 1 and 2 to 45% to 55% in steps 6, 7, and 8 (Table 10).

The scale is based on assessment of good-quality stereoscopic photographs by trained graders using a detailed protocol and measuring grids (Figure 1). It is intended for use in epidemiologic

studies and clinical trials and can be modified to meet the needs of the individual study. We anticipate that it can be readily adapted to categorize persons rather than individual eyes and believe it will be more useful in future analyses than the 4 groups used to categorize participants at entry into AREDS, which were not based on an analysis of outcome data.

A simpler scale that can be used clinically is needed, and information from this and previous AREDS reports will be useful in developing one. Two examples follow. In participants without advanced AMD in either eye, eyes with drusen area of 0.5 DA or greater and without pigmentary abnormalities had a 5-year risk of advanced AMD of about 12%; adding increased pigment (any amount) and/or mild depigmentation (less than circle I-2, about 0.25 DD) doubled the risk; adding more extensive depigmentation or noncentral GA doubled the risk again (Table 6, bottom row). Presence of large (or very large) drusen in both eyes vs only one eye of a participant is also a useful clinical indicator of risk of progression to advanced AMD in at least one eye of the participant: 27% if there are large drusen in both eyes (or noncentral GA in at least one eye) vs 6% for participants with large drusen in only one eye (or with extensive intermediate drusen in one or both eyes).[2] In participants with large drusen in only one eye, drusen area was 0.5 DA or greater in that eye in 10%, while in participants with large drusen in both eyes, drusen area was 0.5 DA or greater in at least one eye in 71% (data not shown). A simplified scale is presented in the companion report.[13]

Several limitations of the scale should be recognized. Many of the subgroups that were combined to produce the steps of the scale were small and outcome rates low; biologic or grading variability could have had large effects (Table 6). Participants were mostly non-Hispanic whites, and age, sex, race, and other risk factors were not considered.[8,16] Some predictive power may have been lost by excluding drusen size and/or predominance of soft indistinct drusen from the scale. However, the parallel increases across the steps of the scale in persons with and without neovascular AMD in one eye at baseline (Figure 4) and the similarities between our results and those of others (Table 15) are reassuring. Further analyses using the longer follow-up of AREDS participants now available may provide support for use of progression on the scale as a surrogate outcome, or may suggest modifications of the scale.

In conclusion, stereoscopic color photographs collected during 5 years of follow-up in more than 3000 AREDS participants have been used to develop a 9-step severity scale, on which the 5-year risk of advanced AMD increases from less than 1% to about 50%. The scale provides convenient risk categories and has acceptable reproducibility. Progression along it may prove to be useful as a surrogate for progression to advanced AMD.

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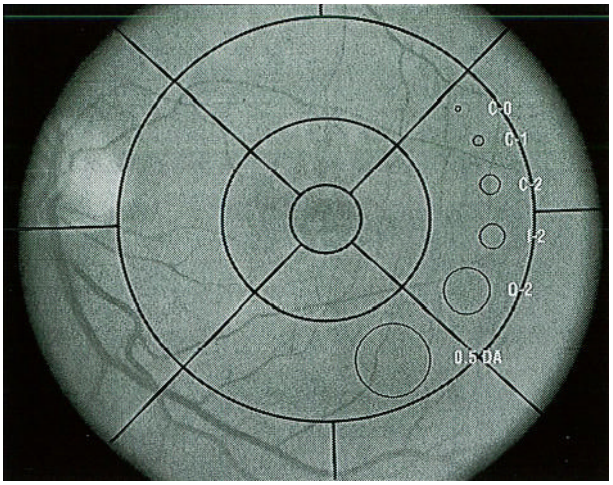

Figure 1.
Grid and standard circles used in assessing size, area, and location of abnormalities. The radii of the grid circles are one-third, 1, and 2 disc diameters, respectively, and their areas are 4/9, 4, and 16 disc areas (DAs). When the diameter of the optic disc is assumed to be 1500 μm, the radius of the central circle of the grid is 500 μm, that of the middle (inner) circle is 1500 μm, and that of the outer circle is 3000 μm. The standard circles have the following diameters and areas: C-0, 63 μm and 0.0017 DA; C-1, 125 μm and 0.0069 DA; C-2, 250 μm and 0.028 DA; I-2, 354 μm and 0.056 DA; O-2, 650 μm and 0.19 DA; and 0.5 DA, 1061 μm and 0.50 DA. An additional circle, I-1 (diameter, 175 μm; not shown in the figure) is used to define the smallest area of depigmentation that can be classified as geographic atrophy.

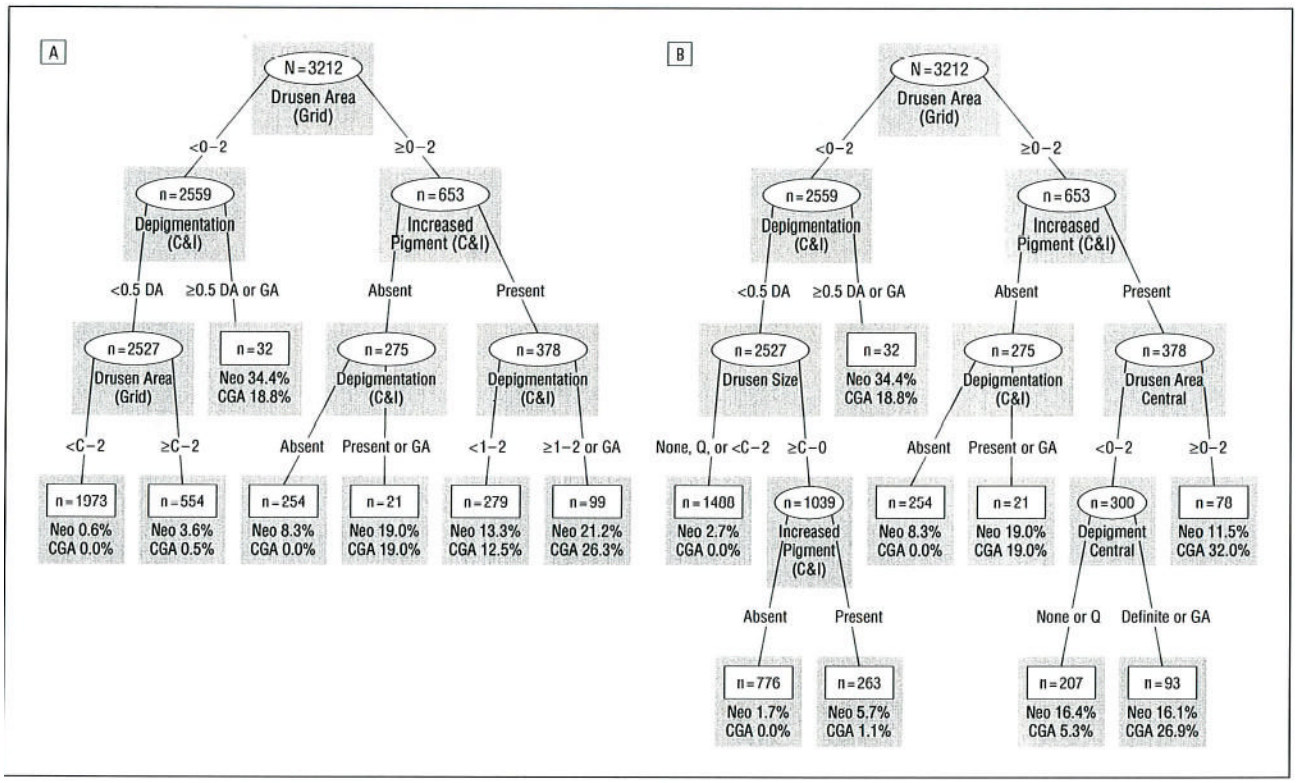

Figure 2.

Tree-structured analyses of progression to neovascular age-related macular degeneration or central geographic atrophy (CGA) within 5 years. A, Drusen area, increased pigment, and depigmentation–geographic atrophy (GA) as used in Table 2 and Table 4 were the only variables considered. B, To the variables in part A, drusen size and predominance of soft indistinct drusen were added and drusen area, increased pigment, and depigmentation were entered for each of the 3 nested zones. DA indicates disc area; C&I, central and inner circles; Neo, neovascular age-related macular degeneration.

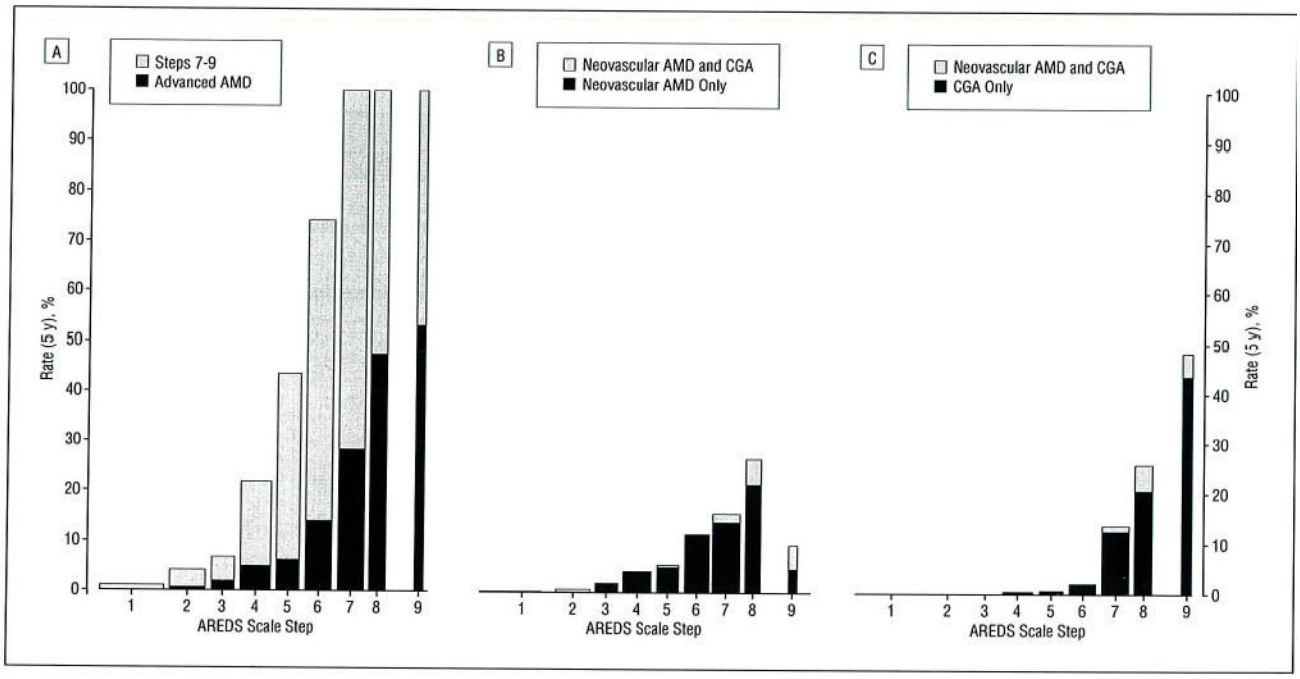

Figure 3.

Five-year progression rates in 6426 eyes of 3214 patients free of advanced age-related macular degeneration (AMD) in both eyes at baseline. The width of the bars is proportional to the number of eyes in the Age-Related Eye Disease Study (AREDS) scale step at baseline. A, Progression to scale steps 7 to 9 and to advanced AMD (neovascularAMD, central geographic atrophy [CGA], or both). Progression to steps 7 to 9 is shown as 100% for eyes in these steps at baseline. B, Progression to neovascular AMD alone or with CGA as well. C, Progression to CGA alone or with neovascular AMD as well.

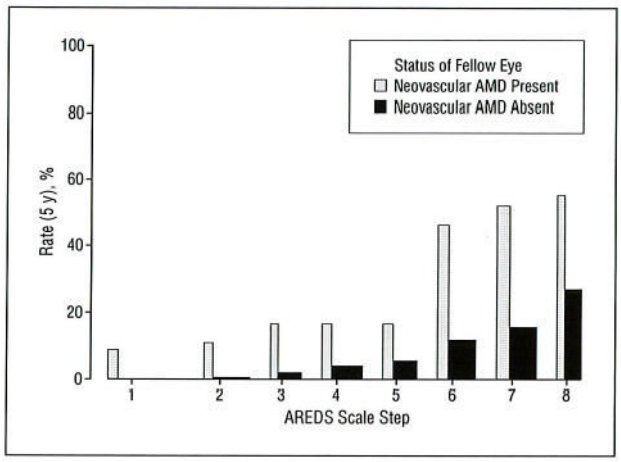

Figure 4.
Five-year rates of neovascular age-related macular degeneration (AMD) (with or without central geographic atrophy) in eyes with and without neovascular AMD in the fellow eye at baseline. The width of the bars is proportional to the number of eyes in the Age-Related Eye Disease Study (AREDS) scale step at baseline.

Table 1

AREDS Grading Scales

Grade	Largest Drusen Size	Drusen Area	Increased Pigment	Depigmentation	Geographic Atrophy	Predominance of Soft Indistinct Drusen
0	None	None, Q,* or <C-0	None	None	None	None
1	Questionable*	≥C-0, <C-1	Questionable*	Questionable*	Questionable*	Questionable*
2	<C-0	≥C-1,<C-2	<C-0	<I-2	<I-2	Present, not predominant
3	≥C-0, <C-1	≥C-2, <I-2	≥C-0, <C-1	≥I-2, <O-2	≥I-2, <O-2	Predominant in 1 of 3 zones
4	≥C-1,<C-2	≥I-2, <O-2	≥C-1,<C-2	≥O-2, <0.5 DA	≥O-2, <0.5 DA	2 of 3 zones
5	≥C-2	≥O-2, <0.5 DA	≥C-2, <O-2	≥0.5, < 1.0 DA	≥0.5, <1.0 DA	3 of 3 zones
6	NA	≥0.5, <1.0 DA	≥O-2	≥1.0, <2.0DA	≥1.0, <2.0 DA	MA
7	NA	≥1.0 DA	Unrelated to AMD	≥2.0 DA	≥2.0 DA	NA
8	Cannot grade	Cannot grade	Cannot grade	Cannot grade	Cannot grade	Cannot grade

Abbreviations: AMD, age-related macular degeneration; AREDS, Age-Related Eye Disease Study; DA, disc area; NA, not applicable.

*The “Questionable” category is chosen when the grader is at least 50%, but not 90%, sure that the abnormality is present.

Table 2

Five-Year Rates of Advanced AMD,* by Drusen Area and Maximum Drusen Size at Baseline

Drusen Area	Maximum Drusen Size, No. (%)							
	None	Questionable	Small: <C-0 (<63 µm)	Intermediate: ≥C-0, <C-1 (63–124 µm)	Large: ≥C-1, <C-2 (125–249 µm)	Very Large: ≥C-2 (≥250 µm)	Total	*P* Value, Trend Test
None, questionable, <C-0								
At risk	155	91	633				**879**	
NeoAMD	0	1	0				**1**	
CGA	0	0	1				**1**	
Total†	0	1(1.1)	1 (0.2)				**2** (0.2)	.94
≥C-0. <C-1								
At risk			463	180			**643**	
NeoAMD			1	5			**6**	
CGA			0	0			**0**	
Total†			1 (0.2)	6 (3.3)			**7** (1.1)	.001
≥C-1,<C-2								
At risk			133	256	74		**463**	
NeoAMD			1	5	1		**7**	
CGA			1	0	1		**2**	
Total†			2 (1.5)	7 (2.7)	2 (2.7)		**11** (2.4)	.52
≥C-2, <I-2								
At risk			13	144	155	3	**315**	
NeoAMD			1	3	7	0	**11**	
CGA			0	1	1	0	**2**	
Total†			1 (7.7)	4 (2.8)	8 (5.2)	0	**13** (4.1)	.67
≥I-2, <O-2								
At risk			5	86	140	28	**259**	
NeoAMD			0	2	9	1	**12**	
CGA			0	1	3	0	**4**	
Total†			0	4 (4.7)	14 (10.0)	1 (3.6)	**19** (7.3)	.48
≥O-2, <0.5 DA								
At risk			2	28	95	61	**186**	
NeoAMD			0	1	7	8	**16**	
CGA			0	1	3	4	**8**	
Total†			0	2 (7.1)	10 (10.5)	14 (23.0)	**26** (14.0)	.01
≥0.5 DA, <1.0 DA								
At risk			0	11	68	85	**164**	
NeoAMD				1	8	11	**20**	
CGA				2	5	14	**21**	
Total†				3 (27.3)	14 (20.6)	25 (29.4)	**42** (25.6)	.37
≥1.0 DA								
At risk			0	8	71	224	**303**	
NeoAMD				1	7	31	**39**	
CGA				0	10	26	**36**	
Total†				1 (12.5)	17 (23.9)	62 (27.7)	**80** (26.4)	.30
Total								
At risk	**155**	**91**	**1249**	**713**	**603**	**401**	**3212**	
NeoAMD	**0**	**1**	**3**	**18**	**39**	**51**	**112**	
CGA	**0**	**0**	**2**	**5**	**23**	**44**	**74**	
Total†	**0**	**1** (1.1)	**5** (0.4)	**27** (3.8)	**65** (10.8)	**102** (25.4)	**200** (6.2)	
P value, trend test	NA	NA	.02	.01	<.001	.01	NA	NA

Abbreviations: AMD, age-related macular degeneration; CGA, geographic atrophy involving center of macula; DA, disc area; NA, not applicable; NeoAMD, neovascular AMD.

*In the right eyes of 3212 participants free of advanced AMD in both eyes at baseline. Cells that cannot, by definition, have entries are blank.

†Numbers given for NeoAMD and CGA represent eyes with this outcome only; where the total exceeds the sum of NeoAMD + CGA, the difference represents eyes that were graded as both NeoAMD and CGA, usually at different visits.

Table 3

Five-Year Rates of Advanced AMD,* by Drusen Area and Predominance of Soft Indistinct Drusen At Baseline

Drusen Area	Predominance of Soft Indistinct Drusen, No. (%)						
	Absent	Present, Not Predominant	Predominant in 1 of 3 Zones	Predominant in 2 of 3 Zones	Predominant in 3 of 3 Zones	Total	*P* Value, Trend Test
None, questionable, <C-0							
At risk	879					**879**	
NeoAMD	1					**1**	
CGA	1					**1**	
Total†	2 (0.2)					**2** (0.2)	
≥C-0. <C-1							
At risk	602	6	35	0	0	**643**	
NeoAMD	3	0	3			**6**	
CGA	0	0	0			**0**	
Total†	4 (0.7)	0	3 (8.6)			**7** (1.1)	.004
≥C-1, <C-2							
At risk	294	20	121	27	1	**463**	
NeoAMD	6	0	0	1	0	**7**	
CGA	1	1	0	0	0	**2**	
Total†	7 (2.4)	1 (5.0)	1 (0.8)	2 (7.4)	0	**11** (2.4)	.83
≥C-2, <I-2							
At risk	102	32	113	55	13	**315**	
NeoAMD	4	1	3	2	1	**11**	
CGA	1	0	0	0	1	**2**	
Total†	5 (4.9)	1 (3.1)	3 (2.7)	2 (3.6)	2 (15.4)	13 (4.1)	.75
≥I-2, <O-2							
At risk	43	30	73	76	37	**259**	
NeoAMD	0	1	3	3	5	**12**	
CGA	1	1	0	1	1	**4**	
Total†	1 (2.3)	2 (6.7)	5 (6.8)	5 (6.6)	6 (16.2)	**19** (7.3)	.04
≥O-2, <0.5 DA							
At risk	26	15	33	66	46	**186**	
NeoAMD	0	1	2	5	8	**16**	
CGA	0	0	3	4	1	**8**	
Total†	0	1 (6.7)	5 (15.2)	10 (15.2)	10 (21.7)	**26** (14.0)	.005
≥0.5 DA, <1.0 DA							
At risk	23	11	11	52	67	**164**	
NeoAMD	1	1	1	7	10	**20**	
CGA	3	1	5	6	6	**21**	
Total†	4 (17.4)	2 (18.2)	6 (54.5)	14 (26.9)	16 (23.9)	**42** (25.6)	.7
≥1.0 DA							
At risk	34	22	44	59	144	**303**	
NeoAMD	2	1	8	6	22	**39**	
CGA	3	1	7	8	17	**36**	
Total†	5 (14.7)	2 (9.1)	15 (34.1)	15 (25.4)	43 (29.9)	**80** (26.4)	.04
Total							
At risk	**2003**	**136**	**430**	**335**	**308**	**3212**	
NeoAMD	**17**	**5**	**20**	**24**	**46**	**112**	
CGA	**10**	**4**	**15**	**19**	**26**	**74**	
Total†	**28** (1.4)	**9** (6.6)	**38** (8.8)	**48** (14.3)	**77** (25.0)	**200** (6.2)	
P value, trend test	<.001	.17	<.001	<.001	.03	NA	NA

Abbreviations: AMD, age-related macular degeneration; CGA, geographic atrophy involving center of macula; DA, disc area; NA, not applicable; NeoAMD, neovascular AMD.

[*] In the right eyes of 3212 participants free of advanced AMD in both eyes at baseline. Cells that cannot, by definition, have entries are blank.

[†] Numbers given for NeoAMD and CGA represent eyes with this outcome only; where the total exceeds the sum of NeoAMD +CGA, the difference represents eyes that were graded as both NeoAMD and CGA, usually at different visits.

Table 4

Five-Year Rate of Advanced AMD,* by Area of Increased Pigmentation and by Area of Depigmentation–Presence of Geographic Atrophy at Baseline

Increased Pigment	Depigmentation, No. (%)							
	None	Questionable	<I-2	≥I-2, <O-2	≥O-2, <0.5 DA	≥0.5 DA	GA, No. (%)	Total
None								
At risk	2412	24	5	8	1	6	8	**2464**
NeoAMD	38	1	0	0	0	1	1	**41**
CGA	0	1	0	0	0	1	3	**5**
Total†	38 (1.6)	2 (8.3)	0	0	0	3 (50.0)	5 (62.5)	**48** (1.9)
Questionable								
At risk	52	5	2	5	1	0	1	**66**
NeoAMD	7	0	0	0	0		0	**7**
CGA	1	0	0	0	0		1	**2**
Total†	9 (17.3)	0	0	0	0		1 (100.0)	**10** (15.2)
<C-0								
At risk	46	6	0	3	2	2	0	**59**
NeoAMD	2	0		0	0	0		**2**
CGA	2	0		1	0	1		**4**
Total†	4 (8.7)	0		1 (33.3)	0	2 (100.0)		**7** (11.9)
≥C-0, <C-1								
At risk	101	19	21	12	3	2	8	**166**
NeoAMD	12	0	0	1	0	0	0	**13**
CGA	3	1	0	0	1	0	3	**8**
Total†	16 (15.8)	1 (5.3)	0	1 (8.3)	1 (33.3)	1 (50.0)	3 (37.5)	**23** (13.9)
≥C-1, <C-2								
At risk	114	39	36	34	18	9	9	**259**
NeoAMD	6	3	4	5	5	3	0	**26**
CGA	10	1	4	2	1	1	4	**23**
Total†	16 (14.0)	4 (10.3)	8 (22.2)	7 (20.6)	6 (33.3)	4 (44.4)	4 (44.4)	**49** (18.9)
≥C-2, <O-2								
At risk	65	23	23	29	12	23	8	**183**
NeoAMD	7	0	1	3	2	5	1	**19**
CGA	11	1	2	7	2	3	2	**28**
Total†	21 (32.3)	2 (8.7)	3 (13.0)	10 (34.5)	4 (33.3)	10 (43.5)	3 (37.5)	**53** (29.0)
≥ O-2								
At risk	3	1	1	1	2	6	1	**15**
NeoAMD	1	0	0	1	0	2	0	**4**
CGA	0	1	0	0	1	1	1	**4**
Total†	1 (33.3)	1 (100.0)	0	1 (100.0)	1 (50.0)	5 (83.3)	1 (100.0)	**10** (66.7)
Total								
At risk	**2793**	**117**	**88**	**92**	**39**	**48**	**35**	**3212**
NeoAMD	**73**	**4**	**5**	**10**	**7**	**11**	**2**	**112**
CGA	**27**	**5**	**6**	**10**	**5**	**7**	**14**	**74**
Total†	**105** (3.8)	**10** (8.5)	**11** (12.5)	**20** (21.7)	**12** (30.8)	**25** (52.1)	**17** (48.6)	**200** (6.2)

Abbreviations: AMD, age-related macular degeneration; CGA, geographic atrophy involving center of macula; DA, disc area; GA, geographic atrophy; NeoAMD, neovascular AMD.

*In the right eyes of 3212 participants free of advanced AMD in both eyes at baseline.

†Numbers given for NeoAMD and CGA represent eyes with this outcome only; where the total exceeds the sum of NeoAMD + CGA, the difference represents eyes that were graded as both NeoAMD and CGA, usually at different visits.

Table 5

Five-Year Rates of Advanced AMD,* by Severity of Pigmentary Abnormalities at Baseline

Step	Pigmentary Abnormalities	No. at Risk	No. (%)			
			NeoAMD	CGA	Both	Total
1	None	2412	38 (1.6)	0	0	**38** (1.6)
2	Increased pigment ≥questionable and/or depigmentation <I-2	586	44 (7.5)	38 (6.5)	6 (1.0)	**88** (15.0)
3	Depigmentation ≥I-2, <0.5 DA	131	17 (13.0)	15 (11.5)	0	**32** (24.4)
4	Depigmentation ≥0.5 DA	48	11 (22.9)	7 (14.6)	7 (14.6)	**25** (52.1)
5	Noncentral GA ≥questionable	35	2 (5.2)	14 (40.0)	1 (2.9)	**17** (48.6)
	Total	**3212**	**112** (3.5)	**74** (2.3)	**14** (0.4)	**200** (6.2)

Abbreviations: AMD, age-related macular degeneration; CGA, geographic atrophy involving center of macula; DA, disc area; GA, geographic atrophy; NeoAMD, neovascular AMD.

* In the right eyes of 3212 participants free of advanced AMD in both eyes at baseline.

Table 6

Five-Year Rates of Advanced AMD and (for Eyes That Did Not Progress to Advanced AMD) Rates of Progression From Scale Steps 1 to 6 to Steps 7 to 9 for Right and Left Eyes of Participants Free of Advanced AMD in Both Eyes at Baseline

	Pigment Abnormalities: Increased Pigment Depigmentation Geographic Atrophy											
	0 0 0		≥Q 0 0	≥0 ≥Q, <I-2 0	≥0 ≥I-2, <0.5 DA 0		≥0 ≥0.5 DA 0		≥0 ≥0 ≥Q		Total	
Drusen Area	**R**	**L**	**R**	**L**	**R**	**L**	**R**	**L**	**R**	**L**	**R**	**L**
<C-1												
No. of eyes	1430	1463	68	66	17	19	5	3	2	1	**1522**	**1552**
To steps 7–9, %	0.3	0.7	8.8	6.1	5.9	42.1	NA	NA	NA	NA	NA	NA
AdvAMD, %	0.3	0.3	0.0	0.0	5.9	5.3	60.0	0.0	50.0	0.0	0.6	0.3
≥C-1, <C-2												
No. of eyes	367	398	78	71	13	12	4	5	1	5	**463**	**491**
To steps 7–9, %	2.2	2.5	12.8	9.9	23.1	16.7	NA	NA	NA	NA	NA	NA
AdvAMD, %	1.1	0.3	3.8	5.6	0.0	8.3	75.0	40.0	100.0	40.0	2.4	2.0
≥C-2, <I-2												
No. of eyes	206	172	74	63	26	11	8	6	1	0	**315**	**252**
To steps 7–9, %	2.9	5.2	20.3	23.8	34.6	36.4	NA	NA	NA	NA	NA	NA
AdvAMD, %	2.9	0.6	4.1	9.5	3.8	18.2	37.5	33.3	0.0	0.0	4.1	4.4
≥I-2, < O-2												
No. of eyes	155	151	78	73	15	16	9	12	2	3	**259**	**255**
To steps 7–9, %	12.9	18.5	37.2	31.5	60.0	37.5	NA	NA	NA	NA	NA	NA
AdvAMD, %	1.9	6.6	10.3	5.5	13.3	12.5	55.6	0.0	50.0	66.7	7.3	7.1
≥O-2, <0.5 DA												
No. of eyes	98	94	61	76	12	8	8	7	7	4	**186**	**189**
To steps 7–9, %	39.8	40.4	67.2	53.9	NA	NA	NA	NA	NA	NA	NA	NA
AdvAMD, %	3.1	5.3	18.0	18.4	41.7	50.0	50.0	57.1	42.9	75.0	14.0	15.9
≥0.5 DA												
No. of eyes	156	159	227	241	48	48	14	13	22	14	**467**	**475**
To steps 7–9, %	62.2	59.7	NA	MA	NA	NA	NA	NA	NA	NA	NA	NA
AdvAMD, %	11.5	12.6	27.8	27.0	47.9	56.3	50.0	53.8	50.0	64.3	26.1	26.9
Total												
No. of eyes	**2412**	**2437**	**586**	**590**	**131**	**114**	**48**	**46**	**35**	**27**	**3212**	**3214***
To steps 7–9, %	7.3	7.8	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
AdvAMD, %	1.6	1.7	15.0	15.8	24.4	32.5	52.1	32.6	48.6	59.3	6.2	6.3

Abbreviations: AdvAMD, advanced AMD; AMD, age-related macular degeneration; DA, disc area; NA, not applicable; L, left eye; R, right eye.

* For 2 of the 3214 patients whose left eyes are included in the table, the grading for the right eye was “cannot grade” for 1 or more characteristics at either the baseline or the 5-year visit.

Scale Steps: 1 2 3 4 5 6 7 8 9

Table 7

Five-Year Rates of Advanced AMD and (for Eyes That Did Not Progress to Advanced AMD) Rates of Progression From Scale Steps 1 to 6 to Step 7 or 8 or to Step 9, for Right and Left Eyes Combined, of Participants Free of Advanced AMD in Both Eyes at Baseline

		No. (%)				
Step	**No. at Risk**	**Step 7 or 8**	**Step 9**	**NeoAMD**	**CGA**	**N + C**
1	2893	11 (0.4)	4 (0.1)	8 (0.3)	0	0
2	899	21 (2.3)	7 (0.8)	5 (0.6)	0	0
3	378	12 (3.2)	3 (0.8)	7 (1.9)	0	0
4	653	90 (13.8)	19 (2.9)	28 (4.3)	3 (0.5)	1 (0.2)
5	380	118 (31.1)	24 (6.3)	20 (5.3)	2 (0.5)	1 (0.3)
6	483	249 (51.6)	40 (8.3)	54 (11.2)	10 (2.1)	3 (0.6)
7	488	NA	93 (19.1)	64 (13.1)	61 (12.5)	12 (2.5)
8	190	NA	37 (19.5)	40 (21.1)	39 (20.5)	11 (5.8)
9	62	NA	NA	3 (4.8)	27 (43.5)	3 (4.8)
Total	**6426**	**501** (7.8)	**227** (3.5)	**229** (3.6)	**142** (2.2)	**31** (0.5)

Abbreviations: AMD, age-related macular degeneration; CGA, geographic atrophy involving center of macula; NA, not applicable; NeoAMD, neovascular AMD; N + C, NeoAMD + CGA.

Table 8

Definitions of Scale Steps

Step	Drusen Area	Increased Pigment		Depigmentation-GA
1	<C-1	0		0
2	≥C-1, <C-2	0		0
	<C-1	≥Q	and/or	≥Q, <I-2
3	≥C-2, <I-2	0		0
4	I-2, <O-2	0		0
	≥C-1, <I-2	≥Q	and/or	≥Q, <I-2
	<C-2	≥0		≥I-2, <0.5 DA
5	≥O-2, <0.5 DA	0		0
	≥I-2, <O-2	≥Q		≥Q, <I-2
	≥C-2, <I-2	≥0	and/or	≥I-2, <0.5 DA
6	≥0.5 DA	0		0
	≥O-2, <0.5 DA	≥Q	and/or	≥Q, <I-2
	≥I-2, <O-2	≥0		≥I-2, <0.5 DA
7	≥0.5 DA	≥Q	and/or	≥Q, <I-2
	≥O-2, <0.5 DA	≥0		≥I-2, <0.5 DA
8	≥0.5 DA	≥0		≥I-2, <0.5 DA
	Any	≥0		≥0.5 DA
9	Any	≥0		Noncentral GA

Abbreviations: DA, disc area; GA, geographic atrophy.

Table 9

Five-Year Rates of Advanced AMD and (for Eyes That Did Not Progress to Advanced AMD) Rates of Progression From Scale Steps 1 to 6 to Steps 7 to 9 for the Eyes at Risk of Participants With Neovascular AMD in the Fellow Eye at Baseline

	Pigment Abnormalities, No. (%): Increased Pigment Depigmentation Geographic Atrophy						
Drusen Area	**0 0 0**	**≥Q 0 0**	**≥0 ≥Q, <I-2 0**	**≥0 ≥I-2, <0.5 DA 0**	**≥0 ≥0.5 DA 0**	**≥0 ≥0 ≥Q**	**Total**
<C-1							
No. of eyes	68		9	3	0	0	**80**
To steps 7–9	2 (2.9)		2 (22.2)	1 (33.3)			NA
NeoAMD	6		0	0			**6**
CGA	0		0	0			**0**
Total AdvAMD*	6 (8.8)		0	0			**6** (7.5)
≥C-1, <C-2							
No. of eyes	45		7	4	2	3	**61**
To steps 7–9	4 (8.9)		1 (14.3)	1 (25.0)	NA	NA	NA
NeoAMD	6		3	2	0	1	**12**
CGA	0		0	0	0	2	**2**
Total AdvAMD*	6 (13.3)		3 (42.9)	2 (50.0)	1 (50.0)	3 (100.0)	**15** (24.6)
≥C-2, <I-2							
No. of eyes	36		15	4	2	1	**58**
To steps 7–9	0		1 (6.7)	2 (50.0)	NA	NA	NA
NeoAMD	5		3	1	2	0	**11**
CGA	0		1	1	0	0	**2**
Total AdvAMD*	6 (16.7)		4 (26.7)	2 (50.0)	2 (100.0)	1 (100.0)	**15** (25.9)
≥I-2, <O-2							
No. of eyes	32		36	6	4	6	**84**
To steps 7–9	9 (28.1)		13 (36.1)	1 (16.7)	NA	NA	NA
NeoAMD	8		11	4	2	1	**26**
CGA	0		0	0	0	0	**0**
Total AdvAMD*	8 (25.0)		12 (33.3)	4 (66.7)	2 (50.0)	2 (33.3)	**28** (33.3)
≥O-2, <0.5 DA							
No. of eyes	24		31	8	4	6	**73**
To steps 7–9	8 (33.3)		15 (48.4)	NA	NA	NA	NA
NeoAMD	9		10	2	2	1	**24**
CGA	0		3	1	1	2	**7**
Total AdvAMD*	10 (41.7)		14 (45.2)	5 (62.5)	3 (75.0)	4 (66.7)	**36** (49.3)
≥0.5 DA							
No. of eyes	47		107	20	6	7	**187**
To steps 7–9	16 (34.0)		NA	NA	NA	NA	NA
NeoAMD	24		49	12	1	2	**88**
CGA	0		4	1	3	1	**9**
Total AdvAMD*	24 (51.1)		60 (56.1)	14 (70.0)	4 (66.7)	4 (57.1)	**106** (56.7)
Total							
No. of eyes	**252**		**205**	**45**	**18**	**23**	**543**
To steps 7–9	39 (15.5)		NA	NA	NA	NA	NA
NeoAMD	**58**		**76**	**21**	**7**	**5**	**167**
CGA	**0**		**8**	**3**	**4**	**5**	**20**
Total AdvAMD*	**60** (23.8)		**93** (45.4)	**27** (60.0)	**12** (66.7)	**14** (60.9)	**206** (37.9)

Abbreviations: AdvAMD, advanced AMD; AMD, age-related macular degeneration; CGA, geographic atrophy involving center of macula; DA, disc area; NA, not applicable; NeoAMD, neovascular AMD.

* Numbers given for NeoAMD and CGA represent eyes with this outcome only; where the total exceeds the sum of NeoAMD + CGA, the difference represents eyes that were graded as both NeoAMD and CGA, usually at different visits.

Scale Steps: 1 2 3 4 5 6 7 8 9

Table 10

Five-Year Rates of Advanced AMD and (for Eyes That Did Not Progress to Advanced AMD) Rates of Progression From Scale Steps 1 to 6 to Step 7 or 8 or to Step 9, for Eyes at Risk of Participants With NeoAMD in the Fellow Eye at Baseline

		No. (%)				
Step	**No. at Risk**	**Steps 7–8**	**Step 9**	**NeoAMD**	**CGA**	**N + C**
1	68	1 (1.5)	1 (1.5)	6 (8.8)	0	0
2	54	6 (11.1)	0	6 (11.1)	0	0
3	36	0	0	5 (13.9)	0	1 (2.8)
4	61	10 (16.4)	3 (4.9)	16 (26.2)	1 (1.6)	0
5	64	18 (28.1)	5 (7.8)	21 (32.8)	1 (1.6)	2 (3.1)
6	84	24 (28.6)	8 (9.5)	38 (45.2)	3 (3.6)	1 (1.2)
7	115	NA	20 (17.4)	51 (44.4)	5 (4.4)	9 (7.8)
8	38	NA	5 (13.2)	19 (50.0)	5 (13.2)	2 (5.3)
9	23	NA	NA	5 (21.7)	5 (21.7)	4 (17.4)
Total	**543**	**59** (10.9)	**42** (7.7)	**167** (30.8)	**20** (3.7)	**19** (3.5)

Abbreviations: AMD, age-related macular degeneration; CGA, geographic atrophy involving center of macula; NA, not applicable; NeoAMD, neovascular AMD; N + C, NeoAMD + CGA.

Table 11

Transitions From Baseline to Years 2, 4, and 5 for Eyes With 3-Step or Greater Change Between Baseline and 5-Year Visit

Type of Transition*	No. (%)	
	Progression	Improvement
Abrupt: 2- and 4-y grades same as baseline or 5-y and in order, eg, 3336, 3666, 3366 (not 3436)	102 (30.5)	10 (31.3)
Stepwise: 2- and/or 4-y grades between baseline and 5-y and in order, eg, 3346, 3356, 3456 (not 3436)	157 (47.0)	11 (34.4)
Variable		
1 step at 1 visit, eg, 3436	39 (11.7)	7 (21.9)
1 step at each of 2 visits or 2 steps at 1 visit, eg, 3276, 3536	24 (7.2)	2 (6.3)
Greater, eg, 3275	12 (3.6)	2 (6.3)
Total	**334 (100.0)**	**32 (100.0)**

*Examples are given only for progression.

Table 12

Intergrader Reproducibility of Scale: Original Grade by Regrading*

	Regrading												
Original AREDS Scale Step	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**CGA**	**NeoAMD**	**NeoAMD + CGA**	**Total**
1	252	54	12	6	3	1	0	1	0	0	0	0	**329**
2	35	72	12	11	4	1	0	5	0	0	1	0	**141**
3	4	14	16	11	2	0	0	1	0	0	0	0	**48**
4	6	5	16	58	21	10	1	4	2	0	0	0	**123**
5	0	0	2	19	24	13	3	4	0	0	1	0	**66**
6	0	0	0	7	10	34	9	6	1	0	2	0	**69**
7	0	0	0	1	2	9	41	13	1	0	3	0	**70**
8	1	1	1	3	2	4	5	23	6	2	1	0	**49**
9	0	1	0	0	0	2	4	8	42	8	1	0	**66**
CGA	0	0	0	0	0	0	2	6	8	52	1	3	**72**
NeoAMD	0	0	0	1	0	2	6	3	1	1	160	8	**182**
NeoAMD + CGA	0	0	0	0	0	0	0	2	0	2	3	3	**10**
Total	**298**	**147**	**59**	**117**	**68**	**76**	**71**	**76**	**61**	**65**	**173**	**14**	**1225**

Abbreviations: AREDS, Age-Related Eye Disease Study; CGA, geographic atrophy involving center of macula; NeoAMD, neovascular age-related macular degeneration.

*Complete agreement, 63.4%; agreement within 1 step, 86.6%; agreement within 2 steps, 93.6%; κ (SE) = 0.58 (0.015); κ (SE) weighted 0.75 for 1 off diagonal = 0.73 (0.013).

Table 13

Five-Year Rates of Advanced AMD (or Right and Left Eyes Combined of Participants Free of Advanced AMD in Both Eyes at Baseline, by Treatment Assignment

	Placebo		A, Z, and A + Z*		A + Z		All Groups Combined	
Step	**No. at Risk**	**AdvAMD, No. (%)**	**No. at Risk**	**AdvAMD, No. (%)**	**No. at Risk**	**AdvAMD, No. (%)**	**No. at Risk**	**AdvAMD, No. (%)**
1	1219	3 (0.2)	1674	5 (0.3)	224	2 (0.9)	2893	8 (0.3)
2	225	1 (0.4)	674	4 (0.6)	228	0	899	5 (0.6)
3	96	3 (3.1)	282	4 (1.4)	87	4 (4.6)	378	7 (1.9)
4	147	7 (4.8)	506	25 (4.9)	178	11 (6.2)	653	32 (4.9)
5	112	8 (7.1)	268	15 (5.6)	102	6 (5.9)	380	23 (6.1)
6	119	17 (14.3)	364	50 (13.7)	125	17 (13.6)	483	67 (13.9)
7	139	40 (28.8)	349	97 (27.8)	106	27 (25.5)	488	137 (28.1)
8	49	27 (55.1)	141	63 (44.7)	45	23 (51.1)	190	90 (47.4)
9	18	11 (61.1)	44	22 (50.0)	9	3 (33.3)	62	33 (53.2)
Steps 2–9†	**905**	**114** (12.6)	**2628**	**280** (10.7)	**880**	**91** (10.3)	**3533**	**394** (11.2)

Abbreviations: A, antioxidants; AdvAMD, advanced AMD; AMD, age-related macular degeneration; Z, zinc.

*All 3 treatment groups combined.

†Step 1 is excluded from the total because of imbalances caused by inclusion in this step, in the placebo and antioxidant-only treatment groups, of patients who were free of AMD (both eyes had no or only occasional small drusen and no pigment abnormalities) and therefore were enrolled only in the cataract trial and randomized to placebo or antioxidants alone. There were about 1000 such eyes in step 1 in each of the first 2 columns of the table. *P* value for placebo vs A + Z = .16 and for placebo vs A, Z, and A+Z combined = .12.

Table 14

Five-Year Rates of Advanced AMD for the Eye at Risk in Participants With Neovascular AMD in the Fellow Eye at Baseline, by Treatment Assignment

	Placebo		A, Z, and A + Z*		A + Z		All Groups Combined	
Step	**No. at Risk**	**AdvAMD, No. (%)**	**No. at Risk**	**AdvAMD, No. (%)**	**No. at Risk**	**AdvAMD, No. (%)**	**No. at Risk**	**AdvAMD, No. (%)**
1–3	38	7 (18.4)	120	11 (9.2)	40	2 (5.0)	158	18 (11.4)
4–5	27	12 (44.4)	98	29 (29.6)	30	8 (26.7)	125	41 (32.8)
6–7	50	33 (66.0)	149	74 (49.7)	42	20 (47.6)	199	107 (53.8)
8–9	15	9 (60.0)	46	31 (67.4)	12	7 (58.3)	61	40 (65.6)
Total†	**130**	**61** (46.9)	**413**	**145** (35.1)	**124**	**37** (29.8)	**543**	**206** (37.9)

Abbreviations: A, antioxidants; AdvAMD, advanced AMD; AMD, age-related macular degeneration; Z, zinc.

*All 3 active treatments groups combined.

†For combined treatment vs placebo, P=.02. For A + Z vs placebo, P=.008.

Table 15

Five-Year Progression Rates to Advanced AMD in 4 Studies

	BDES*		BMES†			AREDS§	
	No. at Risk	AdvAMD, %	No. at Risk	AdvAMD, %	Rotterdam‡AdvAMD, %	No. at Risk	AdvAMD, %
Drusen size (largest)							
<63 μm	2139	0.0	1803	0.3	NA	1249	0.4
≥63 μm, <125 μm	516	0.6	355	6.5	NA	713	3.8
≥125 μm, <250 μm	228	2.6	108	13.9	NA	603	10.8
≥250 μm	78	14.1			NA	401	25.4
Drusen type (most severe)							
Hard distinct	2453	0.0	1984	0.4	0.3	2003	1.4
Soft distinct	244	0.8	105	4.8	3.0		
Soft indistinct	269	6.3	69	23.2	18.0	1209	14.2
Drusen area							
<0.16 DA	NA	NA	NA	NA	0.7	2313	2.2‖
≥0.16, <1.6 DA	NA	NA	NA	NA	5.0	350	19.4
≥1.6 DA	NA	NA	NA	NA	26.0	303	26.4
Drusen area (soft indistinct)							
<0.04 DA	71	0.0	NA	NA	NA	423	3.5¶
≥0.04, <0.09 DA	68	1.5	NA	NA	NA	216	8.3
≥0.09, <0.22 DA	67	6.0	NA	NA	NA		
≥0.22 DA	66	18.2	NA	NA	NA	570	24.4
Drusen area (size ≥ 125 μm)							
None or <0.06 DA	NA	NA	2071	0.6	NA	2440	1.8
≥0.06, <0.5 DA	NA	NA	39	10.3	NA	324	12.0
≥0.5 DA	NA	NA	35	31.4	NA	448	26.3
Increased pigment							
Absent	3175	0.1	2095	0.5	0.5	2464	1.9#
<0.014 DA(circle I-1)	225	7.1	139	14.4	10.7	550	16.2
≥0.014 DA					8.2	198	31.8
Depigmentation							
Absent	3276	2.7	NA	NA	0.7	2793	3.8**
<0.07 DA	107	9.3	NA	NA	5.0	205	10.2
≥0.07 DA			NA	NA	12.3	179	31.8

Abbreviations: AdvAMD, advanced AMD; AMD, age-related macular degeneration; AREDS, Age-Related Eye Disease Study; BDES, Beaver Dam Eye Study; BMES, Blue Mountains Eye Study; DA, disc area; NA, not available; Rotterdam, Rotterdam Study.

*Data are for right eyes; less than 1% had advanced AMD in fellow eye at baseline. Each of 9 subfields was graded and results were combined. Outcome is neovascular AMD or (any) geographic atrophy.

†Data are for right eyes; less than 1% had advanced AMD in fellow eye at baseline. The grid as a whole was graded. Outcome is neovascular AMD or (any) geographic atrophy.

‡Estimated from Figure 7 of van Leeuwen et al[9]; numbers of eyes were not given. Outcome is neovascular AMD or (any) geographic atrophy.

§All treatment groups combined. Outcome is neovascular AMD or geographic atrophy involving center of macula.

‖For AREDS data, categories are less than 0.19 DA (circle O-2); greater than or equal to 0.19, less than 1.0 DA; less than or equal to 1.0 DA.

¶For AREDS data, categories are less than 0.06 DA (circle I-2); greater than or equal to 0.06, less than 0.19 DA; greater than or equal to 0.19 DA.

[#] For AREDS data, categories are absent, less than 0.03 DA (circle C-2); greater than or equal to 0.03 DA.

[**] For AREDS data, categories are absent, less than 0.06 DA; greater than or equal to 0.06 DA.