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.

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 and zinc to slow the development or progression of cataract and lens opacities as well as a randomized controlled trial designed as both a study of the clinical course of AMD and a test for differential treatment effect (AMD categories 2, 3 and 4). 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 previ-
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.\(^4\) 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.

Submitted for Publication: August 10, 2007; final revision received November 12, 2007; accepted November 13, 2007.

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Financial Disclosure: None reported.

**REFERENCES**


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**Table. Effect of AREDS Treatment on Progression to Advanced AMD**

<table>
<thead>
<tr>
<th>Categories</th>
<th>Categories 3 and 4&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>P Value</td>
<td>OR (99% CI)</td>
</tr>
<tr>
<td>Antioxidants (main effect)</td>
<td>0.84 (0.67-1.06)</td>
</tr>
<tr>
<td>Zinc (main effect)</td>
<td>0.79 (0.63-0.99)</td>
</tr>
<tr>
<td>Antioxidants vs placebo</td>
<td>0.75 (0.55-1.03)</td>
</tr>
<tr>
<td>Zinc vs placebo</td>
<td>0.71 (0.52-0.98)</td>
</tr>
<tr>
<td>Antioxidants and zinc vs placebo</td>
<td>0.67 (0.49-0.92)</td>
</tr>
</tbody>
</table>

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

<sup>a</sup> Adjusted for AMD category.

<sup>b</sup> Unadjusted.

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**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.\(^4\) 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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**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).\(^8\)

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**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.\(^9,10\)