



# Technical Literature

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## The Beneficial Effects of Oral Supplementation with High Dose Antioxidants, Vitamins, and Minerals in Decreasing the Risk of Age-Related Macular Degeneration: AREDS Review, AREDS II Preview

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### Key Conclusions

- The AREDS study was the first large-scale government funded study to examine the effect of nutritional supplements on AMD risk in humans
- After five years of using a combined supplement of Antioxidants + Zinc, subjects had a 25% decreased risk of developing advanced AMD and a 27% decreased risk of visual acuity loss relative to those using Placebo
- No serious adverse effects were reported as a result of the use of these supplements
- AREDS II will begin in 2006 to test effects of lutein and zeaxanthin, omega-3 FA, and reduced zinc formulas on progression of AMD

### Introduction

The second Age-Related Eye Disease Study (AREDS II) will soon be initiated to test the effects of micronutrient xanthophylls (lutein and zeaxanthin) on progression of age-related macular degeneration (AMD) (7,8). This major clinical trial was developed after an earlier study (AREDS) found AMD to be a nutrition responsive disorder by showing that high levels of antioxidants and zinc significantly reduce the risk of advanced AMD. A review of the findings from the AREDS and a preview of the AREDS II, which will include treatment with supplemental, purified lutein supplied as FloraGLO® Lutein, are presented in this paper.

Age-related macular degeneration (AMD) is a degenerative disease that causes progressive loss of central vision and is the leading cause of blindness in the Western world among those age 50 and older (1). According to the 2000 U.S. census, AMD is the leading cause of blindness for caucasian Americans (54.4% cases). A 70% increase in that number is expected by 2020 due to aging of the U.S. population (2). While at this time there is no recognized cure for this disease, several environmental and behavioral risk factors have been identified that, if altered, may reduce the risk or progression of this disease. Risk factors include smoking, excess sunlight exposure, and nutrient status.

AREDS tested the effect of providing high daily doses of certain nutrients as supplements to subjects with various stages of AMD. For over six years, patients were carefully monitored for progression of the disease as well as other parameters, such as visual function and visual

acuity (3). Post-clinical follow-up of study participants included analysis of the potential public health impact of AREDS findings (4,5) and an assessment of the effects of AMD and the AREDS intervention on mortality (6). The AREDS results together with growing evidence of other protective factors for AMD, have prompted the initiation of AREDS II to test the effects of micronutrient xanthophylls (lutein and zeaxanthin) and omega-3 fatty acids on progression of AMD and cataracts (7,8).

## AREDS Study Summary

In total, 3,640 patients at varying stages of AMD, age 55 to 80 years, were enrolled in a multi-center trial. Patients were assigned randomly to receive one of four daily oral supplements: Placebo, Zinc (80 mg Zn as zinc oxide and 2 mg Cu as cupric oxide), Antioxidants (500 mg vitamin C, 400 IU vitamin E, 15 mg  $\beta$ -carotene), and Antioxidants + Zinc.

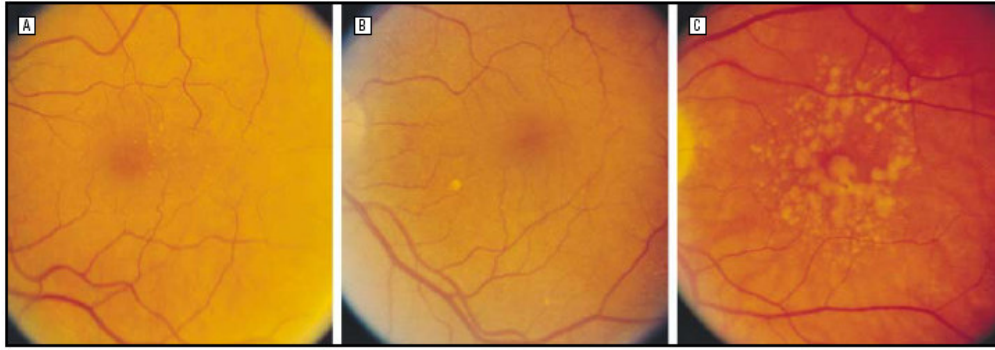
The AREDS has described a system for classifying AMD that places an individual into four progressive levels, based on presence and size of drusen, area of drusen, and presence of pigment abnormalities (9) (**Table 1**) as determined from stereoscopic color fundus photographs (**Figure 1**). Patients were divided into the four categories according to degree of disease at the beginning of the study before receiving supplements. Those in Category 1 were only assigned the Placebo and Antioxidant supplements and were not administered Zinc or Antioxidants + Zinc treatments.

**Table 1.** AREDS Grading System

AMD Category	Definition	AMD Risk*
1	Drusen size < 63 $\mu\text{m}$ and total area < 125 $\mu\text{m}^2$	
2	(a) Drusen size > 63 $\mu\text{m}$ but <125 $\mu\text{m}$ , or (b) Drusen total area $\geq$ 125 $\mu\text{m}^2$ , or (c) RPE abnormalities consistent with AMD	1.3%
3	(a) Drusen size $\geq$ 125 $\mu\text{m}$ , or (b) Drusen size $\geq$ 63 $\mu\text{m}$ and total area > 360 $\mu\text{m}^2$ (c) Drusen size $\geq$ 63 $\mu\text{m}$ and total area > 660 $\mu\text{m}^2$ (d) Geographic atrophy (>180 $\mu\text{m}$ ) but none at center of macula	18%
4 (advanced)	(a) Geographic atrophy in central subfield with involvement of macula, or (b) Evidence of neovascular AMD	43%

\* Presented by Dr. Chew at the 2006 ARVO Summer Research Conference, "Toward the Prevention of Age-Related Macular Degeneration".

Among patients from Category 2 (early AMD), so few advanced to later stages of AMD across all treatments after five years, it was impossible to assess treatment effects. Therefore, their results were excluded from the analysis of effects on AMD progression. Patients in Categories 3 and 4 (intermediate AMD and advanced AMD in one eye, respectively) began the study with far more advanced disease symptoms, and their progression was much more quantifiable. Patients were followed and the progression of AMD was monitored from 1992 to 1998. Compliance was assessed by counting the number of remaining supplements and by monitoring serum nutrient levels at years one and five. Two primary outcomes of assessment were measured: progression to advanced AMD and decrease in visual function acuity score by at least 15-letters. Analysis of secondary outcomes, including development of vascularization and geographic atrophy, were limited to patients in Categories 3 and 4.



**Figure 1.** Fundus photographs of eyes from participants in the AREDS trial illustrating the appearance of those in Categories 2 (A) and 3 (B,C).

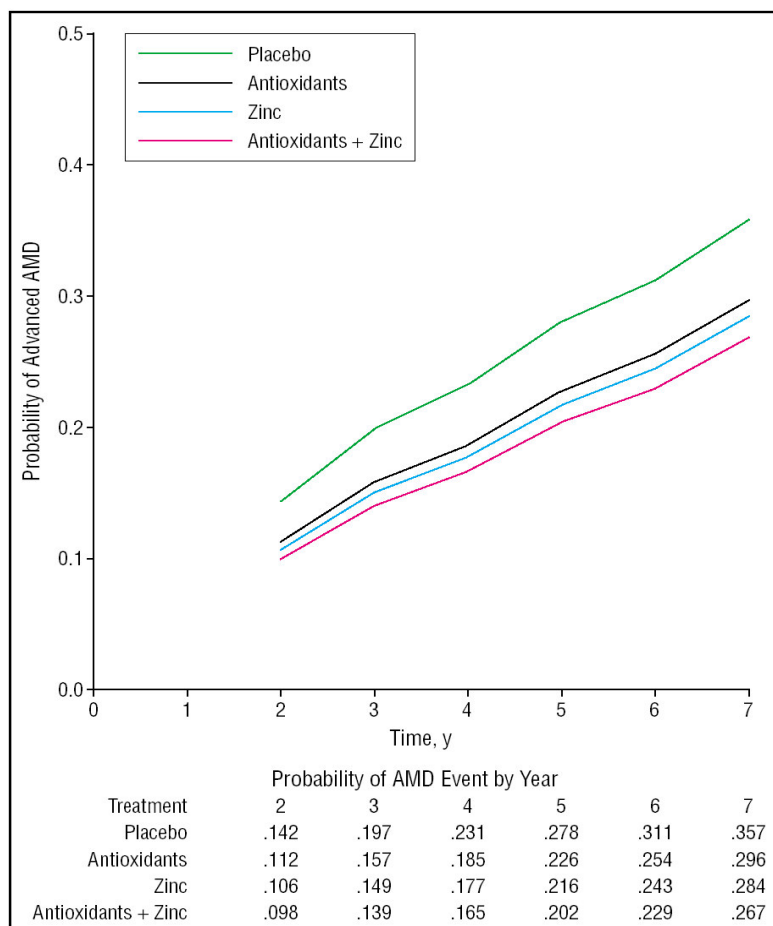
(A), Left eye in Category 2 shows nonextensive intermediate drusen, mostly located superotemporal to the center of the macula. No drusen is 125  $\mu\text{m}$  or greater in diameter, although some are 63  $\mu\text{m}$  or greater and their cumulative area is less than AREDS circle O-2 (about 0.2 disc areas). (B), One left eye in Category 3 depicts the lower limit of the category, having 1 large drusen ( $\geq 125 \mu\text{m}$  in diameter) in the 8-o'clock position from the center of the macula, while another left eye, (C) shows many large drusen (totaling at least 1 disc area) scattered throughout the macula.

Overall, subject follow-up continued through 2005. During this period of data analysis, researchers issued a report of the potential public health impact of AREDS (4,5) and an assessment of the effects of AREDS or the AREDS components on mortality associated with AMD progression (6).

## Results

For nearly all parameters tested, treatment with Antioxidants + Zinc resulted in the most benefit relative to Placebo. While other treatments had significant inverse effects on progression of AMD and reduction in visual acuity loss in subjects who began the study in disease Category 3 or 4, the combined treatment of Antioxidants + Zinc had the largest and most significant effect ( $p \leq .01$ ). At five years, subjects who were administered the Antioxidants + Zinc had an estimated 28.6% decreased risk for progression to advanced AMD relative to Placebo-treated patients (estimates derived from odds ratios). The probability of progressing to advanced AMD over time for patients in Categories 3 and 4 based on repeated-measures analysis is shown in **Figure 2** (obtained from the published manuscript (3)).

A treatment effect was observed with the combination of Antioxidants + Zinc eliciting the strongest influence. This effect was consistent for the reduction of visual acuity loss (VAL), with patients in Categories 3 and 4 with advanced symptoms realizing the greatest decrease in VAL of 27% at five years. When patients in Categories 2, 3 and 4 were combined, the loss reduction was 21% at five years. Upon analysis of the components of advanced AMD, patients administered the Antioxidants + Zinc supplement had a statistically significant reduced risk of developing neovascularization ( $\downarrow 28\%$ ) compared with Placebo. A trend was also observed for a reduction in geographic atrophy in patients who began the study with more advanced AMD (Categories 3 and 4).



**Figure 2.** Repeated-measures estimates of the probability of development of advanced age-related macular degeneration (AMD).

Data derived from at least one study eye of participants in Categories 3 and 4 by treatment group. The study eye is an eye without disqualifying lesions or evidence of advanced AMD, and with a visual acuity score of greater than 73 letters (20/32 or better) at baseline. Events before year 2 reflect only photocoagulation. AREDS 2001.

Patients in Categories 1 and 2 showed little if any disease progression over the course of the study and no treatment benefit, regardless of intervention, was evident. Thus, the effect of supplementation could not be accurately evaluated in these categories. Study compliance was high as the measurement of various serum nutrients indicated a definite serum response for each nutrient. There were no statistically significant differences in safety outcomes and no serious side effects were reported for any intervention.

A post-study analysis of the potential public health impact of the AREDS formulation on reducing AMD-related blindness in the United States estimated that eight million people at least 55 years old had intermediate to advanced AMD in 2003 and would be considered at high risk for AMD progression (4). If the 1.3 million individuals expected to develop advanced AMD would undergo treatment with AREDS supplements, it is estimated that the sight of 329,000 patients would be saved over the next five years.

At baseline, the median age of AREDS participants was 69 years. During the six and one-half years of post-study follow-up, 11% (534) of the 4753 AREDS participants had died (6). Mortality rates increased with severity of macular pathology. Participants with late AMD or advanced VAL in one eye (Category 4) had a significant increased risk of mortality compared with AMD free participants (Category 1). Advanced AMD was also associated with cardiovascular deaths. Lower mortality rates were observed among participants assigned to receive Zinc compared to Placebo and Antioxidant alone groups receiving no zinc.

## Discussion

The AREDS results clearly show that nutritional intervention in the form of supplements can delay the progression of AMD for patients in Categories 3 and 4, and can reduce AMD-associated vision loss for patients in stages as early as Category 2 (3). Of the treatments provided, the combined supplement of Antioxidants + Zinc had the strongest effect. This effect was most evident in patients in Categories 3 and 4, and was consistently demonstrated for all parameters assessed in those patients, including VAL and vascularization pathology associated with AMD. These findings between visual function and pathology strongly suggest that multiple nutrients may be required for maintenance of eye health. The study findings are consistent with a report by Dr. Stuart Richer in 1996 showing the beneficial effect of an antioxidant and zinc-containing supplement on visual function in AMD patients (10).

While treatment with Antioxidants + Zinc offered the greatest risk reduction for developing advanced AMD (25%), a substantial reduction of risk was estimated for treatment with Antioxidants alone (17%). Therefore, supplementation with Antioxidants alone may be the preferred alternative for patients concerned about potential negative effects of zinc consumption (such as anemia, decreased HDL cholesterol, upset stomach) or for whom zinc is otherwise contraindicated. Both treatments confer a substantial benefit considering the study finding that participants receiving Placebo within Categories 3 and 4 had probabilities of progression to AMD by five years as high as 27% and 43%, respectively.

Due to the lack of overall progression of disease symptoms in Categories 1 and 2, the effect of supplementation could not be accurately evaluated. At the outset of the study, Category 1 participants were essentially free of AMD abnormalities, while Category 2 participants had only mild abnormalities. The finding of slow rates of disease progression in these patients (1.3% in five years for Category 2, and <1% for Category 1) does not exclude the potential benefit of nutritional supplements with respect to reducing the risk of AMD for individuals in these categories who may exhibit disease symptoms later.

Dr. Emily Chew reported at the 2006 ARVO Summer Research Conference that the formulation used in AREDS was developed based on the available scientific information and recommendations of experts in the field of the best antioxidants commercially available at the time of AREDS initiation. Now, over ten years later, an accumulation of compelling, well documented evidence of the beneficial effects of lutein on AMD and general eye health (11) has lead the AREDS II scientific panel to recognize value in adding supplemental purified lutein to the AREDS II treatment matrix.

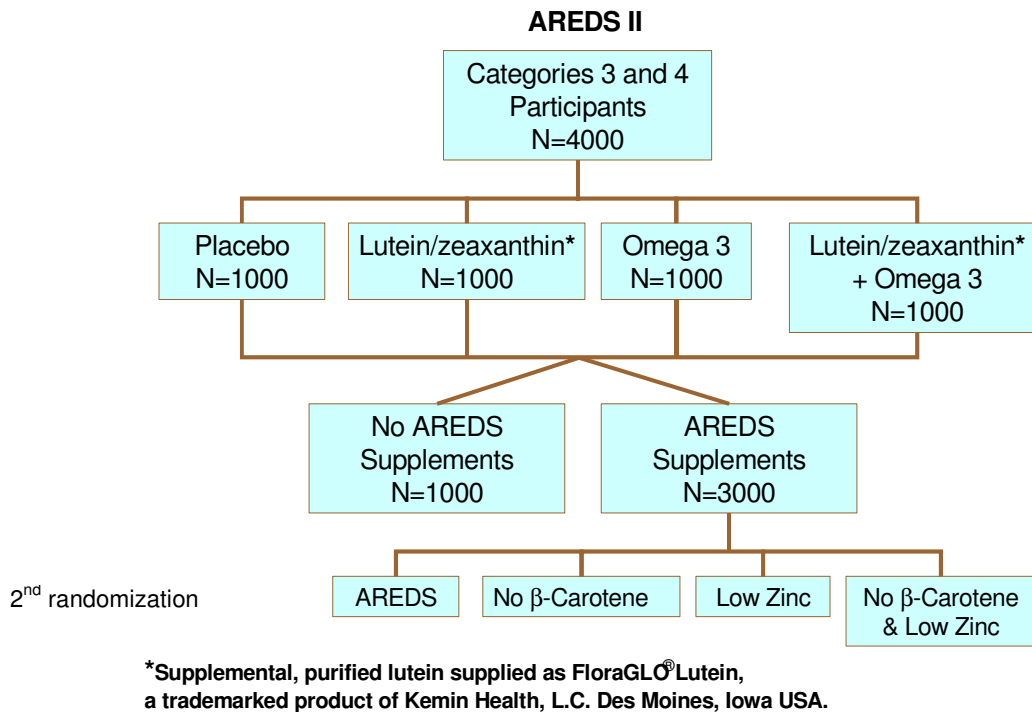
While lutein was not part of the antioxidant interventions used, the AREDS results corroborate findings of previous studies examining the beneficial effect of lutein supplementation on visual function in AMD patients (12) and the association of lutein intake with reduced AMD risk (13). The available data showing reduced risk of AMD with dietary intake of lutein/zeaxanthin suggest that lutein may further improve the slowing effects on AMD progression seen with the AREDS supplement formulation.

The study follow-up identified a significant increase in risk of mortality associated with progression to advanced AMD. The findings also suggest an important potential impact of an AREDS type nutritional supplement on public health.

## AREDS II

A second randomized clinical trial, AREDS II, sponsored by the National Eye Institute, with over 80 participating research centers, will aim to refine and improve on the AREDS findings by investigating micronutrient xanthophylls (lutein and zeaxanthin) and omega-3 long chain polyunsaturated fatty acids (LCPFA) (fish oil) (**Figure 3**). The effects of oral supplementation with four possible treatments will be evaluated: **lutein/zeaxanthin** (10 mg/d, 2 mg/d respectively), **omega-3 LCPFA** (1 g/d), **lutein/zeaxanthin plus omega-3**, or **placebo**. AREDS data and epidemiological studies have shown the link between lower dietary intakes of omega-3 and lutein, and increased risk of AMD.

Since previous findings showed primary efficacy in advanced AMD patients, the AREDS II will enroll 4000 patients with Categories 3 and 4 AMD beginning in late 2006 (7,8). Due to the severity of their condition, all subjects will be allowed to take the original AREDS formulation during AREDS II treatment. Patients who elect to receive the original AREDS formula will be subject to a secondary randomization to formula variations including no beta-carotene, reduced zinc, and the combination of no beta-carotene and lower zinc. Due to the increased risk of lung cancer associated with  $\beta$ -carotene consumption, smokers who enroll in the study will be randomized to receive the no- $\beta$ -carotene treatment. All subjects will consume Centrum vitamins during the course of the study.



**Figure 3.** AREDS II Study design

In summary, AREDS, the largest clinical AMD study to date, showed that nutritional intervention in the form of an Antioxidant + Zinc supplement slows the progression of AMD and the decline in visual function associated with the disease. This study supports the evaluation in AREDS II of nutritional intervention with supplemental FloraGLO® Lutein to reduce the incidence of AMD.

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