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Ten-Year Follow-up of Age-Related Macular Degeneration in the Age-Related Eye Disease Study:

AREDS Report No. 36

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Abstract

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IMPORTANCE—Providing long-term follow-up of the natural history of age-related macular degeneration (AMD) and associated risk factors will facilitate future epidemiologic studies and clinical trials.

OBJECTIVE—To describe 10-year progression rates to intermediate or advanced AMD.

DESIGN, SETTING, AND PARTICIPANTS—We observed the Age-Related Eye Disease Study (AREDS) participants for an additional 5 years after a randomized clinical trial of antioxidant vitamins and minerals was completed. Observation occurred at 11 clinical sites of medical retinal practices from academic institutions and community medical centers. Participants aged 55 to 80 years with no AMD or AMD of varying severity (n = 4757) were followed up in the AREDS trial for a median duration of 6.5 years. When the trial ended, 3549 of the 4203 surviving participants were followed for 5 additional years.

EXPOSURE—Treatment with antioxidant vitamins and minerals.

MAIN OUTCOMES AND MEASURES—Development of varying stages of AMD and changes in visual acuity. The rates of progression to large drusen and advanced AMD (neovascular AMD or central geographic atrophy) were evaluated using annual fundus photographs assessed centrally. Best-corrected visual acuity was measured at annual study visits.

RESULTS—The risk of progression to advanced AMD increased with increasing age ($P = .01$) and severity of drusen. Women ($P = .005$) and current smokers ($P < .001$) were at increased risk of neovascular AMD. In the oldest participants with the most severe AMD status at baseline, the risks of developing neovascular AMD and central geographic atrophy by 10 years were 48.1% and 26.0%, respectively. Similarly, rates of progression to large drusen increased with increasing severity of drusen at baseline, with 70.9% of participants with bilateral medium drusen progressing to large drusen and 13.8% to advanced AMD in 10 years. Median visual acuity at 10 years in eyes that had large drusen at baseline but never developed advanced AMD was 20/25; eyes that developed advanced AMD had a median visual acuity of 20/200.

CONCLUSIONS AND RELEVANCE—The natural history of AMD demonstrates relentless loss of vision in persons who developed advanced AMD. These progression data and the risk factor analyses may be helpful to investigators conducting research in clinic populations.

Age-related macular degeneration (AMD) is a leading cause of blindness in the United States and the developed world, with a 2-fold increase in prevalence expected by the year 2020.[1] Population-based studies have provided data on progression rates for the development of early AMD but only a limited amount of data on progression rates for the development of the advanced stages of AMD.[2,3] In 1992, the Age-Related Eye Disease Study (AREDS) Research Group enrolled participants with varying degrees of AMD severity in a study of the clinical course and prognosis of AMD and age-related cataracts. The study included a randomized clinical trial to evaluate the effect of high doses of antioxidant vitamins (vitamin C, vitamin E, and beta carotene) and zinc (with copper) on progression to advanced AMD. In 2001, at the end of the clinical trial, the study reported that the AREDS vitamin-mineral formulation was effective in retarding progression to advanced AMD.[4] The AREDS participants continued to be followed up until 2005 in an observational study that tracked the subsequent course of AMD in the participants. The long-term effects of the AREDS formulation on AMD have been summarized in another

report.[5] The purpose of this report is to present 10-year data on the clinical course of AMD, including rates of development of intermediate and advanced AMD and accompanying changes in visual acuity.

Methods

Study Population

The AREDS design has been described elsewhere[6] but is briefly summarized here. Eleven retinal specialty clinics enrolled 4757 participants aged 55 to 80 years from November 13, 1992, through January 15, 1998. The participants had best-corrected visual acuity of 20/32 or better and the absence of advanced AMD in at least 1 eye. Study eyes had media that were sufficiently clear to obtain adequate-quality stereoscopic fundus photographs of the macula. Each clinical center obtained institutional review board approval for the study procedures, and all participants signed the study's informed consent form.

As described previously,[4,5] participants were recruited into 1 of 4 AMD categories based primarily on the size and extent of drusen in each eye and the presence or absence of advanced AMD. The participants were randomly assigned to 1 of the following 4 treatment groups: placebo, zinc, antioxidants, or antioxidants plus zinc. The antioxidants consisted of vitamin C (500 mg), vitamin E (400 IU), and beta carotene (15 mg). Zinc was given as zinc oxide (80 mg) with copper as cupric oxide (2 mg). The participants were followed up until 2001, when the trial ended. Of the 4203 surviving participants, 3549 (84.4%) consented to be followed up through 2005 to track the long-term course of AMD. Each clinical center obtained approval from their institutional review board for human subjects for the follow-up study, and each participant signed another informed consent form.

Procedures

Comprehensive eye examinations were conducted at baseline and semiannually throughout the clinical trial that ended in 2001. Annual visits were conducted through 2005. Using the Early Treatment Diabetic Retinopathy Study (ETDRS) logarithm of the minimum angle of resolution chart, certified examiners measured best-corrected visual acuity with a standardized refraction and best-corrected visual acuity protocol. Baseline data were collected, including age, race, sex, educational level, smoking history, body mass index, use of medications, and history of diabetes mellitus, hypertension, angina, and arthritis. Stereoscopic fundus photographs of the macula were taken at baseline and annually beginning 2 years after enrollment and continuing through the follow-up study. Photographs were graded centrally using standardized grading procedures.

Outcomes

The 2 primary study outcomes in the clinical trial were (1) progression to advanced AMD consisting of neovascular (NV) AMD or geographic atrophy involving the center of the macula (CGA) and (2) visual acuity loss of at least 15 letters from baseline in the study eyes. Progression to NV AMD for a study eye was based on clinical center reports of photocoagulation or other therapies, such as photodynamic therapy, for choroidal neovascularization or photographic documentation at the centralized University

of Wisconsin Fundus Photographic Reading Center of any of the following: nondrusenoid retinal pigment epithelial (RPE) detachment, serous or hemorrhagic retinal detachment, hemorrhage under the retina or the RPE, and/or subretinal fibrosis. Geographic atrophy involving the center of the macula was judged by the reading center to be present when the center of the macula was probably or definitely involved.[7] In addition to reporting on progression to advanced AMD, we also evaluated progression to large drusen or worse in eyes with no evidence of large drusen at baseline.

Statistical Analysis

We used a Cox proportional hazards regression model to compute the probabilities for progression to advanced AMD (CGA or NV AMD) stratified by baseline drusen status during the 10 years of follow-up. We used the life-table method to estimate unadjusted rates of progression to large drusen and advanced AMD within 10 years from entry to the study. The method was applied to various groups of participants and eyes classified by severity of AMD at baseline. Participants lost to follow-up or who died during the course of the study were censored at the time of the last contact. We used the log-rank *P* value for comparing groups. Severity was based on drusen size and the absence or presence of AMD RPE abnormalities (ie, hypopigmentation, hyperpigmentation, or non-CGA). Small drusen are defined as less than 63 μm; medium drusen, 63 to less than 125 μm; and large drusen, at least 125 μm. Life-table rates were also calculated for persons using the simplified 5-level severity scale categories.[8] The categories rank baseline risk according to the number of eyes with large drusen and pigment abnormalities. The scale uses a patient scoring system that assigns to each eye a risk score of 1 for the presence of large drusen and a risk score of 1 for the presence of AMD RPE abnormalities. Advanced AMD is given a score of 2 for the affected eye. In the absence of large drusen in both eyes, the presence of medium drusen in both eyes warrants a score of 1. Scores are summed across eyes and range from 0 to 4 (5 steps). In addition, we examined change in median visual acuity during the 10 years by drusen size, type of NV AMD lesion, and type of advanced AMD (CGA or NV AMD).

Results

A total of 4757 participants were enrolled in the AREDS clinical trial from 1992 through 1998. At the end of the clinical trial in April 2001, the follow-up study enrolled 3549 of the 4203 surviving participants (84.4%). Annual visits for the follow-up study started in 2001 and continued through November 2005. The Table describes the AREDS cohort who participated in the follow-up study. Information regarding active vs inactive participants is also presented in the Table. Participants enrolled in the follow-up phase were more likely to be younger, nonsmokers, and white; were more likely to have less severe AMD, higher educational levels, and lower blood pressure; and were less likely to have diabetes mellitus than those who were not active participants. The rates of loss to follow-up in the clinical trial and the follow-up study were 2.4% and 3.7%, respectively. Participants were followed up for a median of 10.5 years.

Retinal Outcomes

Risk Factors—eFigure 1 in the Supplement demonstrates that, by 10 years, the rates of development of CGA and NV AMD increased with increasing severity of baseline AMD. The eTable in the Supplement shows the percentages and *P* values. Baseline AMD severity categories, from least to most severe, included no or small drusen in either eye, medium drusen in 1 eye, bilateral medium drusen, large drusen in 1 eye, bilateral large drusen, and large drusen in 1 eye with the presence of advanced AMD in the fellow eye (NV AMD or CGA). Increasing age was found to increase the risk of NV AMD (hazard ratio [HR] for 65–69 vs 55–64 years, 1.33; 70–74 vs 55–64 years, 1.53; and ≥75 vs 55–64 years, 1.86 [$P = .01$, $P < .001$, and $P < .001$, respectively]) (eFigure 1A) and CGA (65–69 vs 55–64 years, 1.10; 70–74 vs 55–64 years, 1.58; and ≥75 vs 55–64 years, 1.43 [$P = .59$, $P = .007$, and $P = .07$, respectively]) (eFigure 1B). Female sex (HR, 1.23 [$P = .005$]) and current smoking (1.56 [$P < .001$]) were associated with the development of NV AMD (eFigure 1C-F). Assignment to the AREDS formulation in the original clinical trial appeared to decrease the probability of developing NV AMD but not CGA (eFigure 1G and H). For those in the oldest group (75 to 80 years) who were in the most severe AMD category at baseline, rates approximated 26.0% for CGA and 48.1% for NV AMD by 10 years. Analyses of race as a risk factor for progression to NV AMD showed that white vs other races resulted in an HR of 2.83 (P = .01) (eFigure 1I). Educational status and body mass index were not significant risk factors for NV AMD or CGA progression.

Progression in Participants Without Large Drusen or Advanced AMD—The probability of development of large drusen (or worse) in at least 1 eye was examined in 2248 participants without large drusen or advanced AMD in either eye at baseline (eFigure 2A in the Supplement). The risk of developing large drusen in participants with no drusen or only small drusen at baseline was low at 17.0% and 12.8%, respectively, by 10 years. However, 36.5% of participants with medium drusen in 1 eye and 70.9% of those with bilateral medium drusen at baseline developed large drusen by 10 years.

eFigure 2B displays the probability of developing advanced AMD in the same participants. The risk of developing advanced AMD by 10 years in participants with no drusen and small drusen at baseline was very low at 0% and 1.5%, respectively. Among participants with medium drusen in both eyes at enrollment, 13.8% developed advanced AMD by 10 years.

Progression in Eyes Developing Large Drusen and RPE Changes—eFigure 3A in the Supplement displays the rates of development of advanced AMD in eyes with no evidence of large drusen or AMD RPE abnormalities at baseline and who developed both during the study (570 eyes of 483 participants with no advanced AMD in either eye at baseline). Time 0 corresponds to the time of the first detection of large drusen and RPE changes. The rate of developing advanced AMD in these eyes was 9.1% by 5 years (eFigure 3A). Because of the limited duration of follow-up after the development of large drusen, we chose to present only the 5-year rates. eFigure 3B demonstrates the life-table estimates of development of advanced AMD in the years after the development of large drusen and RPE abnormalities in participants with advanced AMD in the fellow eye (85 eyes of 85 participants). The rate of development of advanced AMD by 5 years was 32.8%, a more

than 3-fold increase when compared with those participants who had no advanced AMD at baseline. Among the 309 eyes that developed large drusen but no RPE changes ever, only 1 developed advanced AMD by 10 years.

Progression in Participants With Bilateral Large Drusen and No Advanced AMD, With or Without RPE Changes—Among participants with bilateral large drusen and no evidence of advanced AMD or AMD RPE changes in either eye at baseline (n = 241), 36.1% developed advanced AMD in at least 1 eye by 10 years (eFigure 4A in the Supplement); 31.5% developed NV AMD, and 9.9% developed CGA (eFigure 4A). In those participants with bilateral large drusen and AMD RPE changes and no advanced AMD at baseline (n = 636), 66.2% developed advanced AMD at 10 years; 45.5%, NV AMD; and 44.3%, CGA (eFigure 4B).

Progression in Right Eyes With Large Drusen by Location of Large Drusen and Presence/Absence of AMD RPE Abnormalities—The proposition that large drusen located within 1 disc diameter of the center of the macula (the central plus the 4 inner subfields of the ETDRS grid, often termed the *central zone*) may carry a worse prognosis for progression to advanced AMD than those farther from the center is explored in eFigure 5 in the Supplement for the right eyes of 1222 participants with large drusen and no advanced AMD in either eye at baseline. For eyes free of RPE abnormalities, comparison of progression rates for eyes with large drusen limited to the central zone and rates for eyes with large drusen limited to the outer ring of the grid (the 4 outer subfields combined) supports this concept (10-year rates of 21.7% and 3.6%, respectively). As might be expected, the rate was higher (37.6%) when both locations were involved. All 3 of these rates increased when RPE abnormalities were present, but the difference by location narrowed and appeared to reverse slightly (10-year rates of 39.0% and 42.4%, respectively). For eyes with large drusen in the ring only, fewer had RPE abnormalities than did not (68 vs 154), whereas for eyes with large drusen in both locations, the reverse was true (373 vs 186). Groups with lower progression rates tended to have greater proportions of eyes with very few large drusen, defined as eyes with a total drusen area in the grid of less than the area of standard circle C-2 (according to the AREDS AMD measurement tool developed by the reading center), which equals the size of 4 drusen at the lower threshold of the large drusen category. Among eyes with no RPE abnormalities, large drusen were limited to the outer ring in 24.0% and to the central zone in 11.6%. None of the eyes with large drusen in both locations met this definition. Corresponding proportions for eyes with RPE abnormalities were 2.9%, 8.3%, and 0.3%, respectively.

Progression in Eyes With the Fellow Eye Having Advanced AMD—The presence of advanced AMD in the fellow eye at baseline increased the rates of progression to advanced AMD in study eyes. eFigure 6A in the Supplement demonstrates the rates of developing advanced AMD in eyes with no advanced AMD in the fellow eye (n = 3808), stratified by baseline drusen size and AMD RPE abnormalities. eFigure 6B displays the rates for advanced AMD in those participants whose fellow eye had advanced AMD at baseline (n = 752). These rates are also displayed according to the size of drusen and the presence of RPE abnormalities at baseline. In eyes with no or small drusen, the rates of

development of advanced AMD by 10 years were 8.6% (eFigure 6B) and 0.7% (eFigure 6A) in those with advanced AMD in the fellow eye and those without advanced AMD in the fellow eye, respectively. Similarly, when advanced AMD was not present in the fellow eye, the rate of development of advanced AMD was only 4.3% in eyes with medium drusen at baseline (eFigure 6A), which increased to 26.4% when advanced AMD was present in the fellow eye (eFigure 6B). Having large drusen or AMD RPE abnormalities increased the rate of developing advanced AMD to 61.1% (eFigure 6B) by 10 years in those with advanced AMD in the fellow eye, whereas the rate was only 21.2% (eFigure 6A) in those without advanced AMD in the fellow eye. When AMD RPE abnormalities and large drusen were present at baseline in eyes and the fellow eye was affected with advanced AMD, the rate was 76.8% (eFigure 6B), whereas the rate was decreased to 49.7% (eFigure 6A) in those without advanced AMD in the fellow eye.

Development of NV AMD in Eyes Developing Geographic Atrophy—In eyes that developed any geographic atrophy (981 eyes of 718 participants), the risk of subsequently developing NV AMD in that eye markedly increased when NV AMD was present in the fellow eye at baseline. By 5 years, 36.4% of eyes that developed geographic atrophy had also developed NV AMD when the fellow eye had NV AMD at baseline compared with 16.0% when it did not (eFigure 7 in the Supplement).

Progression to Advanced AMD Using the AREDS Simple Scale—The risk of progression to advanced AMD increased with increasing scores on the AREDS simple scale (eFigure 8 in the Supplement). By 10 years, participants with a simple score of 0 had almost no risk of developing NV AMD or CGA. For participants in the highest risk category, the risk of developing advanced AMD was 71.4% at 10 years. The 10-year rates of developing CGA and NV AMD for these high-risk participants were 53.9% and 47.6%, respectively.

Visual Acuity Outcomes

Eyes With No Progression to Large Drusen or Advanced AMD—In eyes that had few or no drusen at baseline and did not develop large drusen during the study, the median visual acuity at baseline was 86 letters (Snellen equivalent of 20/20). At 10 years, the median visual acuity score for these eyes had lost more than 2 letters (eFigure 9A in the Supplement). For eyes that had large drusen at baseline but did not develop advanced AMD during follow-up, we noted a similar loss of about 2 letters in median visual acuity score (20/25). In contrast, in eyes with large drusen that developed advanced AMD, the median visual acuity was 20/200.

Eyes That Progressed to Advanced AMD—eFigure 9B and C in the Supplement present visual acuity data 1 year before the visit at which advanced AMD was recorded (year −1), visual acuity data at the visit when advanced AMD was recorded (year 0), and subsequent annual visual acuity data. eFigure 9B demonstrates that vision was impaired even before the visit at which NV AMD was recorded. All study eyes were required to have a visual acuity score of at least 74 (Snellen equivalent of 20/32) at baseline. In the year before the AMD event, depending on the lesion on which the diagnosis was based, median visual acuity scores ranged from 60 to 77 (Snellen equivalent of 20/63 to 20/32).

Most severely affected were participants with a diagnosis based on subretinal fibrosis. Less severely affected were those with a diagnosis based on the presence of serous sensory retinal detachment.

eFigure 9C compares visual loss in participants who developed CGA with those who developed NV AMD. The occurrence of both forms of advanced AMD is heralded by some decrease in vision 1 year before the event, somewhat more so with CGA than with NV AMD. After the occurrence of advanced AMD, the rates of visual loss continued in both forms of advanced AMD, with a slightly less rapid rate in those with CGA.

Discussion

We have used 10-year follow-up data from the AREDS to estimate rates of progression to intermediate and advanced AMD and to examine the effect of retinal risk factors on these rates. Increasing severity of drusen at baseline, the presence of large drusen within 1 disc diameter of the fovea or the central zone, the presence of bilateral medium drusen, the presence of advanced AMD in the fellow eye, and the simultaneous presence of large drusen and AMD RPE abnormalities all increased the risk of progression to advanced AMD. In addition to the importance of large drusen as a risk factor, we note that medium drusen, in particular when present bilaterally, increase the risk of advanced AMD. The long-term data also demonstrate the importance of AMD RPE abnormalities.

Increasing age is associated with NV AMD and CGA. Female sex and current smoking increase the risk of progression to NV AMD. The age and smoking findings have been reported in population-based studies.[9] Assignment to the AREDS formulation in the AREDS clinical trial decreased the probability of developing NV AMD but not CGA, even 5 years after the trial ended.[5]

The long-term visual acuity results are of interest because AREDS participants may constitute one of the last cohorts in whom the natural history of NV AMD is not affected by the administration of intravitreal injections of anti–vascular endothelial growth factor agents, which are now widely used. The course of advanced AMD is characterized by relentless loss of vision in the NV and CGA forms of the disease. Visual acuity changes are evident 1 year before the diagnosis of AMD. Further research is needed to develop techniques for earlier detection and treatment of early disease so that final visual acuity results might be improved.

This study has limitations. These data may not be generalizable to the overall population 55 years or older because the study draws from a group of participants who are better nourished, more highly educated, and healthier than the population at large. However, the risk factors and rates of development of disease are not dissimilar to those reported in other clinical studies.

Strengths of the study are numerous. The study observed a very large cohort of participants with varying risk of progressing to advanced AMD. Among the surviving participants in the clinical trial, 84.4% were followed up in the observational portion of the study. The rates of loss to and unavailability for follow-up were low in the clinical trial (2.4%) and in the follow-up study (3.7%). Major ocular out-come measurements were determined centrally

using standardized procedures. The rigorous design of the original clinical trial, the high proportion of participants who participated in the follow-up study, the low rates of loss to and unavailability for follow-up, and the careful monitoring of end points suggest that the long-term findings are representative of this clinic population.

Conclusions

The major risk factors associated with progression to advanced AMD include increasing age, severity of drusen, AMD RPE abnormalities, and advanced AMD in the fellow eye. The natural history of AMD demonstrates relentless loss of vision in persons with advanced AMD. These clinic-based data provide important information for investigators who are interested in designing controlled clinical trials or epidemiologic studies of AMD in clinic-based populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Role of the Sponsor:

National Institutes of Health staff had an active role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, and approval of the manuscript; and decision to submit the manuscript for publication.

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Table.

Comparison of Participants and Nonparticipants in AREDS Follow-up Study[a]

	No. of Surviving AREDS Participants	AREDS Participants Active in the Follow-up Study, %	*P* Value[b]
All	4203	84.4	
AMD category			
1	1031	88.5	<.001
2	960	85.8	
3	1435	83.8	
4	777	78.6	
AREDS treatment assignment			
Placebo	1312	83.8	.61
Antioxidants	1301	85.3	
Zinc	806	83.5	
Antioxidants plus zinc	784	84.9	
Age, y			
<65	957	90.4	<.001
65–69	1432	87.6	
≥70	1814	78.8	
Sex			
Female	2412	84.2	.69
Male	1791	84.7	
Educational level[c]			
High school or less	1460	80.7	<.001
Some college	1285	83.7	
College graduate	1455	88.8	
Race			
Nonwhite	179	77.1	.006
White	4024	84.8	
Smoking status			

	No. of Surviving AREDS Participants	AREDS Participants Active in the Follow-up Study, %	*P* Value[b]
Never	1931	87.1	<.001
Former	1974	83.2	
Current	298	75.5	
BMI[d]			
<24.9	1369	85.1	.08
25.0–29.9	1761	85.2	
≥30.0	1071	82.3	
Hypertension			
Normal	2611	86.6	<.001
Controlled	993	82.0	
Uncontrolled and treated	280	76.8	
Uncontrolled and untreated	319	81.5	
Angina			
No	3802	84.8	.07
Yes	401	81.3	
Diabetes mellitus			
No	3886	84.8	.007
Yes	317	81.3	

Abbreviations: AMD, age-related macular degeneration; AREDS, Age-Related Eye Disease Study; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

[a]Of the original 4757 AREDS participants enrolled in the controlled clinical trial (1992–2001), 554 (11.6%) died at the end of the clinical trial, with 4203 surviving at the beginning of the follow-up study (October 1, 2001).

[b]Calculated by the χ^2 test.

[c]Three partipants were missing data.

[d]Two participants were missing data.