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## AREDS2: Perspectives, Recommendations, and Unanswered Questions

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### Abstract

**Purpose of review**—This review provides a perspective on the AREDS2 including: a summary of the goals and rationale of the study, major findings, subsequent management recommendations, and questions which remain to be answered.

**Recent findings**—The primary goal of the AREDS2 was to evaluate the efficacy and safety of lutein plus zeaxanthin and/or omega-3 long-chain polyunsaturated acid (LCPUFA) supplementation in reducing the risk of developing advanced AMD. AREDS2 also investigated the effects of omitting beta carotene and reducing the concentration of zinc from the original AREDS formulation. While primary analysis from the AREDS2 did not reveal a benefit of daily supplementation with lutein/zeaxanthin on AMD progression, secondary exploratory analyses suggested that lutein/zeaxanthin were helpful in reducing this risk. Comparison of low dose to higher dose zinc showed no significant benefit.

**Summary**—The overall evidence on the beneficial and adverse effects from AREDS2 and other studies suggests that lutein/zeaxanthin could be more appropriate than beta carotene in AREDS-type supplements. Questions remain regarding the AREDS2 study results such as: whether the findings are generalizable to the population as a whole, what is the long-term safety profile of lutein/zeaxanthin supplementation, should other carotenoids be included in AREDS-type supplements, and at what optimal doses.

### Keywords

age-related macular degeneration; antioxidant vitamins; omega-3 fatty acids; lutein; zeaxanthin

### Introduction

Age-related macular degeneration (AMD) is the leading cause of blindness in developed countries.[1,2] An estimated 21 million individuals are affected worldwide, and as the population ages, these numbers are projected to increase significantly.[3] The introduction of intravitreal therapies targeted at inhibition of vascular endothelial growth factor (VEGF),

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#### Conflicts of Interest

None of the authors have a conflict of interest.

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has provided effective treatment for the neovascular form of AMD.[4] At present, no such therapy exists for the atrophic form of AMD.[5] In the original Age-Related Eye Disease Study (AREDS), supplements containing vitamin C, vitamin E, beta carotene, and zinc were shown to reduce the 5-year likelihood of developing advanced AMD by an estimated 25% in at risk individuals.[6] Furthermore, this treatment effect persisted in those who continued to be monitored at the 5 year time point following cessation of this controlled, randomized, clinical trial.[7\*] The Age-Related Eye Diseases Study 2 (AREDS2) was designed to further investigate whether inclusion of lutein/zeaxanthin and/or omega-3 long-chain polyunsaturated fatty acids (LCPUFAs) to the original AREDS formulation would additionally reduce the risk for progression to advanced AMD. The present review summarizes the goals and rationale for undertaking the AREDS2, significant findings, treatment recommendations, and questions which remain to be answered.

## Systematic Review of the Literature

The literature search to support this review was performed between December 1, 2013 and December 31, 2013. Databases used to identify relevant articles included Medline, Pubmed, Scopus, EMBASE, The Cochrane Library, and Google Scholar. The abstracts and bibliographies of English language publications, pertaining to human studies, published between January 1, 2011 and December 31, 2013 were reviewed and included when appropriate. Our goal was to produce a meaningful and concise summary of the relevant literature published in the past 24 months pertaining to the perspectives, treatment recommendations, and questions which remain to be answered from AREDS2.

## Perspective on the AREDS2: Goals and Rationale

The AREDS2 is a large, multi-centered, phase III, randomized, double-masked, placebo-controlled, 2 × 2 factorial-designed clinical trial.[8\*\*] The primary goal of the AREDS2 was to evaluate the efficacy and safety of lutein plus zeaxanthin and/or omega-3 LCPUFA supplementation in reducing the risk of developing advanced AMD. The study also aimed to investigate the effects of omitting beta carotene and reducing the concentration of zinc from the original AREDS formulation.

The rationale for including lutein/zeaxanthin and/or omega-3 LCPUFAs in AREDS supplements originated from observational studies that suggested a link between higher dietary consumption of these compounds and decreased risk of developing advanced AMD. [9-19] This association was known at the start of the original AREDS, and lutein was considered for the initial formulation, however it was not commercially available at the time. A second reason for supplementation with lutein and zeaxanthin is that both are major constituents comprising the macular pigment. The anti-oxidative properties of these compounds, as well as their ability to reduce exposure to harmful ultra-violet light, may protect the outer retina and retinal pigment epithelium (RPE) from oxidative stress and contribute to cell membrane stability.[20,21] In a small prospective study, functional improvement was observed in the multi-focal electroretinograms (ERGs) of 15 AMD patients treated with oral supplementation with lutein and zeaxanthin compared to age-matched controls.[22]

A second randomization in the AREDS2 evaluated the effect of removing beta carotene and/or lowering the level of zinc from that found in the original AREDS formulation. The rationale for removing beta carotene was secondary to reports that suggested an increased risk for developing lung cancer in cigarette smokers taking supplements containing beta carotene.[23,24] The reasoning behind lowering zinc levels was that while a dose of 80 mg was used in the original AREDS formulation based on a prior trial suggesting efficacy, there was also evidence to suggest that the maximal level absorbed was closer to 25 mg.[25,26]

For its primary analysis, the AREDS2 enrolled 4,203 participants, aged 50 to 85 years, between October 17, 2006, and September 28, 2008, at 82 clinical sites across the United States.[8\*\*] Participants were considered at risk for developing advanced AMD in that 66% had bilateral large drusen and 34% had large drusen and advanced AMD in 1 eye.[8\*\*] In addition to taking the original or a variation of the first generation AREDS supplements, participants were randomly assigned, with equal probability, in a factorial design to receive one of four study formulations daily: (1) placebo, (2) lutein (10 mg)/zeaxanthin (2 mg), (3) omega-3 LCPUFAs, specifically docosahexaenoic acid (DHA, 350 mg) and eicosapentaenoic acid (EPA, 650 mg), or (4) both lutein/zeaxanthin and DHA/EPA (Table 1).

Of the 4,203 participants, 3,036 (72%) agreed to a secondary randomization which aimed to evaluate the effect of eliminating beta carotene and reducing the zinc level from that found in the original AREDS supplements. The four alternative formulations were (1) the AREDS formulation (vitamin C, 500 mg; vitamin E, 400 IU; beta carotene, 15 mg; zinc oxide, 80 mg; and cupric oxide, 2 mg), (2) the AREDS formulation minus beta carotene, (3) the AREDS formulation with low zinc (25 mg), or (4) the AREDS formulation minus beta carotene and including low zinc (Table 2).[27\*\*] Due to the concern for increased risk of lung cancer associated with exposure to beta carotene supplementation, current smokers and former smokers who had discontinued tobacco use within 1 year prior to randomization were assigned to one of the two arms that excluded beta carotene.

Individuals were followed at annual study visits which included a comprehensive eye examination with best-corrected visual acuity (BCVA) testing using an electronic version of the Early Treatment Diabetic Retinopathy Study (ETDRS) technique. Standardized, stereoscopic fundus photographs were obtained at each visit. Individuals were also contacted by telephone 6 months between visits and 3 months following randomization to obtain information on AMD treatment (for example, the need for intravitreal therapy) and adverse events. The main outcome measure of the AREDS2 was documented development of advanced AMD based on central, masked grading of annual fundus photographs or by treatment history.

## Summary of Major Findings from AREDS2

In its primary analysis, the AREDS2 demonstrated no beneficial or harmful effect of adding lutein/zeaxanthin, omega-3 LCPUFAs, or the combination on the progression to advanced AMD or changes in visual acuity compared with placebo.[28\*\*]

### **Lutein/Zeaxanthin Versus Beta Carotene**

In a secondary exploratory analysis, individuals randomized to lutein/zeaxanthin and the AREDS formulation without beta carotene (n = 1114 eyes) were compared to those assigned to no lutein/zeaxanthin and the original AREDS formulation containing beta carotene (n = 1117 eyes). In this analysis, the hazard ratios were 0.82 (95% CI, 0.69-0.96; P = .02) for progression to advanced AMD, 0.78 (95% CI, 0.64-0.94; P = .01) for developing neovascular AMD, and 0.94 (95% CI, 0.70-1.26; P = .67) for evolution of central geographic atrophy.[27\*\*]

### **Lutein/Zeaxanthin Plus Beta Carotene Versus Beta Carotene**

Patients assigned to lutein/zeaxanthin and AREDS supplements with beta carotene (n = 1104 eyes) were compared to those taking supplements without lutein/zeaxanthin and AREDS supplements containing beta carotene (n = 1117 eyes). This resulted in hazard ratios of 0.82 (95% CI, 0.69-0.97; P = .02) for development of advanced AMD, 0.72 (95% CI, 0.59-0.89; P = .002) for progression to neovascular AMD, and 1.07 (95% CI, 0.81-1.42; P = .62) for evolution of central geographic atrophy.[27\*\*]

### **Lower Zinc Dose and Elimination of Beta Carotene**

Lowering zinc dose (from 80 mg to 25 mg) and eliminating beta carotene had no statistically significant effect on progression to advanced AMD. These secondary analyses resulted in a hazard ratios of 1.06 (95% CI, 0.95-1.19; P = 0.32) and 1.07 (95% CI, 0.94-1.20; P = 0.31), respectively.[27\*\*]

### **Progression to Advanced AMD Based on AMD Status at Enrollment**

When secondary exploratory analysis was limited to those eyes with bilateral large drusen at the study baseline, the comparison of supplements containing lutein/zeaxanthin versus beta carotene yielded hazard ratios of 0.76 (95% CI, 0.61-0.96; P = .02) for progression to advanced AMD, 0.65 (95% CI, 0.49-0.85; P = .002) for development of neovascular AMD, and 0.98 (95% CI, 0.69-1.39; P = .91) for evolution of central geographic atrophy.[27\*\*]

## **Recommendations**

The AREDS2 is a large, multi-centered, placebo-controlled, randomized clinical trial of individuals at risk for developing advanced AMD. In its primary analyses, daily additional supplementation with lutein/zeaxanthin and omega-3 LCPUFAs (DHA/EPA) combined with modified versions of the original AREDS formulation were not shown to further reduce the risk of progression to advanced AMD or to change visual acuity.[28\*\*] However, due to the potential risk of increased incidence of lung cancer in present and former smokers taking beta carotene supplements, AREDS2 and other studies suggested that lutein/zeaxanthin could be a safer carotenoid substitute to beta carotene in AREDS-type supplements.[27\*\*] Based on the potential risks of beta carotene supplementation balanced with its possible benefits, which were only demonstrated in exploratory subgroup analysis, substitution with lutein/zeaxanthin in AREDS supplements for beta-carotene may be appropriate. Given the valid safety concerns in current and former smokers, it is important to have an AREDS-type formulation available to individuals which does not contain beta carotene. In the AREDS2

comparison of low dose zinc (25 mg) to the higher dose (80 mg) used in the original AREDS formulation, there was no statistically significant effect, and there was insufficient evidence to provide a meaningful clinical recommendation.[28\*\*]

## Unanswered Questions

One limitation of AREDS2 is that several of the reported results are based upon secondary exploratory analyses in the setting of negative primary findings. That is, the AREDS2 primary study results did not clearly demonstrate either a beneficial or harmful effect of including lutein/zeaxanthin and/or omega-3 LCPUFAs, however secondary exploratory analyses did suggest that lutein/zeaxanthin reduced the risk for progression to advanced AMD.[27\*\*] It is important to note that individuals studied in AREDS2 were well-nourished and characterized by above average intake of dietary nutrients.[27\*\*] The question then remains as to whether the results of AREDS2 can be generalized to United States population as a whole and to other populations around the world.[27\*\*,29\*]

Another aspect for further consideration is the long-term safety profile of lutein/zeaxanthin supplementation. The substitution of these compounds for beta carotene, seems reasonable, given their potential benefit as well as safety concerns related to increased risk of lung cancer in smokers using beta carotene containing supplements. However, the AREDS2 results have only recently been reported, and some have challenged that the long-term effects and possible adverse events associated with lutein/zeaxanthin supplementation are not yet known.[29\*]

Furthermore, whether lutein and zeaxanthin are the optimal carotenoids to include in AREDS-type supplements remains unanswered. There are over 600 known carotenoids, only less than two dozen are found in human tissue and blood, and lutein and zeaxanthin plus mesozexanthin, a metabolite of lutein, are the few xanthophylls found in the eye. Lutein and zeaxanthin are acquired through dietary sources, however the accumulation of these carotenoids in the retina has been shown to be dependent upon many variables, including several genetic factors.[30\*] A recent twin study which investigated the role of genetics on the macular response to dietary carotenoids suggested that 27% of this response is heritable. [31\*] Further investigation regarding the optimal doses of lutein and zeaxanthin may be helpful.

## Conclusion

In the era of preventative medicine, large-scale, multi-centered, placebo-controlled, randomized clinical trials, like the AREDS2, have been invaluable in studying potential therapies which may help to reduce the risk of progression to advanced AMD. While primary analysis of the AREDS2 data did not reveal a clear benefit of daily supplementation with lutein/zeaxanthin and/or omega-3 LCPUFAs (DHA/EPA) on AMD progression, secondary exploratory analyses did suggest that lutein/zeaxanthin were helpful in reducing this risk. Given this fact, along with safety concerns related to beta carotene supplementation, the totality of evidence on beneficial and adverse effects from AREDS2

and other studies suggests that lutein/zeaxanthin could be more appropriate than beta carotene in AREDS-type supplements.

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### Key Points

- The AREDS2 is a large, multi-centered, phase III, randomized, double-masked, placebo-controlled clinical trial the primary goal of which was to evaluate the efficacy and safety of lutein plus zeaxanthin and/or omega-3 LCPUFA supplementation in reducing the risk of developing advanced AMD and also to investigate the effects of omitting beta carotene and reducing the concentration of zinc from the original AREDS formulation.
- While primary analysis of the AREDS2 data did not reveal a clear benefit of daily supplementation with lutein/zeaxanthin and/or omega-3 LCPUFAs (DHA/EPA) on AMD progression, secondary exploratory analyses did suggest that lutein/zeaxanthin were helpful in reducing this risk.
- Questions still remain regarding the AREDS2 study results such as: whether or not the findings can be generalized to the population as a whole, what is the long-term safety profile of supplementation with lutein/zeaxanthin, which other carotenoids should be included in AREDS-type supplements, and do we have the optimal doses?

**Table 1**  
**Nutrient formulations included in the primary randomization of the AREDS2**

<b>Study Formulation</b>	<b>Daily Dose</b>
Placebo	---
Lutein/Zeaxanthin	10 mg/2 mg
DHA/EPA	350 mg/650 mg
Lutein/Zeaxanthin + DHA/EPA	10 mg/2 mg + 350 mg/650 mg

DHA: docosahexaenoic acid, EPA: eicosapentaenoic acid

**Table 2**  
**Four alternative formulations in the secondary randomization of AREDS2**

<b>Formulations</b>	<b>Vitamin C</b>	<b>Vitamin E</b>	<b>Beta Carotene</b>	<b>Zinc Oxide</b>	<b>Cupric Oxide</b>
1	500 mg	400 IU	15 mg	80 mg	2 mg
2	500 mg	400 IU	0 mg	80 mg	2 mg
3	500 mg	400 IU	15 mg	25 mg	2 mg
4	500 mg	400 IU	0 mg	25 mg	2 mg