

## Original Investigation | CLINICAL TRIAL

# Secondary Analyses of the Effects of Lutein/Zeaxanthin on Age-Related Macular Degeneration Progression

## AREDS2 Report No. 3

The Age-Related Eye Disease Study 2 (AREDS2) Research Group\*

**IMPORTANCE** The Age-Related Eye Disease Study (AREDS) formulation for the treatment of age-related macular degeneration (AMD) contains vitamin C, vitamin E, beta carotene, and zinc with copper. The Age-Related Eye Disease Study 2 (AREDS2) assessed the value of substituting lutein/zeaxanthin in the AREDS formulation because of the demonstrated risk for lung cancer from beta carotene in smokers and former smokers and because lutein and zeaxanthin are important components in the retina.

**OBJECTIVE** To further examine the effect of lutein/zeaxanthin supplementation on progression to late AMD.

**DESIGN, SETTING, PARTICIPANTS** The Age-Related Eye Disease Study 2 is a multicenter, double-masked randomized trial of 4203 participants, aged 50 to 85 years, at risk for developing late AMD; 66% of patients had bilateral large drusen and 34% had large drusen and late AMD in 1 eye.

**INTERVENTIONS** In addition to taking the original or a variation of the AREDS supplement, participants were randomly assigned in a factorial design to 1 of the following 4 groups: placebo; lutein/zeaxanthin, 10 mg/2 mg; omega-3 long-chain polyunsaturated fatty acids, 1.0 g; or the combination.

**MAIN OUTCOMES AND MEASURES** Documented development of late AMD by central, masked grading of annual retinal photographs or by treatment history.

**RESULTS** In exploratory analysis of lutein/zeaxanthin vs no lutein/zeaxanthin, the hazard ratio of the development of late AMD was 0.90 (95% CI, 0.82-0.99;  $P = .04$ ). Exploratory analyses of direct comparison of lutein/zeaxanthin vs beta carotene showed hazard ratios of 0.82 (95% CI, 0.69-0.96;  $P = .02$ ) for development of late AMD, 0.78 (95% CI, 0.64-0.94;  $P = .01$ ) for development of neovascular AMD, and 0.94 (95% CI, 0.70-1.26;  $P = .67$ ) for development of central geographic atrophy. In analyses restricted to eyes with bilateral large drusen at baseline, the direct comparison of lutein/zeaxanthin vs beta carotene showed hazard ratios of 0.76 (95% CI, 0.61-0.96;  $P = .02$ ) for progression to late AMD, 0.65 (95% CI, 0.49-0.85;  $P = .002$ ) for neovascular AMD, and 0.98 (95% CI, 0.69-1.39;  $P = .91$ ) for central geographic atrophy.

**CONCLUSION AND RELEVANCE** 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 the AREDS-type supplements.

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Age-related macular degeneration (AMD) is the leading cause of blindness in the United States.<sup>1</sup> Despite widespread use of highly effective intravitreal injections of drugs that inhibit vascular endothelial growth factor for neovascular AMD,<sup>2</sup> there is still no effective therapy for the atrophic form of AMD. We have demonstrated that the original Age-Related Eye Disease Study (AREDS) formulation consisting of vitamin C, vitamin E, beta carotene, and zinc reduced the 5-year risk for developing late AMD in persons at risk by an estimated 25%.<sup>3</sup> This beneficial treatment effect, mostly for reducing the risk for progression to neovascular AMD, persisted for the 5 years following cessation of the controlled, randomized clinical trial.<sup>4</sup> Observational studies suggest that higher dietary intake of lutein/zeaxanthin and/or omega-3 long-chain polyunsaturated fatty acids (LCPUFAs) are associated with a decreased risk for developing late AMD.<sup>5-20</sup> Lutein had been considered for use in the original AREDS formulation because of this reported association. However, lutein was not commercially available at the start of AREDS. Lutein and zeaxanthin are of interest because they are the major components of the macular pigment and may serve a variety of functions including filtering of presumably damaging blue and ultraviolet light and providing antioxidant capability.<sup>21</sup>

The Age-Related Eye Diseases Study 2 (AREDS2) was designed to test whether adding the oral supplements of lutein/zeaxanthin and/or omega-3 LCPUFAs to the AREDS formulation might further reduce the risk for progression to late AMD. The primary analyses in AREDS2 compared each individual treatment group of approximately 1000 participants with the placebo group of approximately 1000 participants. These AREDS2 primary analyses demonstrated no beneficial or harmful effect of lutein/zeaxanthin, omega-3 LCPUFAs, or the combination on the progression to late AMD compared with placebo.<sup>22</sup> A prespecified analysis consisting of a comparison of lutein/zeaxanthin vs no lutein/zeaxanthin (main effect) using the entire study cohort of approximately 4000 participants

demonstrated a beneficial effect of lutein/zeaxanthin (hazard ratio [HR], 0.90; 95% CI, 0.82-0.99; *P* = .04) for progression to late AMD. This beneficial effect was beyond the effects of the AREDS supplements, while we found no such indication of a beneficial effect of omega-3 LCPUFAs.

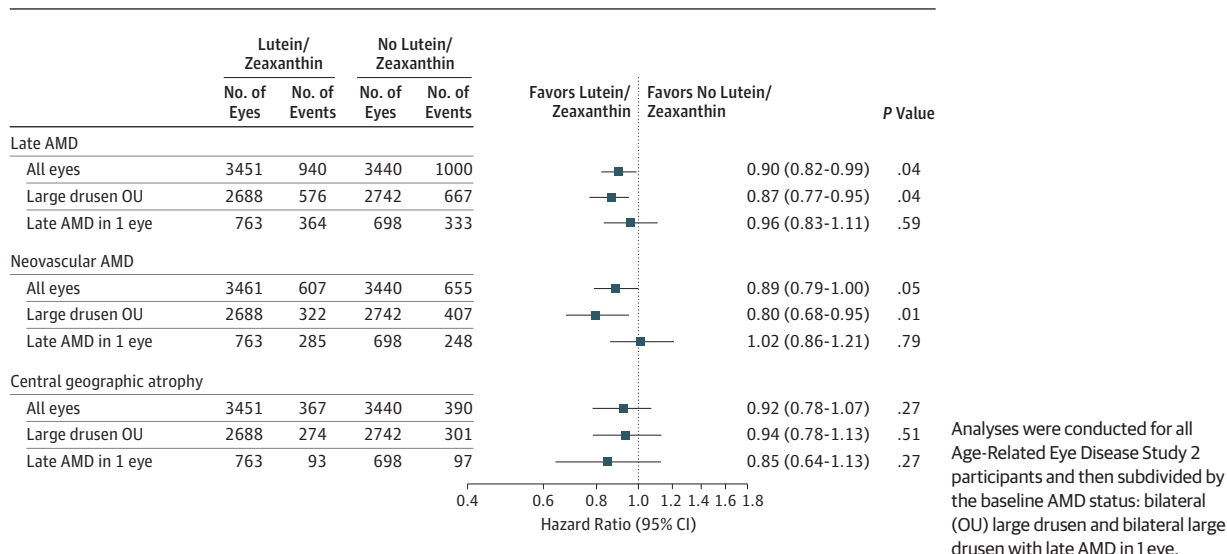
In addition, we reported prespecified analyses of the main effect of lutein/zeaxanthin that were stratified by quintiles of baseline dietary lutein/zeaxanthin intake. For persons in the lowest quintile (lowest dietary intake), comparison of lutein/zeaxanthin vs no lutein/zeaxanthin resulted in a HR of 0.74 (95% CI, 0.59-0.94; *P* = .01) for progression to late AMD.<sup>22</sup> Previous exploratory analyses were performed to evaluate the effects of lutein/zeaxanthin vs no lutein/zeaxanthin on the 2 forms of late AMD. The HRs were 0.89 (95% CI, 0.79-1.00; *P* = .05) for the development of neovascular AMD and 0.92 (95% CI, 0.78-1.07; *P* = .27) for development of central geographic atrophy (CGA) (Figure 1). In this article, we present detailed results from both prespecified and exploratory analyses examining the effect of lutein/zeaxanthin supplementation on progression to late AMD.

## Methods

### Study Population

Details of the study design have been published previously.<sup>23</sup> The Age-Related Eye Diseases Study 2 restricted enrollment to people at high risk for progressing to late AMD and those with either bilateral large drusen or large drusen in 1 eye and late AMD in the fellow eye. A total of 4203 participants, with a mean (SD) age of 73.1 (7.7) years, were enrolled between October 17, 2006, and September 28, 2008, at 82 clinical sites across the United States. Candidates were considered eligible only if they took at least 75% of the run-in medications (study's placebo and AREDS formulation) and if they agreed to take the AREDS2 supplements and stop the use of other study supple-

Figure 1. Comparison of Lutein/Zeaxanthin vs No Lutein/Zeaxanthin for the Development of Late Age-Related Macular Degeneration (AMD), Neovascular AMD, and Central Geographic Atrophy



ments. Of the 4203 participants, 3036 (72%) agreed to the secondary randomization evaluating the modifications to the AREDS supplements (eFigure 1 in Supplement). They had to satisfy the specified inclusion and exclusion criteria.<sup>22</sup> Institutional review boards from the clinical sites approved the AREDS2 research protocol and all participants provided written informed consent.

### Interventions

The Age-Related Eye Diseases Study 2 is a randomized, double-masked, placebo-controlled, 2 × 2 factorial trial evaluating the risks and benefits of adding lutein/zeaxanthin, 10 mg/2 mg, and/or omega-3 LCPUFAs, specifically docosahexaenoic acid (DHA, 350 mg) and eicosapentaenoic acid (EPA, 650 mg), to the original AREDS formulation, or one of the variations of the AREDS formulation for the treatment of AMD. Study participants were randomized with equal probability to take 1 of the following study supplements daily: (1) placebo; (2) lutein/zeaxanthin; (3) DHA/EPA; or (4) lutein/zeaxanthin and DHA/EPA.

Because they are known to be at high risk for developing late AMD, all AREDS2 participants also were offered the original or a modified version of the AREDS formulation. A second randomization was conducted to evaluate the effect of eliminating beta carotene and/or lowering the zinc levels in the original AREDS formulation. Because beta carotene has been reported to increase the risk for lung cancer in cigarette smokers,<sup>24,25</sup> a version of the AREDS formulation without beta carotene was tested. A dose of 80 mg of zinc was used in the original AREDS formulation because this dose was used in an earlier trial suggesting efficacy.<sup>26</sup> A lower dose of zinc (25 mg) was tested in AREDS2 based on data suggesting this dose may be the maximal level that is absorbed.<sup>27</sup> Those who consented to the optional secondary randomization were randomly assigned to: (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 low zinc. Current smokers and former smokers who had quit within 1 year before randomization and who agreed to this secondary randomization were randomized to 1 of the 2 arms without beta carotene. Participants who did not consent to this secondary randomization were provided with the original AREDS supplements, if they were not current smokers or had not smoked within the past year. Centrum Silver (Pfizer Inc) was offered to all study participants to standardize multivitamin intake. Participants and study personnel were masked to treatment assignment in each randomization.

### Follow-up

Briefly, follow-up study visits were scheduled annually with telephone contacts at 6 months between visits and at 3 months postrandomization to collect information on AMD treatment and adverse events. Study visits included a comprehensive eye examination with best-corrected visual acuity (VA) using an electronic version of the Early Treatment Diabetic Retinopathy Study VA technique and standardized stereoscopic fun-

cus photographs. Masked graders assessed the photographs at the reading center using a standardized protocol.

Pill counts at each annual visit and fasting blood samples at baseline and years 1, 3, and 5 were used to evaluate compliance with treatment assignments. Participants were followed up until October 2012, resulting in a median follow-up of 4.9 years (interquartile range, 4.3-5.1 years).

### Outcome Measures

The primary outcome was the development of late AMD, defined as atrophy involving the center of the macula or neovascular changes of AMD that were detected on central grading of the stereoscopic fundus photographs for (1) definite central geographic atrophy, (2) retinal features of choroidal neovascularization, or (3) history of treatment for AMD. Prespecified secondary outcomes included progression along the detailed 11-step AREDS AMD scale<sup>28</sup> and VA losses of 10 or more letters or 15 or more letters from baseline. Eyes that received treatment for neovascular AMD were counted as events in both analyses. Such eyes may also have experienced decreased vision prior to onset of neovascular AMD. When this occurred, the decrease in vision was counted as the event.

Exploratory secondary analyses included progression to the 2 forms of late AMD, neovascular AMD, or CGA: (1) progression to late AMD stratified by baseline AMD status; (2) progression to more severe vision loss of worse than 20/100; (3) progression to loss of 30 or more letters from baseline; (4) analyses of a head-to-head comparison of the AREDS formulation minus beta carotene but with lutein/zeaxanthin added vs the original AREDS formulation including beta carotene but without lutein/zeaxanthin; and (5) analyses of the AREDS formulation with beta carotene and lutein/zeaxanthin vs the AREDS formulation with beta carotene (without lutein/zeaxanthin).

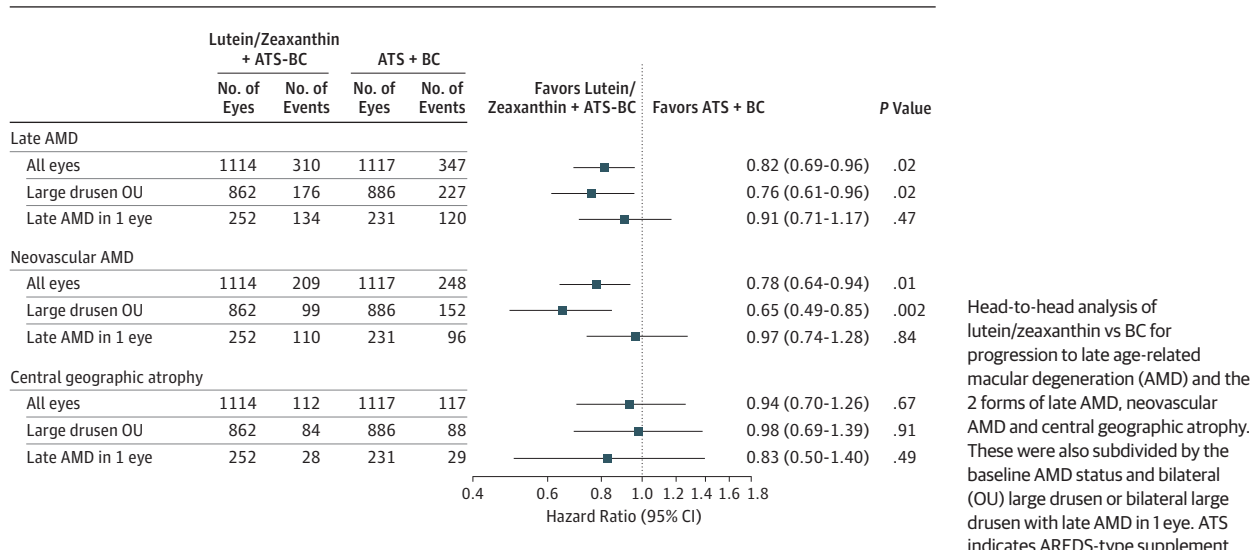
### Statistical Analyses

The unit of analysis for ophthalmic outcomes was by eye. The secondary and exploratory ophthalmic outcomes were assessed using Cox proportional hazards models with the Wei et al<sup>29</sup> method for obtaining robust variance estimates that adjusted for dependence among multiple event times (multiple study eyes) adjusted for baseline AMD status only. The assumptions for proportional hazards models were tested and met for all outcomes. Participants lost to follow-up or who died during the course of the study were censored at the time of the last contact. Hazard ratios and 95% CIs were computed. When analyses were restricted to participants taking beta carotene, these analyses were restricted to nonsmokers only because they were the only participants eligible for randomization to beta carotene vs no beta carotene. All analyses were conducted following the intention-to-treat principle and using SAS software version 9.2 (SAS Institute Inc).

## Results

Baseline characteristics of the AREDS2 cohort were comparable across the 4 treatment groups in the primary randomization.<sup>22</sup> The baseline characteristics of the partici-

Figure 2. Comparison of Lutein/Zeaxanthin Plus Age-Related Eye Disease Study (AREDS) Supplements Without Beta Carotene (BC) vs AREDS Supplements With BC and No Lutein/Zeaxanthin



Head-to-head analysis of lutein/zeaxanthin vs BC for progression to late age-related macular degeneration (AMD) and the 2 forms of late AMD, neovascular AMD and central geographic atrophy. These were also subdivided by the baseline AMD status and bilateral (OU) large drusen or bilateral large drusen with late AMD in 1 eye. ATS indicates AREDS-type supplement.

pants assigned to lutein/zeaxanthin vs no lutein/zeaxanthin (eTable 1 in Supplement) as well as the cohort randomized to beta carotene vs no beta carotene (eTable 2 in Supplement) were comparable. The ocular and other characteristics regarding compliance and follow-up are found in eAppendix 1 (Supplement).

**Dietary and Serum Levels of Lutein/Zeaxanthin**

Compared with general-population participants sampled in the National Health and Nutrition Survey 2005-2006 of similar ages,<sup>22</sup> AREDS2 participants had a much higher dietary intake and mean serum levels of lutein/zeaxanthin. Baseline dietary intake of the study nutrients, including those of the AREDS supplements, was balanced across treatment groups.<sup>22</sup>

The serum levels of the study nutrients at baseline were balanced across the treatment groups.<sup>22</sup> The median baseline serum levels of lutein/zeaxanthin in participants randomized to lutein/zeaxanthin increased by 190% to 210% at years 1, 3, and 5, while those randomized to placebo showed essentially no change. Participants randomized to lutein/zeaxanthin and beta carotene had a similar increase in serum lutein/zeaxanthin as those randomized to lutein/zeaxanthin without beta carotene; however, at year 5, these levels were lower in the participants receiving lutein/zeaxanthin and beta carotene than observed in those randomized to lutein/zeaxanthin alone (*P* = .05) (eTable 3 in Supplement).

**Lutein/Zeaxanthin vs Beta Carotene**

In an exploratory subgroup analysis, participants assigned to lutein/zeaxanthin and the AREDS formulation minus beta carotene (*n* = 1114 eyes) were compared with those assigned to no lutein/zeaxanthin and the original AREDS formulation with beta carotene (*n* = 1117 eyes); HRs were 0.82 (95% CI, 0.69-0.96; *P* = .02) for progression to late AMD, 0.78 (95% CI, 0.64-0.94; *P* = .01) for neovascular AMD, and 0.94 (95% CI, 0.70-1.26; *P* = .67) for CGA (Figure 2).

**Lutein/Zeaxanthin Plus Beta Carotene vs Beta Carotene**

Further exploratory analyses compared participants assigned to lutein/zeaxanthin and AREDS supplements with beta carotene (*n* = 1104 eyes) vs no lutein/zeaxanthin and AREDS supplements with beta carotene (*n* = 1117 eyes), with HRs of 0.82 (95% CI, 0.69-0.97; *P* = .02) for development of late AMD, 0.72 (95% CI, 0.59-0.89; *P* = .002) for neovascular AMD, and 1.07 (95% CI, 0.81-1.42; *P* = .62) for CGA (eFigure 2 in Supplement).

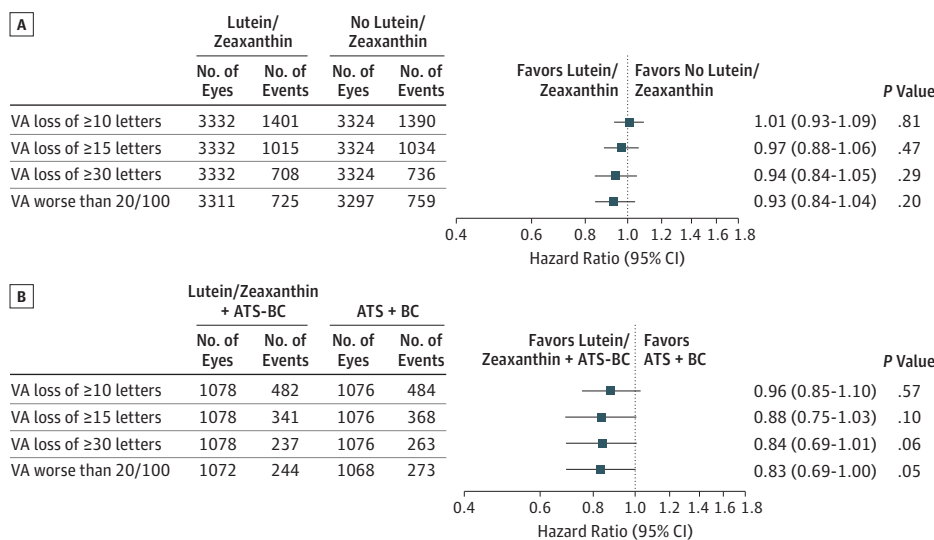
**Progression to Late AMD Stratified by Baseline AMD Status**

In exploratory analyses stratified by baseline AMD severity and bilateral large drusen or late AMD in 1 eye, the lutein/zeaxanthin vs no lutein/zeaxanthin comparison for progression to late AMD demonstrated HRs of 0.87 (95% CI, 0.77-0.95; *P* = .04) for those who had bilateral large drusen at baseline and 0.96 (95% CI, 0.83-1.11; *P* = .59) for those with late AMD in 1 eye (Figure 1). For the development of neovascular AMD in the comparison of lutein/zeaxanthin vs no lutein/zeaxanthin, the results included HRs of 0.80 (95% CI, 0.68-0.95; *P* = .01) and 1.02 (95% CI, 0.86-1.21; *P* = .79) for bilateral large drusen and late AMD in 1 eye at baseline, respectively (Figure 1). Again, when comparing lutein/zeaxanthin vs no lutein/zeaxanthin for the development of CGA, the results included HRs of 0.94 (95% CI, 0.78-1.13; *P* = .51) and 0.85 (95% CI, 0.64-1.13; *P* = .27) for bilateral large drusen and late AMD in 1 eye at baseline, respectively (Figure 2).

**Progression Along the AREDS AMD Scale**

A detailed severity scale for AMD progression was developed using the AREDS data.<sup>28</sup> A prespecified analysis compared lutein/zeaxanthin vs no lutein/zeaxanthin for progression along the scale or the development of late AMD. Eyes with the most severe stages of AMD at baseline (steps 10 and 11, which indicated CGA and neovascular AMD, respectively) were excluded from these analyses. Comparison of lutein/zeaxanthin vs no lutein/zeaxanthin for progression along the

Figure 3. Comparisons of Treatments



A, Comparison of lutein/zeaxanthin vs no lutein/zeaxanthin for effects on visual acuity (VA) loss ( $\geq 10$  letters,  $\geq 15$  letters, and  $\geq 30$  letters lost compared with baseline) and the development of VA worse than 20/100. B, Comparison of lutein/zeaxanthin plus AREDS supplement without beta carotene (BC) vs AREDS formulation with beta carotene (without lutein/zeaxanthin) on VA outcomes. ATS indicates AREDS-type supplement.

AREDS AMD scale showed a HR of 0.96 (95% CI, 0.89-1.03;  $P = .26$ ) for 2 or more step changes. Additionally, in similar analyses restricted to those randomly assigned to lutein/zeaxanthin and AREDS supplements minus beta carotene vs no lutein/zeaxanthin and AREDS supplements with beta carotene, a HR of 0.87 (95% CI, 0.77-0.98;  $P = .03$ ) was found for 2 or more step progression. Similar analyses that evaluated various combinations of lutein/zeaxanthin plus beta carotene vs beta carotene alone were supportive of lutein/zeaxanthin (data not shown).

### Visual Acuity Outcomes

The prespecified secondary analyses of lutein/zeaxanthin vs no lutein/zeaxanthin for outcomes were vision loss with a decrease in VA from baseline of 15 or more letters and vision loss of 10 or more letters from baseline and demonstrated no apparent treatment effect, with HRs of 1.01 (95% CI, 0.93-1.09;  $P = .81$ ) and 0.97 (95% CI, 0.88-1.06;  $P = .47$ ) for a loss of 10 or more letters and a loss of 15 or more letters, respectively (Figure 3A). Exploratory comparisons of lutein/zeaxanthin vs no lutein/zeaxanthin for vision loss of 30 or more letters from baseline or the need for AMD treatment and for VA worse than 20/100 or the need for treatment resulted in HRs of 0.94 (95% CI, 0.84-1.05;  $P = .29$ ) and 0.93 (95% CI, 0.84-1.04;  $P = .20$ ), respectively.

The exploratory comparison of lutein/zeaxanthin and the AREDS formulation without beta carotene vs AREDS formulation with beta carotene for the various VA outcomes are demonstrated in Figure 3B. Those comparisons of the head-to-head analyses of lutein/zeaxanthin vs beta carotene favored lutein/zeaxanthin for reducing the VA loss from baseline.

### Discussion

In this large, multicentered, placebo-controlled randomized clinical trial of people at high risk for developing late AMD, daily

additional supplementation with lutein/zeaxanthin and omega-3 LCPUFAs (DHA/EPA) combined with modified versions of the AREDS formulation showed no clinically or statistically significant overall effect on progression to late AMD in the primary analyses. Because DHA/EPA and the varying doses of zinc appeared to have no apparent effect on the outcome,<sup>22</sup> the prespecified comparison of those taking and not taking lutein/zeaxanthin (main-effects analysis) was appropriate.

This prespecified main-effects analysis demonstrated a favorable effect of lutein/zeaxanthin for progression to late AMD. Other prespecified analyses included the main effects of lutein/zeaxanthin on progression along the AMD scale and on VA outcomes of losses of 10 or more letters or 15 or more letters from baseline. Visual acuity outcomes showed no difference, while the remaining results generally favored lutein/zeaxanthin.

Exploratory analyses included stratified analyses by baseline AMD status and progression to the 2 forms of late AMD. Other exploratory analyses included the comparison of the secondary randomization of participants assigned to various combinations of the carotenoids (lutein/zeaxanthin plus the AREDS formulation with or without beta carotene vs AREDS with beta carotene) for progression to the 2 forms of late AMD, severe visual loss outcomes, and progression along the AMD scale. The pure head-to-head exploratory analyses of lutein/zeaxanthin alone vs beta carotene alone showed beneficial effects of lutein/zeaxanthin for reducing progression to late AMD particularly neovascular AMD. These data were further strengthened by the additional analyses of comparison of those assigned to lutein/zeaxanthin plus beta carotene vs beta carotene alone because lutein/zeaxanthin was again beneficial in reducing the risk for late AMD and neovascular AMD. These analyses suggest that beta carotene does not contribute to a synergistic effect to lutein/zeaxanthin because of similar point estimates in favor of lutein/zeaxanthin in these comparisons. Additional exploratory analyses of lutein/zeaxanthin plus the AREDS formulation with beta

carotene vs lutein/zeaxanthin plus AREDS without beta carotene revealed a HR of 1.00 (95% CI, 0.84-1.19). These analyses support the notion that lutein/zeaxanthin may be an important carotenoid to consider for the AREDS supplement.

When the analyses were conducted to evaluate the treatment effect on the 2 forms of late AMD, there was a trend toward a reduction particularly in the rates of development of neovascular AMD, although the lower rates of development of CGA in AREDS2 may have limited our power to evaluate the treatment effect on geographic atrophy. Similarly in AREDS, the long-term assessment of the beneficial effects of the AREDS formulation was most prominent in preventing the development of neovascular AMD.<sup>4</sup> It is plausible that the AREDS formulation and the addition of lutein/zeaxanthin did not have any effect on geographic atrophy. The AREDS long-term follow-up data<sup>30</sup> demonstrated that 30% of participants with geographic atrophy will develop neovascular AMD in 5 years, further providing evidence for participants with geographic atrophy to consider taking the AREDS formulation.

Additional exploratory analyses restricted to AREDS2 participants with bilateral large drusen at baseline also pointed toward a beneficial effect of lutein/zeaxanthin for progression to late AMD but not for participants with baseline late AMD in 1 eye. Inadequate sample size may be a reason for different results based on baseline AMD status or it may be owing to problems with subgroup analyses. In contrast, in the original AREDS, the beneficial effect of the AREDS formulation was demonstrated in the subgroup analyses of those participants with late AMD in 1 eye at baseline. Based on current clinical data, it would be difficult to speculate whether there is a different mechanism of action with progression to late disease in participants who had different baseline AMD severities.

In AREDS, there was also an accompanying statistically significant reduction in VA loss in those assigned to the AREDS formulation, while the beneficial effect of lutein/zeaxanthin was evident only in the AREDS2 exploratory analyses of the more severe VA loss. This may be partially explained by the introduction of anti-vascular endothelial growth factor therapy for neovascular AMD since the start of AREDS2 resulting in less vision loss. The comparison group of the AREDS cohort was a true placebo group, while the AREDS2 comparison group included participants taking the AREDS formulation. This may account for VA improvements evident in AREDS.

In analyses restricted to nonsmokers, incident lung cancers were more frequent in the AREDS participants assigned beta carotene (28 of 1348 [2.1%]) than those not assigned to beta

carotene (11 of 1341 [0.9%]) ( $P = .04$ ;  $\chi^2$  goodness-of-fit test for equal proportions).<sup>22</sup> Of those who developed lung cancer, 91% were former smokers. We specifically evaluated the rate of incident lung cancer in all participants including smokers. There were similar rates of lung cancer in the lutein/zeaxanthin and no-lutein/zeaxanthin groups (33 of 2123 [1.6%] vs 31 of 2080 [1.5%];  $P = .80$ ), with 62% occurring in former smokers in both treatment arms. These data, combined with results from previous studies, suggest that beta carotene supplements should not be recommended for current or former smokers, who comprise a large proportion of the population older than age 60 years. In AREDS and AREDS2, 50% were former smokers and 7% to 13% were current smokers. Estimates of the proportion of smokers and former smokers in population-based studies exceed 50% and the proportion of current smokers may be as high as 25%.<sup>31-34</sup> Providing an AREDS formulation without beta carotene would eliminate the risk for lung cancer that is associated with beta carotene supplementation.

The strengths of this study included the high statistical precision for our primary outcomes, low rates of losses to follow-up, and consistently good adherence to the treatment regimen. There were several limitations of this study. Generalizability of our results may be limited because the AREDS2 population appeared to be well nourished with above-average intake of dietary nutrients. Another major limitation of this report was that it was largely based on exploratory analyses in the face of negative primary study results. Multiple comparisons were conducted without adjustments. Whether a more stringent 99% confidence bounds should have been performed is balanced by the fact that an individual association cannot be more or less likely to be caused by chance based on how many other associations were assessed.<sup>35,36</sup> Ultimately, we reported both significant and nonsignificant findings along with corresponding confidence intervals and  $P$  values. The interpretations of the results were based not just on the  $P$  values but also on previous analyses of nutrition and AMD and biologic plausibility of the results. When all subgroup analyses that evaluated the effect of lutein/zeaxanthin supplementation on progression to late AMD were inspected, point estimates were uniformly in the direction of a protective effect. For safety reasons, especially for current and former smokers, it is important to have an AREDS-type formulation without beta carotene. The totality of evidence on the beneficial and adverse effects from AREDS2 and other studies suggest that lutein/zeaxanthin could be more appropriate than beta carotene for the new AREDS2 formulation.

#### ARTICLE INFORMATION

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**Study supervision:** Chew, Clemons, SanGiovanni, Danis, Ferris, Elman, Bressler, Friberg, Wong, Toth.

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