

Long-Term Effects of Vitamins C and E, β -Carotene, and Zinc on Age-related Macular Degeneration

AREDS Report No. 35

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Objective: To describe the long-term effects (10 years) of the Age-Related Eye Disease Study (AREDS) formulation of high-dose antioxidants and zinc supplement on progression of age-related macular degeneration (AMD).

Design: Multicenter, randomized, controlled, clinical trial followed by an epidemiologic follow-up study.

Participants: We enrolled 4757 participants with varying severity of AMD in the clinical trial; 3549 surviving participants consented to the follow-up study.

Methods: Participants were randomly assigned to antioxidants C, E, and β -carotene and/or zinc versus placebo during the clinical trial. For participants with intermediate or advanced AMD in 1 eye, the AREDS formulation delayed the progression to advanced AMD. Participants were then enrolled in a follow-up study. Eye examinations were conducted with annual fundus photographs and best-corrected visual acuity assessments. Medical histories and mortality were obtained for safety monitoring. Repeated measures logistic regression was used in the primary analyses.

Main Outcome Measures: Photographic assessment of progression to, or history of treatment for, advanced AMD (neovascular [NV] or central geographic atrophy [CGA]), and moderate visual acuity loss from baseline (≥ 15 letters).

Results: Comparison of the participants originally assigned to placebo in AREDS categories 3 and 4 at baseline with those originally assigned to AREDS formulation at 10 years demonstrated a significant ($P < 0.001$) odds reduction in the risk of developing advanced AMD or the development of NV AMD (odds ratio [OR], 0.66, 95% confidence interval [CI], 0.53–0.83 and OR, 0.60; 95% CI, 0.47–0.78, respectively). No significant reduction ($P = 0.93$) was seen for the CGA (OR, 1.02; 95% CI, 0.71–1.45). A significant reduction ($P = 0.002$) for the development of moderate vision loss was seen (OR 0.71; 95% CI, 0.57–0.88). No adverse effects were associated with the AREDS formulation. Mortality was reduced in participants assigned to zinc, especially death from circulatory diseases.

Conclusions: Five years after the clinical trial ended, the beneficial effects of the AREDS formulation persisted for development of NV AMD but not for CGA. These results are consistent with the original recommendations that persons with intermediate or advanced AMD in 1 eye should consider taking the AREDS formulation.

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In 2001, the Age-Related Eye Disease Study (AREDS) Research Group reported results from a randomized, controlled, clinical trial showing that a high-dose of antioxidant vitamins plus zinc formulation was effective in retarding the progression of age-related macular degeneration (AMD).¹ Use of the formulation was recommended for patients at moderate to high risk of progression to advanced AMD (AREDS categories 3 and 4).

After the cessation of the clinical trial in 2001, the participants were followed until 2005 to observe the subsequent natural history of AMD in the cohort. This report describes the long-term effects of the AREDS formulation on progression of AMD during 10 years of follow-up, in particular the effects on persons for whom treatment with the AREDS formulation has been recommended. Long-term possible adverse effects associated with the original

treatment assignments in the clinical trial were also examined. The effect of the treatments on mortality was evaluated.

Materials and Methods

Study Population

Details of the design and methods of the AREDS have been presented elsewhere,² but are briefly summarized here. Eleven retinal specialty clinics enrolled 4757 participants in AREDS from 1992 through 1998. Participants were 55 to 80 years of age at enrollment and had best-corrected visual acuity of $\geq 20/32$ in at least one eye. Media were sufficiently clear to obtain adequate-quality stereoscopic fundus photographs of the macula. The institutional review board for each clinical center approved the protocol, and informed consent was obtained from all participants.

Participants were recruited based on the severity of AMD and were placed into 4 AREDS AMD categories according to the size and extent of drusen in each eye, the presence of advanced AMD, and visual acuity, as previously described. The AREDS AMD category 1 consisted of persons free of AMD with < 5 small drusen ($< 63 \mu\text{m}$). Category 2 participants had early AMD with multiple small drusen or nonextensive intermediate drusen ($63\text{--}124 \mu\text{m}$), pigment abnormalities, or a combination of the two. Category 3 participants had no advanced AMD but had ≥ 1 large drusen ($125 \mu\text{m}$), extensive area of intermediate drusen, or geographic atrophy (GA) not involving the center of macula. Category 4 participants had advanced AMD, central GA (CGA) or neovascular (NV) AMD in 1 eye. The fellow eye of category 4 participants and both eyes of participants in the other categories were the study eyes.

The 4757 participants enrolled for a clinical trial of antioxidant vitamins and zinc were followed until 2001, when the trial was completed. Of the 4203 participants (84.4%) who were alive at the end of the trial, 3549 subsequently consented to additional follow-up through 2005.

Study Drug Assignment

Participants in the clinical trial were randomly assigned to 1 of 4 treatment groups: placebo, zinc, antioxidants, or antioxidants plus zinc. The antioxidants consisted of vitamins C (500 mg), E (400 IU), and β -carotene (15 mg). Zinc was given as zinc oxide (80 mg) along with copper as cupric oxide (2 mg) daily. The study medications were tablets with matching size, shape, and color in all 4 treatment groups. In addition, participants were offered a multivitamin-mineral supplement with recommended dietary allowance doses (Centrum; Pfizer, New York, NY) that was provided by the study. Median follow-up in the randomized trial was 6.5 years. After termination of the clinical trial, participants were invited to continue in a follow-up observational study. When the AREDS formulation became available for distribution, participants with at least intermediate AMD (AREDS category 3) were offered the antioxidant plus zinc formulation and treatment use was monitored.

Procedures

Eye examinations were conducted at baseline and semiannually throughout the clinical trial, which ended in 2001. Only annual visits were conducted through 2005. Best-corrected visual acuity was assessed by certified examiners using the Early Treatment of Diabetic Retinopathy Study logarithm of the minimum angle of resolution chart and a standardized protocol. Demographic information and medical history were obtained at baseline. Data were collected on age, race, sex, education, smoking, body mass index,

use of medications, and history of diabetes, 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 at a reading center using standardized grading procedures. Mortality data were collected from hospital records, death certificates, and a national death index search.

Outcomes

The 2 primary outcomes evaluated were progression to advanced AMD and visual acuity loss of ≥ 15 letters from baseline in study eyes. Progression to NV AMD was based on clinical center reports of photocoagulation or other therapies such as photodynamic therapy for choroidal neovascularization or photographic documentation at the reading center of any of the following: non-drusenoid retinal pigment epithelial detachment, serous or hemorrhagic retinal detachment, hemorrhage under the retina or the retinal pigment epithelium, and/or subretinal fibrosis. Central GA was present if the center subfield was involved (approximately $500\text{-}\mu$ diameter centered on the fovea). Such eyes did not count as CGA when subretinal fibrosis was diagnosed in an eye at the same visit.

Analyses

Primary comparisons for the development of advanced AMD and for a visual acuity decrease were conducted on persons in AREDS categories 3 and 4, the group for whom treatment with the AREDS formulation has been recommended. Although persons in category 2 were at low risk of developing advanced AMD at 10 years, treatment effects were also examined for the entire AMD cohort that included participants in AREDS categories 2, 3, and 4 at baseline. Repeated-measures logistic regression incorporating the generalized estimating equations methodology was used to assess the association of the primary outcomes and the AREDS treatment. The analysis was adjusted for visit and AMD category. Covariate adjusted Cox proportional hazards models predicting mortality were created with AMD category, visual acuity status, nuclear opacity status, cortical opacity status, posterior subcapsular cataract status, history of cataract surgery, and assigned AREDS treatment at baseline as independent variables.

Results

At baseline, 4757 participants were enrolled in the clinical trial from 1992 to 1998. The baseline characteristics of the participants included in the analyses are displayed in Table 1. After cessation 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 ended November 30, 2005. Participants who enrolled in the follow-up study were more likely to be white, younger, nonsmokers, nondiabetics, and to have less severe AMD, a higher educational level, and lower blood pressure 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% and 4%, respectively, with no differences among the treatment groups. Compliance with the treatment assignments was approximately 75% ($\geq 75\%$ of the study medications were taken according to pill count) during the clinical trial. At the end of the trial, use of a supplement of antioxidants plus zinc such as that used in AREDS was recommended for persons with intermediate AMD (AREDS category 3) or worse. Unfortunately, the AREDS formulation was not available immediately after the clinical trial ended. When it became available in 2003, the formulation was supplied to

Table 1. Baseline Characteristics of Age-Related Eye Disease Study (AREDS) Participants Included in Analyses

	Analysis							
	Mortality [†]		Treatment of Categories 2, 3, 4		Treatment of Categories 3, 4		Treatment of Category 4	
	N	%	N	%	N	%	N	%
Total	4753	100.0	3476	100.0	2459	100.0	901	100.0
AMD category								
1	1116	23.5	0	0	0	0	0	0
2	1060	22.3	1017	29.3	0	0	0	0
3	1620	34.1	1558	44.8	1558	63.4	0	0
4	957	20.1	901	25.9	901	36.6	901	100.0
AREDS treatment								
Placebo	1483	31.2	861	24.8	598	24.3	215	23.9
Antioxidants	1480	31.1	891	25.6	636	25.9	239	26.5
Zinc	903	19.0	865	24.9	607	24.7	223	24.8
Antioxidants + zinc	887	18.7	859	24.7	618	25.1	224	24.9
Age, years								
<65	1000	21.0	654	18.8	415	16.9	135	15.0
65–69	1577	33.2	1109	31.9	720	29.3	213	23.6
≥70	2176	45.8	1713	49.3	1324	53.8	553	61.4
Sex								
Female	2655	55.9	1964	56.5	1353	55.0	470	52.2
Male	2098	44.1	1512	43.5	1106	45.0	431	47.8
Education*								
High school or less	1705	35.9	1298	37.4	973	39.6	420	46.6
Some college	1409	29.7	1042	30.0	743	30.2	265	29.4
College graduate	1636	34.4	1134	32.6	741	30.2	216	24.0
Race								
Non-white	207	4.4	121	3.5	65	2.6	14	1.6
White	4546	95.6	3355	96.5	2394	97.4	887	98.4
Smoking status								
Never	2105	44.3	1507	43.4	1003	40.8	316	35.1
Former	2273	47.8	1686	48.5	1225	49.8	464	51.5
Current	375	7.9	283	8.1	231	9.4	121	13.4
BMI*								
<24.9	1550	32.6	1122	32.3	772	31.4	250	27.7
25–29.9	1984	41.8	1458	42.0	1029	41.9	368	40.8
≥30	1216	25.6	895	25.8	657	26.7	283	31.4
Hypertension								
Normal	2869	60.4	2076	59.7	1419	57.7	479	53.2
Controlled	1177	24.8	877	25.2	653	26.6	264	29.3
Uncontrolled and treated	346	7.3	252	7.2	187	7.6	76	8.4
Uncontrolled and untreated	361	7.6	271	7.8	200	8.1	82	9.1
Angina								
No	4264	89.7	3114	89.6	2168	88.2	774	85.9
Yes	489	10.3	362	10.4	291	11.8	127	14.1
Diabetes								
No	4357	91.7	3190	91.8	2249	91.5	814	90.3
Yes	396	8.3	286	8.2	210	8.5	87	9.7

AMD = age-related macular degeneration; BMI = body mass index.

*Three with missing education, and 2 with missing BMI data.

[†]This study cohort includes AMD category 1, 2, 3, and 4 participants.

participants in the study at no cost. The proportion of the participants in AMD categories 3 and 4 taking the AREDS formulation increased from near zero in the first 2 years after the end of the randomized clinical trial to about 70% in the last years of follow-up. The proportions of participants taking the AREDS supplements in the follow-up study were similar in participants originally randomized to placebo and those randomized to each of the active AREDS formulations. The treatment groups also had similar demographic characteristics in the follow-up study.

Effects of AREDS Formulation

Progression to Advanced AMD. Five years after the trial ended, assignment to the antioxidant plus zinc formulation in the AREDS clinical trial compared with assignment to placebo continued to be associated with a significantly reduced odds of developing advanced AMD among participants in AREDS categories 2, 3, and 4 at baseline (odds ratio [OR], 0.69; 95% confidence interval [CI], 0.56–0.86; $P = 0.001$; Table 2). The

Table 2. Results of the Long Term (10-Year) Treatment with Antioxidants, Zinc, and Combination, the Age-Related Eye Disease Study (AREDS) Formulation

Outcome	Treatment	AMD Categories 2, 3, and 4		AMD Categories 3 and 4		AMD Category 4	
		OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Advanced AMD	Antioxidants	0.74 (0.59–0.92)	0.007	0.70 (0.56–0.88)	0.002	0.64 (0.46–0.91)	0.012
	Zinc	0.87 (0.70–1.07)	0.183	0.82 (0.66–1.02)	0.081	0.68 (0.49–0.96)	0.026
	Antioxidants+zinc	0.69 (0.56–0.86)	0.001	0.66 (0.53–0.83)	<0.001	0.56 (0.40–0.79)	<0.001
Neovascular AMD	Antioxidants	0.73 (0.58–0.93)	0.011	0.71 (0.56–0.91)	0.007	0.69 (0.48–0.98)	0.041
	Zinc	0.83 (0.65–1.05)	0.119	0.79 (0.62–1.00)	0.054	0.65 (0.45–0.93)	0.018
	Antioxidants+zinc	0.64 (0.50–0.82)	<0.001	0.60 (0.47–0.78)	<0.001	0.44 (0.30–0.65)	<0.001
Central geographic atrophy	Antioxidants	0.76 (0.52–1.10)	0.146	0.77 (0.53–1.11)	0.162	0.73 (0.40–1.31)	0.292
	Zinc	1.12 (0.79–1.61)	0.520	1.12 (0.79–1.59)	0.528	1.16 (0.67–2.02)	0.601
	Antioxidants+zinc	0.99 (0.69–1.43)	0.975	1.02 (0.71–1.45)	0.927	1.43 (0.83–2.47)	0.195
15+ Letters visual acuity loss	Antioxidants	0.88 (0.73–1.06)	0.185	0.83 (0.67–1.02)	0.078	0.75 (0.53–1.06)	0.106
	Zinc	0.89 (0.74–1.08)	0.232	0.86 (0.70–1.07)	0.174	0.68 (0.48–0.96)	0.031
	Antioxidants+zinc	0.76 (0.63–0.93)	0.007	0.71 (0.57–0.88)	0.002	0.54 (0.38–0.78)	<0.001
Visual acuity <20/100	Antioxidants	0.87 (0.68–1.11)	0.247	0.82 (0.64–1.07)	0.140	0.76 (0.52–1.12)	0.163
	Zinc	0.91 (0.71–1.15)	0.420	0.88 (0.69–1.14)	0.331	0.66 (0.45–0.98)	0.038
	Antioxidants+zinc	0.75 (0.58–0.97)	0.026	0.72 (0.56–0.94)	0.015	0.58 (0.38–0.86)	0.007

AMD = age-related macular degeneration; CI = confidence interval; OR = odds ratio.

OR for the development of NV AMD was 0.64 (95% CI, 0.50–0.82; $P < 0.001$) and the OR for the development of CGA was 0.99 (95% CI, 0.69–1.43; $P = 0.975$). In categories 2, 3, and 4 participants randomly assigned to antioxidants alone at baseline, the ORs for the development of advanced AMD, especially for the development of NV AMD, were also in the direction of benefit and statistically significant (Table 2).

For participants in AREDS categories 3 and 4 (the group for whom treatment with the AREDS formulation has been recommended), assignment to the antioxidant plus zinc formulation in the clinical trial continued to be associated with significantly reduced odds of developing advanced AMD (OR, 0.66; 95% CI, 0.53–0.83; $P < 0.001$; Table 2; Fig 1A). The rates of progression to advanced AMD at 10 years were 44% and 34% for participants assigned to placebo and the AREDS formulation (combined antioxidants and zinc), respectively (Fig 1A). The OR for developing NV AMD was 0.60 (95% CI, 0.47–0.78; $P \leq 0.001$; Fig 2; Table 2). For CGA, the OR was 1.02 (95% CI, 0.71–1.45; $P = 0.927$; Fig 2; Table 2). For AREDS category 3 and 4 participants, there was also a significant reduction in the odds of advanced AMD and NV AMD among those originally assigned to antioxidants alone.

In separate analyses of category 3 and 4 participants, only those in AMD category 4 had a significantly reduced odds of developing advanced AMD (OR, 0.56; 95% CI, 0.40–0.79; $P < 0.001$) and NV AMD (OR, 0.44; 95% CI, 0.30–0.65; $P < 0.001$) with assignment to the antioxidant plus zinc formulation (Fig 2; Table 2). For category 4 participants assigned to the zinc-only arm or the antioxidant-only arm, ORs for the development of advanced AMD were also in the direction of benefit.

Visual Acuity Loss. For participants in AREDS AMD categories 2, 3, and 4, the risk of moderate vision loss, defined as loss of 3 lines of vision, was reduced in those assigned to the antioxidant plus zinc supplement compared with those assigned to placebo (OR, 0.76; 95% CI, 0.63–0.93; $P = 0.007$; Fig 2; Table 2). For more severe vision loss (<20/100), the

corresponding OR was 0.75 (95% CI, 0.58–0.97; $P = 0.026$; Fig 2; Table 2). In analyses restricted to participants in AMD categories 3 and 4, the rates of moderate vision loss were 53.8% for the placebo group and 45.7% for the AREDS formulation group at 10 years (Fig 1B). The OR for developing moderate vision loss in the AREDS formulation versus placebo comparison was 0.71 (95% CI, 0.57–0.88; $P = 0.002$). The corresponding OR for the development of more severe vision loss (<20/100) was 0.72 (95% CI, 0.56–0.94; $P = 0.015$; Fig 2; Table 2). Again, in separate analyses of category 3 and category 4 participants, the beneficial effects of the AREDS formulation and of zinc alone in the reduction of moderate vision loss or more severe vision loss were demonstrated only in the AREDS AMD category 4 group. For moderate vision loss, the OR for the AREDS formulation was 0.54 (95% CI, 0.38–0.78; $P < 0.001$) and the OR for zinc alone was 0.68 (95% CI, 0.48–0.96; $P = 0.031$). For more severe vision loss, the OR for the AREDS formulation was 0.58 (95% CI, 0.38–0.86; $P = 0.007$) and for zinc alone was 0.66 (95% CI, 0.45–0.98; $P = 0.038$).

Adverse Effects

No significant increase in hospitalizations was associated with assignment to any of the AREDS supplements in the clinical trial during the 10-year follow-up in logistic regression analyses adjusted for age, sex, smoking status, and treatment.

Morbidity and Mortality

With 10 years of follow-up, associations between mortality and baseline ocular and treatment characteristics were similar to those noted in the 2001 report on the AREDS clinical trial.³ In analyses that examined the main effects of antioxidants and zinc, there was no significant effect of antioxidant vitamins on mortality (hazard ratio [HR], 1.06; 95% CI, 0.93–1.21; $P = 0.39$; Table 3). However, participants randomized to zinc

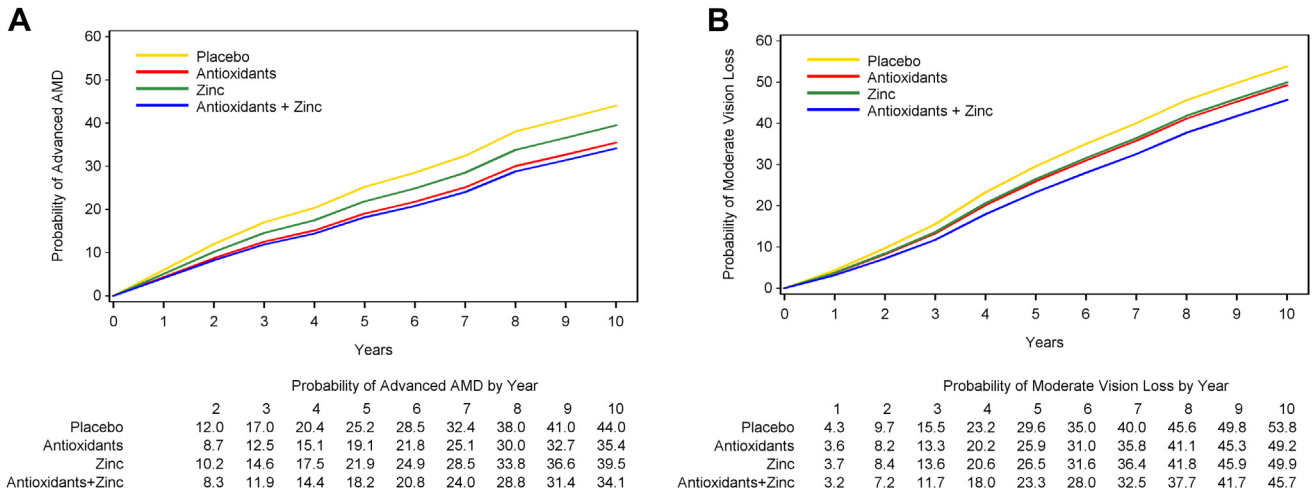


Figure 1. A, Repeated-measures estimates of the probability of development of advanced age-related macular degeneration (AMD) in at least 1 study eye of participants in categories 3 and 4 adjusted by Age-Related Eye Disease Study (AREDS) categories and study visits. The study eye is an eye without evidence of advanced AMD and with a visual acuity score of greater than 73 letters (20/32 or better) at baseline. B, Repeated-measures estimates of the probability of a loss in the visual acuity score of at least 15 letters in at least 1 study eye of participants in AMD categories 3 and 4 by adjusted by AMD categories and study visits. The study eye is an eye without evidence of advanced AMD and with a visual acuity score greater than 73 letters (20/32 or better) at baseline.

continued to show a reduction in all-cause mortality (HR, 0.83; 95% CI, 0.73–0.95; $P = 0.008$), largely related to a decrease in deaths from diseases of the circulatory system. Advanced AMD at baseline was again found to be associated with increased mortality, particularly death from cardiovascular disease (HR, 1.27; 95% CI, 1.05–1.54; $P = 0.01$). Both nuclear cataract (HR, 1.29; 95% CI, 1.10–1.52; $P = 0.002$) and cataract surgery (HR, 1.30; 95% CI, 1.05–1.61; $P = 0.02$) were associated with increased all-cause mortality.

Discussion

The AREDS was an 11-center, double-masked, clinical trial designed to evaluate the effect of high-dose vitamins and zinc on AMD progression and visual acuity. In 2001, after an average follow-up time of 6.3 years, the study reported that treatment with a combination of antioxidants and zinc reduced the risk of progression to advanced AMD in

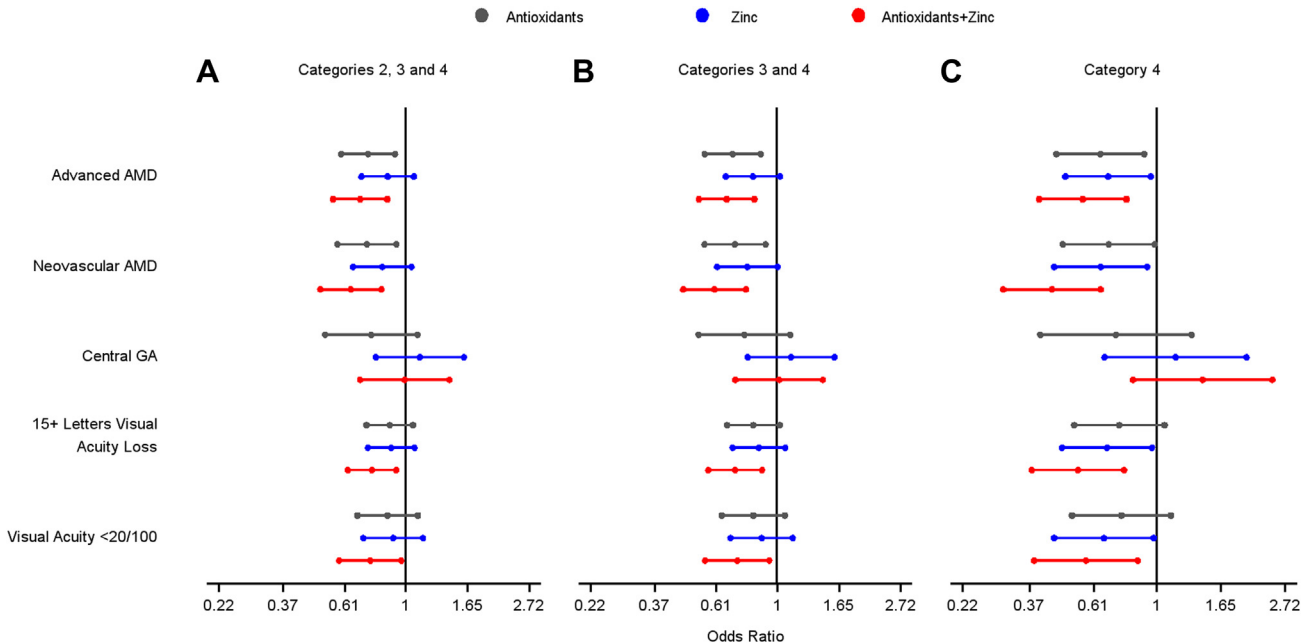


Figure 2. Odds ratios (central dot) and 95% confidence intervals (colored bars) for each original treatment assignment compared with placebo for participants in the following Age-Related Eye Disease Study age-related macular degeneration (AMD) categories: A, Categories 2, 3 and 4; B, categories 3 and 4; and C, category 4. GA = geographic atrophy.

participants in AREDS categories 2, 3, and 4 (OR, 0.72; 95% CI, 0.52–0.98; $P = 0.007$). The risk reduction for those taking the formulation was about 25%. Because so few events were noted for category 2 participants (1.3% by year 5), analyses were also done for those most likely to benefit from an effective treatment, AMD categories 3 and 4, for whom the 5-year event rates were 18% and 43%, respectively. Comparisons with placebo found a significant risk reduction for antioxidants plus zinc (OR, 0.66; 95% CI, 0.47–0.91; $P = 0.001$). At the conclusion of the trial, the study group recommended that persons with at least moderate risk of progression to advanced AMD (categories 3 and 4) should consider taking a supplement similar to the AREDS antioxidant plus zinc formulation.

The AREDS cohort continued to be followed until 2005, with careful monitoring of visual acuity and progression of AMD. Because the AREDS formulation was not available immediately after the trial ended, few participants took the AREDS formulation during the first 2 years of the observational period. The AREDS supplement became available in 2003 and, by the end of follow-up in 2005, about 70% of participants were taking the supplement, which was provided by the study. Equal proportions of participants across the 4 original treatment groups took the supplement in the follow-up phase. Despite the nonavailability of the AREDS supplement in the first 2 years of follow-up and then the use of the supplement by the majority of participants in the last 3 years of follow-up, the beneficial effect of original assignment to antioxidant plus zinc formulation persisted. By year 10, 44% of category 3 and 4 participants originally randomized to placebo had progressed to advanced AMD compared with 34% of those originally randomized to antioxidants and zinc. Also, by the end of the follow-up study participants originally assigned to the antioxidant and zinc formulation compared with those assigned to placebo had a reduced risk of both at least moderate vision loss (≥ 3 lines) and more severe vision loss ($< 20/100$).

Separate analyses of category 3 and 4 participants showed that much of the beneficial effect of the AREDS formulation on progression to advanced AMD and vision loss was driven by the category 4 participants. Point estimates for category 3 participants were in a beneficial direction but were not significant. The smaller number of AMD and vision loss events among category 3 participants may have limited the power to detect associations for this group.

Analyses of the components of the AREDS definition of advanced AMD, development of NV disease, and GA involving the center of the macula were performed on participants in categories 3 and 4. A significant benefit of treatment with antioxidants plus zinc compared with placebo was observed for NV AMD outcomes but not for the development of GA involving the center of the macula. These results are similar to those reported after the clinical trial ended.

It is interesting to note that the persistence of the beneficial effect of tested therapy or therapies in extended follow-up after the cessation of a randomized, controlled clinical trial has been demonstrated in other trials when the follow-up exceeded the length of the clinical trial. The Diabetes Control and Complications Trial found a beneficial effect of intensive glycemic control compared with conventional

glycemic control in reducing both the development and progression of diabetic retinopathy.⁴ This study was extended as an epidemiologic study with additional follow-up through year 10. During follow-up, the measures of glycemic control of both treatment groups became almost equivalent, but the beneficial effects of the intensive glycemic control persisted, albeit somewhat attenuated, at 10 years.⁵ Investigators speculated that this may be because of a “metabolic imprinting,” which may be secondary to a slow accumulation and subsequent slow degradation of glycation endproducts.⁶ Alternatively, it could be an epigenetic phenomenon effect or a combination of these 2 speculations. After stopping the randomized clinical trial portion of the study, continued follow-up also resulted in persistence of beneficial effects of both focal and scattered laser photocoagulation for diabetic retinopathy.^{6,7} Similar beneficial results were also found in the longer follow-up of participants originally enrolled in a study of aspirin use for the prevention of cardiovascular morbidity and mortality.⁸

Possible long-term, adverse effects of the original AREDS treatment assignments also were evaluated out to 10 years of follow-up. No serious adverse effects were noted. No significant effect on mortality was seen among participants randomized to antioxidant vitamins. Among those who were randomized to zinc, there seems to be a significant reduction in mortality, mostly accounted for by a reduction in cardiovascular deaths. Further investigation in this area is warranted.

Several factors need to be considered when interpreting results from the follow-up study. First, the AREDS population differs from the general population in several respects: it is better nourished, more highly educated, and healthier. The effect of this on generalizability of the results to the general population is unknown. Second, the treatment effect is relatively modest and AMD and vision loss events continue to occur in participants taking the AREDS formulation. Third, we still do not know how long someone at risk of advanced AMD should take the supplements. Finally, it is important to remember that the results reported here are from an observational follow-up study of original treatment assignments in the clinical trial. By the end of follow-up, about 70% of the cohort was taking the AREDS formulation. It is not possible to determine the effect of this on the results. However, it is encouraging that the results of the original randomized contrast persisted long after the clinical trial ended.

Strengths of the follow-up study are many. The study followed a very large cohort of subjects at moderate to high risk of progression to advanced AMD. Approximately 12% of the AREDS population died before the beginning of the follow-up study, with no differential survival according to the treatment group. Approximately 84% of the surviving cohort was followed in the observational portion of the study. The rates of loss to follow-up were extraordinarily low in both the clinical trial (2%) and the follow-up study (4%). Major ocular outcome 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 rate of losses to follow-up, and the careful monitoring of endpoints suggest that the long-term findings are representative of this clinic population.

Table 3. Associations of All-Cause and Cause-Specific Mortality With Baseline Ocular and Treatment Characteristics

Characteristic	All-Cause Mortality				Circulatory System	Neoplasms	Other Causes
	Deaths/ Total	Mortality Rate*	Hazard Ratio [†] (95% CI)	Hazard Ratio [‡] (95%CI)	Risk Ratio [‡] (95%CI)	Risk Ratio [‡] (95%CI)	Risk Ratio (95%CI) [‡]
AMD category							
1	191/1116	14	1.0	1.0	1.0	1.0	1.0
2	197/1060	16	1.02 (0.84–1.25)	1.01 (0.83–1.24)	1.15 (0.81–1.64)	0.91 (0.64–1.29)	0.94 (0.66–1.35)
3	349/1620	19	1.09 (0.91–1.30)	1.01 (0.85–1.21)	1.28 (0.93–1.75)	0.80 (0.58–1.10)	0.99 (0.72–1.36)
4	320/957	28	1.62 (1.35–1.95)	1.27 (1.05–1.54)	1.58 (1.14–2.20)	1.12 (0.80–1.56)	1.18 (0.84–1.86)
Nuclear opacity [§]							
Grade <4 in available eye(s)	819/4001	17	1.0	1.0	1.0	1.0	1.0
Grade ≥4 in at least 1 eye	191/617	28	1.30 (1.10–1.53)	1.29 (1.10–1.52)	1.31 (1.00–1.71)	1.29 (0.95–1.75)	1.29 (0.97–1.71)
Cortical opacity [§]							
≤5% in available eye(s)	870/4090	17	1.0	1.0	1.0	1.0	1.0
>5% in at least 1 eye	139/524	26	1.13 (0.94–1.36)	1.06 (0.88–1.27)	1.15 (0.86–1.54)	1.10 (0.78–1.55)	0.89 (0.83–1.26)
PSC [§]							
≤5% in available eye(s)	979/4503	18	1.0	1.0	1.0	1.0	1.0
>5% in at least 1 eye	30/111	26	1.20 (0.83–1.73)	1.11 (0.77–1.61)	1.14 (0.64–2.03)	1.22 (0.63–2.38)	1.08 (0.56–2.11)
Cataract surgery							
No	961/4464	18	1.0	1.0	1.0	1.0	1.0
Yes	96/289	32	1.38 (1.11–1.70)	1.30 (1.05–1.61)	1.38 (0.99–1.92)	1.49 (1.01–2.20)	1.01 (0.66–1.55)
AREDS treatment							
Antioxidant main effect							
No antioxidants	427/1806	20	1.0	1.0	1.0	1.0	1.0
Antioxidants	439/1831	20	1.06 (0.93–1.21)	1.06 (0.93–1.21)	1.20 (0.97–1.49)	1.07 (0.83–1.38)	0.94 (0.74–1.20)
Zinc main effect							
No zinc	465/1847	21	1.0	1.0	1.0	1.0	1.0
Zinc	401/1790	19	0.87 (0.76–0.99)	0.83 (0.73–0.95)	0.80 (0.64–0.99)	0.84 (0.65–1.08)	0.93 (0.73–1.18)

AMD = age-related macular degeneration; AREDS = Age-Related Eye Disease Study; CI = confidence interval; PSC = posterior subcapsular cataract.

*Age- and sex-adjusted mortality for median follow-up (10.5 years).

[†]Age- and sex-adjusted risk ratios.

[‡]Adjusted for significant covariates: age, sex, race, education, smoking status, body mass index, diabetes, angina, cancer, and hypertension.

[§]135 Participants without slit-lamp photographs and 139 participants without retroillumination photographs.

^{||}AMD category 2, 3, and 4 participants only.

In conclusion, participants in the AREDS clinical trial who had been assigned to the antioxidant and zinc formulation continued to show a reduced odds of developing advanced AMD, especially NV AMD, 5 years after the clinical trial ended. We continue to recommend the use of the AREDS formulation in persons with intermediate AMD or advanced AMD in 1 eye and persons at moderate to high risk of developing advanced AMD. Although much of the benefit of the AREDS formulation is driven by efficacy in decreasing the development of NV AMD and not CGA, we believe that all participants with AREDS AMD category 3 and 4 characteristics should consider taking the AREDS formulation. The development of neovascularization in patients with CGA may occur as frequently as 40% in 10 years (AREDS data, submitted for publication). Thus, the simultaneous occurrence of both forms of advanced AMD is common.

Further evaluation of the AREDS formulation is currently underway in the AREDS2, a randomized, controlled clinical trial primarily designed to determine the effects of lutein/zeaxanthin and ω-3 long-chain polyunsaturated fatty acids on progression of AMD. Until the results from AREDS2 become available, the AREDS formulation remains the treatment of choice for persons with intermediate AMD and advanced AMD in 1 eye.

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