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Summary Results and Recommendations From the Age-Related Eye Disease Study

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Age-related macular degeneration (AMD) is the leading cause of blindness in the United States, accounting for more than 50% of all cases.[1] The number of individuals affected is estimated to double by the year 2030 owing to the increasing longevity of the aging population.2 Any therapy that reduces the risk of developing advanced AMD plays an important role in decreasing the burden of this blinding disease on the affected individuals, their families, and society in general.

The Age-Related Eye Disease Study (AREDS) was designed as both a study of the clinical course of AMD and lens opacities as well as a randomized controlled trial of high-dose antioxidants and zinc to reduce progression of these diseases. The results of AREDS revealed a statistically significant benefit of the combination of high-dose antioxidant vitamins and zinc, providing a moderate reduction (34%) of the risk of developing advanced AMD over a median of 6.3 years of follow-up in persons at high risk of developing advanced AMD.[3]

STUDY DESIGN AND ANALYSIS PLAN

The study enrolled 4757 participants from 11 clinical centers between 1992 and 1998. Eligible participants had best-corrected visual acuity of 20/32 or better in at least 1 eye and media sufficiently clear to obtain adequate-quality stereoscopic fundus photographs. Participants were stratified by AMD severity at study entry. The clinical trial investigated the ability of high-dose antioxidant vitamins to slow the development or progression of cataract and of high-dose antioxidant vitamins and zinc to slow the development of advanced AMD. Advanced AMD was defined as (1) photocoagulation or other treatment for choroidal neovascularization (based on clinical center reports) or (2) photographic documentation, as graded by a centralized fundus photograph reading center, of geographic atrophy involving the center of the macula, non-drusenoid retinal pigment epithelial detachment, serous or hemorrhagic retinal detachment, hemorrhage under the retina or the retinal pigment epithelium, or subretinal fibrosis. In the AREDS Manual of Operations, written prior to study initiation, it was estimated that persons in category 1 (few or no drusen) or 2 (small or a few intermediate-sized drusen) would be at low risk of progression to advanced AMD during the trial. For category 1, the risk was anticipated to be so low that

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exposing these participants to risks of high-dose zinc would be inappropriate. Participants in this category were not included in the AMD trial.

The AMD clinical trial included participants with AMD categories 2, 3 (extensive intermediate drusen or large drusen or noncentral geographic atrophy in at least 1 eye), and 4 (advanced AMD or vision loss due to AMD in 1 eye only). The risk of advanced AMD for category 2 was estimated to be about 1% per year. Of the planned 1000 participants in this group, only 50 were expected to develop advanced AMD during the course of the study. Despite low rates of progression, this group was included because there would be sufficient power to assess treatment effects on the progression to category 3 or 4.

RESULTS

There are 2 clinically important preplanned analyses assessing the effect of treatment on progression to advanced AMD. The first includes the full cohort of participants in the AMD trial (AMD categories 2, 3 and 4). Adjusting for the predefined design variable, AMD category, a test for differential treatment effect (*P*=.006, not shown), zinc main effect (*P*=.009), and the treatment effects of 2 of the individual treatment arms, zinc alone (*P*=.006) and zinc plus antioxidants (*P*=.001), were statistically significant. The second analysis was restricted to AMD category 3 and 4 participants, as previously described.[3] Either approach gives the same results (Table).

After 5 years, only 15 category 2 participants had progressed to advanced AMD. This number is far too small to assess any treatment effect on the progression to advanced AMD in this group of patients. In addition, treatment did not slow progression from category 2 to category 3 or 4. Based on this finding, treatment recommendations are limited to those in the high-risk groups for progression to advanced AMD.

The effect of treatment on changes in visual acuity was modest, with about a 25% reduction in loss of 15 or more letters (mean difference of 3 letters) attributed to the combination arm compared with the placebo arm for category 3 and 4 participants.[3]

The lens opacity component of AREDS tested antioxidants vs no antioxidant and found no effect overall or for specific opacity types (nuclear, posterior subcapsular, or cortical cataract or cataract surgery).[4]

ADVERSE EFFECTS

Observed adverse effects were minimal. An increase in genitourinary hospitalizations (eg, unspecified urinary tract infection and prostatic hyperplasia in men and stress incontinence in women) was observed in participants randomized to the zinc arms (7.5% vs 4.9%; *P*=.001).3 Results from other studies suggested that persons who smoke should not take beta-carotene.5,6 None of the treatments had an effect on cognition.[7] An analysis of zinc vs no zinc found a borderline significant benefit of mortality reduction (relative risk, 0.73; 95% confidence interval, 0.61–0.89).[8]

GRADING SCALES

In addition to including a clinical trial, AREDS was designed to investigate the clinical course of AMD. Based on 10 years of follow-up within AREDS, a detailed fundus photograph grading scale and a simplified clinical grading scale for advanced AMD risk assessment has been developed that should be useful for future studies, but requires independent validation.[9,10]

RECOMMENDATIONS

The AREDS design provided important information showing that, in people with few intermediate-sized drusen or extensive small drusen, there is such a low risk of developing advanced AMD that treatment targeting progression to advanced AMD is not warranted. The AREDS-type supplements were found to have a moderate beneficial effect in persons at high risk of advanced AMD, with possible contraindications for smokers or other people who may have reason to avoid 1 or more of the ingredients evaluated in AREDS. With this modest therapeutic effect of the AREDS formulation, the potential effect on public health of the disease burden of AMD is considerable.[11] It is estimated that if the 8 million individuals in the United States who are at high risk of developing advanced AMD received the AREDS formulation, more than 300 000 of the 1 million persons expected to develop advanced AMD (95% confidence interval, 158 000–487 000) would avoid it, and its associated vision loss, during the next 5 years.

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Table

Effect of AREDS Treatment on Progression to Advanced AMD

	Categories 2, 3, and 4[a]		Categories 3 and 4[b]	
Treatment	**OR (99% CI)**	***P* Value**	**OR (99% CI)**	***P* Value**
Antioxidants (main effect)	0.84 (0.67–1.06)	.05	0.83 (0.66–1.06)	.05
Zinc (main effect)	0.79 (0.63–0.99)	.009	0.79 (0.62–0.99)	.009
Antioxidants vs placebo	0.75 (0.55–1.03)	.02	0.76 (0.55–1.05)	.03
Zinc vs placebo	0.71 (0.52–0.98)	.006	0.71 (0.52–0.99)	.008
Antioxidants and zinc vs placebo	0.67 (0.49–0.92)	.001	0.66 (0.47–0.91)	.001

Abbreviations: AMD, age-related macular degeneration; AREDS, Age-Related Eye Disease Study; CI, confidence interval; OR, odds ratio.

[a] Adjusted for AMD category.

[b] Unadjusted.