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A Randomized, Placebo-Controlled, Clinical Trial of High-Dose Supplementation With Vitamins C and E, Beta Carotene, and Zinc for Age-Related Macular Degeneration and Vision Loss:

AREDS Report No. 8

Age-Related Eye Disease Study Research Group

Abstract

Background—Observational and experimental data suggest that antioxidant and/or zinc supplements may delay progression of age-related macular degeneration (AMD) and vision loss.

Objective—To evaluate the effect of high-dose vitamins C and E, beta carotene, and zinc supplements on AMD progression and visual acuity.

Design—The Age-Related Eye Disease Study, an 11-center double-masked clinical trial, enrolled participants in an AMD trial if they had extensive small drusen, intermediate drusen, large drusen, noncentral geographic atrophy, or pigment abnormalities in 1 or both eyes, or advanced AMD or vision loss due to AMD in 1 eye. At least 1 eye had best-corrected visual acuity of 20/32 or better. Participants were randomly assigned to receive daily oral tablets containing: (1) antioxidants (vitamin C, 500 mg; vitamin E, 400 IU; and beta carotene, 15 mg); (2) zinc, 80 mg, as zinc oxide and copper, 2 mg, as cupric oxide; (3) antioxidants plus zinc; or (4) placebo.

Main Outcome Measures—(1) Photographic assessment of progression to or treatment for advanced AMD and (2) at least moderate visual acuity loss from baseline (≥ 15 letters). Primary analyses used repeated-measures logistic regression with a significance level of .01, unadjusted for covariates. Serum level measurements, medical histories, and mortality rates were used for safety monitoring.

Results—Average follow-up of the 3640 enrolled study participants, aged 55–80 years, was 6.3 years, with 2.4% lost to follow-up. Comparison with placebo demonstrated a statistically significant odds reduction for the development of advanced AMD with antioxidants plus zinc (odds ratio [OR], 0.72; 99% confidence interval [CI], 0.52–0.98). The ORs for zinc alone and antioxidants alone are 0.75 (99% CI, 0.55–1.03) and 0.80 (99% CI, 0.59–1.09), respectively. Participants with extensive small drusen, nonextensive intermediate size drusen, or pigment abnormalities had only a 1.3% 5-year probability of progression to advanced AMD. Odds reduction estimates increased when these 1063 participants were excluded (antioxidants plus zinc: OR, 0.66; 99% CI, 0.47–0.91; zinc: OR, 0.71; 99% CI, 0.52–0.99; antioxidants: OR, 0.76; 99% CI, 0.55–1.05). Both zinc and antioxidants plus zinc significantly reduced the odds of developing advanced AMD in this higher-risk group. The only statistically significant reduction in rates of at least moderate visual acuity loss occurred in persons assigned to receive antioxidants plus zinc

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For a list of the Principal Investigators and the AREDS Research Group, see the box on page 1434. The AREDS investigators have no commercial or proprietary interest in the supplements used in this study.

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(OR, 0.73; 99% CI, 0.54–0.99). No statistically significant serious adverse effect was associated with any of the formulations.

Conclusions—Persons older than 55 years should have dilated eye examinations to determine their risk of developing advanced AMD. Those with extensive intermediate size drusen, at least 1 large druse, noncentral geographic atrophy in 1 or both eyes, or advanced AMD or vision loss due to AMD in 1 eye, and without contraindications such as smoking, should consider taking a supplement of antioxidants plus zinc such as that used in this study.

Age-related macular degeneration (AMD) is the leading cause of visual impairment and blindness in the United States and elsewhere among people 65 years or older.^{1–4} At present, there is no proven treatment that slows or prevents the development of advanced AMD. Laser photocoagulation^{5,6} and photodynamic therapy^{7,8} reduce the risk of either moderate or severe visual acuity loss in some persons with the neovascular form of the disease. Other medical and surgical interventions are under investigation but none has been demonstrated as being effective in a large randomized clinical trial.^{9–13}

Oxidative damage to the retina may be involved in the pathogenesis of AMD.^{14–17} However, data from epidemiological studies^{18–26} as well as small randomized clinical trials^{27–29} do not show consistent associations between intake of antioxidants or zinc and risk of AMD. One small, randomized, 2-year, placebo-controlled clinical trial of zinc supplementation found a statistically significant reduction in visual acuity loss in the zinc-treated group and recommended a more definitive trial before a general recommendation could be made for zinc supplementation in those at risk of vision loss from advanced AMD.²⁷ Despite the lack of convincing evidence, the marketing and use of antioxidants and zinc in eye-targeted formulations has become a common practice.³⁰ Inconsistent evidence from observational studies, the small clinical trial of zinc and AMD, and the public health concern regarding the widespread use of unproven, high-dose antioxidant and zinc supplements for AMD led the National Eye Institute (National Institutes of Health, Bethesda, Md) to incorporate a clinical trial as part of the Age-Related Eye Disease Study (AREDS). This randomized clinical trial was designed to evaluate the effect of high doses of zinc and selected antioxidant vitamins (5 to about 15 times the recommended dietary allowance [RDA]³¹) on the development of advanced AMD in a cohort of older persons.³² This report presents the results of a randomized comparison of the risks and benefits of supplementing with either zinc, antioxidants (vitamins C and E and beta carotene), or the combination of both on the rate of progression to advanced AMD and on visual acuity outcomes.

RESULTS

ENROLLMENT AND PARTICIPANT CHARACTERISTICS

A total of 4757 participants were enrolled in AREDS. The 1117 in AMD Category 1 had few if any drusen. Only 5 of these 1117 participants developed advanced AMD during the course of the study, and we cannot assess the effects of antioxidants in this group on this outcome. Therefore, this report focuses on the 3640 study participants enrolled in the AMD clinical trial. Individual clinical centers enrolled 95 to 414 participants in the AMD clinical trial. Of those enrolled, 1063 had extensive small drusen, pigment abnormalities, or at least 1 intermediate size druse (Category 2); 1621 had extensive intermediate drusen, GA not involving the center of the macula, or at least 1 large druse (Category 3); and 956 had advanced AMD or visual acuity less than 20/32 due to AMD in 1 eye (Category 4). Thirty-one participants had no photographic assessment of AMD during annual study follow-up visits, leaving 3609 participants in whom the effect of intervention on AMD could be assessed. Forty-three participants had no ETDRS visual acuity measurements obtained during follow-up, leaving 3597 participants in whom the effect of intervention on visual

acuity could be assessed. Participants without photographic or visual acuity follow-up were evenly distributed across treatment groups.

Participant characteristics by treatment assignment for the 3609 participants with photographic data available from an AREDS clinic are presented in Table 3. The frequency of these characteristics was similar among the 4 treatment groups and no large or statistically significant differences were found. Fifty-six percent of participants were women, 96% were white, and the median age was 69 years. At baseline 8% were current cigarette smokers and 67% chose to take Centrum, a multivitamin supplement. Of those who elected to take Centrum, 30% had been taking multivitamins or a supplement containing a study ingredient for more than 5 years before study entry. After accounting for age, sex, and race, participants in AREDS had higher or similar dietary intake of vitamins A, C, and E, and zinc than the general population sample from the Third National Health and Nutrition Survey (data not shown).⁴⁴ Baseline dietary intake of the study nutrients was balanced across treatment groups.

DATA QUALITY

Only 2.4% of AREDS participants were lost to follow-up (missed at least their last 2 consecutive visits). Losses to follow-up were balanced across treatment groups. As of the 5-year study visit, 13.6% of participants had withdrawn from their study medication—a figure that includes the 18% of current smokers who withdrew from study medication after the results of the clinical trials of beta carotene and lung cancer were announced. By the end of the trial this increased to 14.7%. Figure 3 shows the number of participants with follow-up and adherence to the study medication regimens by year of follow-up. Overall, adherence was estimated to be 75% or greater (ie, participants took 75% or more of their study tablets) for 71% of the participants at 5 years. At the time of the 5-year study visit, 19% of study participants reported taking some nutritional supplements containing at least 1 of the study medication ingredients in addition to the study medication and Centrum (18% for current smokers and 20% for former or nonsmokers). Four participants (0.1%) were reported to have been unmasked during the trial. Compliance with fundus and lens photography decreased during the course of the study. At the last study visit, 16% of participants did not follow the protocol for photography (missed photographs); 9% of expected photographs were missed in the study overall. Of almost 50000 possible follow-up visits, 10% were missed. The frequency of missed visits and mean follow-up time (6.3 years) did not differ by treatment group. Most participants (90%) had at least 5 years of follow-up.

The network of collaborating, non-AREDS clinic physicians provided data for 42 annual follow-up visits and 7 nonannual follow-up visits made by 28 participants. The results reported do not include these data, although inclusion of this information had no discernible effect on results.

PHOTOGRAPHIC QUALITY

More than 99% of fundus photographs taken during the clinical trial were judged by the reading center to be of gradable quality for the development of advanced AMD.

PRIMARY OUTCOME—PROGRESSION TO ADVANCED AMD

By AMD Category—Figure 4 shows repeated-measures probability estimates of AMD events in at least 1 eye by baseline AMD category for participants in the placebo group and demonstrates that Category 2 participants, with extensive small drusen, pigment abnormalities, or at least 1 intermediate size druse (but not extensive in area), had only a 1.3% probability of progression to advanced AMD by year 5. The 5-year estimated probability of progression to advanced AMD in either eye in participants with extensive

intermediate drusen, large drusen, or noncentral GA (Category 3) was 18%. Within the Category 3 group, half of the participants had large drusen in each eye or noncentral GA in at least 1 eye at enrollment, and these participants were 4 times as likely to progress to advanced AMD (about 27% probability of progression to advanced AMD at 5 years in the placebo group) compared with the remaining Category 3 participants (about 6% probability of progression to advanced AMD at 5 years in the placebo group). Participants with advanced AMD in 1 eye or vision loss due to nonadvanced AMD in 1 eye (Category 4) had a 43% expected probability of progression to advanced AMD in the fellow study eye at 5 years. In the original study design, participants in Categories 2, 3, and 4 were pooled for data analysis and that remains the primary analysis. However, by 5 years there were only 15 AMD events in Category 2 distributed across all 4 treatment groups (3 in the placebo group). The low event rate makes it impossible to assess treatment effects in this category for the AMD outcome and less likely that any of the treatments would be recommended. Therefore, analyses are also presented for those participants most likely to benefit from an effective treatment (Categories 3 and 4).

By Treatment—Figure 5 shows repeated-measures estimates of the probability of progressing to advanced AMD over time by treatment for participants in AMD Categories 3 and 4. At 5 years, the estimated probability of progression to advanced AMD was 28% for those assigned to placebo, 23% and 22% for those assigned to antioxidants and zinc, respectively, and 20% for those assigned to antioxidants plus zinc. Treatment effects, estimated by repeated measures, for progression to advanced AMD for participants in Categories 2, 3, and 4 and in Categories 3 and 4, are presented in Table 4. Results include comparisons of the main effects of antioxidants vs no antioxidants and zinc vs no zinc (interactions between treatments are omitted here and throughout because they were not significant) and comparisons of each of the individual treatments vs placebo. When evaluating main effects, there is a suggestive reduction in the risk of developing advanced AMD for persons assigned to zinc (ie, combining those participants taking zinc alone with those taking zinc plus antioxidants; OR, 0.82; 99% confidence interval [CI], 0.66–1.03), and a nonsignificant effect on persons assigned to antioxidants (ie, combining those participants taking antioxidants alone with those taking antioxidants plus zinc; OR, 0.87; 99% CI, 0.70–1.09). Single-arm comparisons with placebo found risk reductions statistically significant for antioxidants plus zinc and suggestive for the zinc arm but not for the antioxidants arm (antioxidants: OR, 0.80; 99% CI, 0.59–1.09; zinc: OR, 0.75; 99% CI, 0.55–1.03; antioxidants plus zinc: OR, 0.72; 99% CI, 0.52–0.98).

The odds reduction increases when the analysis is restricted to participants in Categories 3 and 4, who have more severe AMD (extensive intermediate drusen, large drusen, or noncentral GA in 1 or both eyes or advanced AMD or vision loss due to nonadvanced AMD in 1 eye) and who are at the highest risk for progression to advanced AMD (antioxidants: OR, 0.76; 99% CI, 0.55–1.05; zinc: OR, 0.71; 99% CI, 0.52–0.99; and antioxidants plus zinc: OR, 0.66; 99% CI, 0.47–0.91). An analysis adjusted for age, sex, race, AMD Category, and smoking status at enrollment did not materially alter the size or direction of these estimates. There was no evidence of significant clinic differences in treatment effect. Results from the Cox proportional hazards model (not shown) are consistent with observations from the repeated-measures analysis.

PRIMARY OUTCOME—VISUAL ACUITY LOSS

Figure 6 shows repeated-measures estimates of the probability of at least a 15-letter decrease in the visual acuity score between baseline and each follow-up visit (equivalent to at least a doubling of the initial visual angle) in at least 1 study eye, by treatment, for participants in Categories 3 and 4. At 5 years, the estimated probability of at least a 15-letter decrease in

visual acuity score from baseline was 29% for those assigned to placebo, 26% for those assigned to antioxidants, 25% for those assigned to zinc, and 23% for those assigned to antioxidants plus zinc. Treatment effects are tested using repeated measures and results for all participants in the AMD trial and for participants in Categories 3 and 4 only are presented in Table 5. Comparisons of zinc vs no zinc and antioxidants vs no antioxidants (main effects) showed no statistically significant treatment difference. The antioxidants plus zinc arm (OR, 0.79; 99% CI, 0.60–1.04) showed a suggestive reduction compared with placebo in the risk of visual acuity loss of 15 letters or more, among participants in Categories 2, 3, and 4. There were 175 visual acuity events in participants in Category 2. However, only 13 of these events (7%) were thought by the examining ophthalmologist to be primarily related to macular degeneration. In addition, an advanced AMD event simultaneously occurred with vision loss during at least 1 visit in only 15 of these participants (9%). In an analysis restricted to participants in Categories 3 and 4, whose vision loss was more likely to be associated with progression of AMD, the combination of antioxidants plus zinc statistically significantly reduced the odds of visual acuity loss (OR, 0.73; 99% CI, 0.54–0.99). There are trends that favor treating with zinc alone or antioxidants alone but no statistically significant differences. Comparisons between the group taking the combination of antioxidants plus zinc with the groups taking either zinc or antioxidants were not statistically significant but favor the combination arm (combination vs zinc alone: OR, 0.88; 99% CI, 0.65–1.18; combination vs antioxidants alone: OR, 0.86; 99% CI, 0.63–1.16) (data not shown). An analysis adjusted for age, sex, race, AMD category, and baseline smoking status did not materially alter the size or direction of these OR estimates. Results from an analysis of mean change in visual acuity (data not shown) were consistent with results from the repeated-measures analysis.

Figure 7 shows the proportion of participants in AMD Categories 3 and 4 with evidence of at least a 15-letter decrease in visual acuity in at least 1 study eye at each year of follow-up for participants followed that year without regard to follow-up or visual acuity status at earlier or later years. The antioxidants plus zinc arm had proportionally fewer participants with visual acuity loss at each follow-up visit. Participants assigned to receive zinc or antioxidants also have fewer events than participants assigned to placebo but had a higher proportion of events than participants assigned to antioxidants plus zinc, beginning around year 3.

SECONDARY OUTCOMES

Several secondary visual acuity and AMD outcomes were analyzed to examine the consistency of observed findings with the primary outcomes. Analysis of secondary outcomes is restricted to Categories 3 and 4. Figure 8 shows a summary of the ORs and 99% CIs for each of the treatments compared with placebo for the visual acuity primary and secondary outcomes and the AMD primary and secondary outcomes, respectively.

Other Visual Acuity Outcomes

Visual Acuity Loss Attributable to AMD: An analysis of the development of advanced AMD, coincident with a decrease in visual acuity from baseline of at least 15 letters, in study participants in Categories 3 and 4 is presented in Table 6 (Categories 3 and 4 combined and separately). For participants in Categories 3 and 4, the OR estimates for this combined outcome for the antioxidants arm and the zinc arm compared with placebo are 0.79 (99% CI, 0.55–1.13) and 0.75 (99% CI, 0.53–1.07), respectively. An OR estimate of 0.63 (99% CI, 0.44–0.92) was obtained for the antioxidants plus zinc vs placebo contrast. The OR for antioxidant plus zinc vs placebo estimated separately for participants in Categories 3 (OR, 0.76; 99% CI, 0.45–1.30) and 4 (OR, 0.52; 99% CI, 0.31–0.89) is in the direction of benefit for both groups.

Marked Visual Acuity Loss: Visual acuity in all study eyes was 20/32 or better at baseline. Twenty percent of participants in Categories 3 and 4 experienced a decrease in visual acuity to worse than 20/100 in at least 1 eye. The estimated 5-year probability of this severe vision event from repeated-measures analysis was 17% for participants assigned to placebo compared with 14% for those assigned to antioxidants (OR, 0.80; 99% CI, 0.55–1.16), 13% to zinc (OR, 0.75; 99% CI, 0.52–1.08), and 12% to antioxidants plus zinc (OR, 0.68; 99% CI, 0.46–1.01). The 5-year probability estimate of bilateral visual acuity worse than 20/100 in Category 3 participants assigned to placebo was 11% and was 10% for antioxidants plus zinc (antioxidants plus zinc: OR, 0.86; 99% CI, 0.50–1.49). For Category 4 placebo participants the 5-year probability estimate was 28% and 17% for antioxidants plus zinc (antioxidants plus zinc: OR, 0.53; 99% CI, 0.30–0.94) (data not shown).

The estimated 5-year probability of a 6-line (30-letter) loss in visual acuity from the baseline score was 18% for participants assigned to placebo compared with 15% for participants assigned to either zinc (OR, 0.78; 99% CI, 0.55–1.12) or antioxidants (OR, 0.78; 99% CI, 0.55–1.12), and 13% for participants assigned to antioxidants plus zinc (OR, 0.67; 99% CI, 0.46–0.98).

Visual Acuity Loss in Eyes with Advanced AMD at Baseline: Separate repeated-measures analyses were performed to assess whether study formulations would reduce the risk of losing 15 or more letters in the Category 4 eyes with neovascular AMD at baseline (nonstudy eye). Results are presented in Table 7. Analyses were restricted to eyes without GA at baseline (because there were too few eyes with GA) and with a baseline visual acuity of 20/100 or better (visual acuity score of 49 or more, n=260) and separately for eyes with visual acuity of 20/200 or better (visual acuity score of ≥ 34 , n=352). Odds ratio estimates showed protection for all treatment formulations (antioxidants: OR, 0.35; 99% CI, 0.15–0.81 and OR, 0.56; 99% CI, 0.27–1.13, respectively; zinc: OR, 0.65; 99% CI, 0.28–1.50 and OR, 0.93; 99% CI, 0.46–1.89, respectively; antioxidants plus zinc: OR, 0.53; 99% CI, 0.23–1.24 and OR, 0.72; 99% CI, 0.36–1.46, respectively). The largest benefit was seen for the antioxidants arm but the differences between treatments were not statistically significant.

Components of Advanced AMD—Analyses of the components of the AREDS definition of advanced AMD, neovascular disease development and GA involving the center of the macula, were performed on participants in Categories 3 and 4. Results are presented in Table 8.

Development of Neovascular AMD: Five hundred ninety-two participants developed neovascular disease. A statistically significant benefit of treatment with antioxidants plus zinc compared with placebo was observed for neovascular AMD outcomes in participants in Categories 3 and 4 (OR, .62; 99% CI, 0.43–0.90). Benefit was statistically significant for the zinc vs no zinc main effect (OR, 0.76; 99% CI, 0.58–0.98), was suggestive for the zinc-alone arm (OR, 0.73; 99% CI, 0.51–1.04), and was not significant for antioxidants alone (OR, 0.79; 99% CI, 0.56–1.13).

Development of GA in the Center of the Macula: Among participants in Categories 3 and 4, an analysis of each treatment compared with placebo for the 257 participants who developed central GA in an eye prior to any documentation of neovascular disease in that eye resulted in OR estimates of 0.80 (99% CI, 0.48–1.32) for antioxidants; 0.76 (99% CI, 0.46–1.27) for zinc; and 0.75 (99% CI, 0.45–1.24) for antioxidants plus zinc. None of the ORs were statistically significant but all were in the direction of a benefit from treatment. The magnitude and direction of the treatment effect was similar to the analyses presented for the primary outcome variables and for a neovascular AMD event; however, the number of GA events was considerably lower (592 with any neovascular event vs 257 with GA events)

and the study has only about 40% power to demonstrate a statistically significant OR of 0.75 for one of the treatment arms vs placebo.

During the study, 407 participants without GA at baseline developed at least moderate GA (>360 μm) not necessarily involving the center of the macula. An analysis of treatment effect showed no significant difference; OR estimates are 0.86 (99% CI, 0.55–1.34) for antioxidants, 1.13 (99% CI, 0.74–1.74) for zinc, and 1.08 (99% CI, 0.70–1.65) for antioxidants plus zinc (data not shown).

Progression of AMD in Category 2 Participants—Only 28 participants of the 1063 who began the study in Category 2 progressed to advanced AMD in at least 1 eye at the end of follow-up (15 by year 5). Three hundred sixteen Category 2 participants progressed to Categories 3 or 4. There is no evidence of treatment benefit in delaying the progression of AMD in participants who began the study in Category 2; all OR estimates cluster around 1.00 (data not shown).

ADHERENCE

Serum Levels—Table 9 presents the median baseline value and median percent change from baseline to the 1 and 5 year follow-up examinations for each ingredient of the study treatment as well as for alpha carotene, β -cryptoxanthin, lutein and zeaxanthin combined, vitamin A, and lycopene. Serum levels of each are presented for the 4 treatment groups. These measurements were made at baseline and during follow-up in only 3 of the AREDS clinics on almost 719 participants (88% of those alive at 5 years).

Changes in Serum Levels of Antioxidants and Zinc—Participants assigned to medications containing antioxidants had statistically significant increases in median serum levels from baseline to year 1: about 25% for vitamin C, 82% for vitamin E–cholesterol ratio, and 485% for beta carotene. These increases abated slightly during the 5-year period. Participants assigned to receive study medications not containing antioxidants (placebo and zinc arms) experienced modest median changes during the 5-year period: decreases of 7% and 12% for vitamin C, increases of 6% for vitamin E–cholesterol ratio, and increases of 4% and 0% for beta carotene.

Similarly, participants assigned to medications containing zinc had about an 18% increase in median serum level of zinc from baseline to year 1 and this was maintained during the 5-year period. Participants assigned to receive study medications not containing zinc had small median percent increases in zinc during the same period of 3% and 1%.

These results indicate a definite serum response to each study ingredient. Median percent change in serum level of copper from baseline ranges from a 3% decrease to a 2% increase among all participants regardless of study medication assignment, indicating no differential effect of zinc oxide with added cupric oxide on copper levels.

Changes in Other Serum Levels—Only one of the other serum levels measured had a statistically significant change during follow-up. Participants assigned to receive medications containing antioxidants had a statistically significant increased median percent change in serum levels of alpha carotene from baseline to year 1 of about 43% compared with no change for participants taking nonantioxidant medications. This increase was not seen at year 5 but the difference between the treatments remained significant. Serum levels of lutein and zeaxanthin decreased during the 5-year period, with median percent decreases in year 1 and year 5 of 2% and 13%, respectively, in the placebo arm, and from 7% to 33% in the other treatment arms; however, changes in the treatment arms were not significantly different from the placebo arm ($P>.07$). Vitamin A, β -cryptoxanthin, and lycopene showed

no statistically significant differences in change from baseline by treatment assignment. The effect of Centrum, which contains RDA doses of the study medications, on serum levels of antioxidants and zinc in this population was negligible.

SAFETY OUTCOMES

No clinically or statistically significant difference from baseline in serum levels of cholesterol or hematocrit was observed during the 5-year period (Table 9). In addition, no statistically significant difference between treatment arms in use of lipid-lowering medications at 5 years after enrollment was observed (data not shown). Table 10 presents summaries of the statistically significant differences in safety outcomes (reported cause of hospitalizations, adverse experiences, and self-reported conditions) of nearly 100 comparisons of zinc vs no zinc and antioxidants vs no antioxidants. The analyses were for all participants in the AMD clinical trial who had follow-up examinations.

Potential Adverse Effects—At the time of enrollment, participants were informed of possible adverse effects of and contraindications to the use of study medications: vitamin C (kidney stones), vitamin E (fatigue, muscle weakness, decreased thyroid gland function, increased hemorrhagic stroke risk), beta carotene (yellow skin), zinc (anemia, decreased high-density lipoprotein cholesterol, upset stomach). Participants in the antioxidant arms more frequently reported yellow skin (8.3% vs 6.0%; $P=.008$). Participants in the zinc arms showed an excess of self-reported anemia (13.2% vs 10.2%; $P=.004$) but serum hematocrit levels showed no difference. These few and modest differences are consistent with prestudy information on possible adverse effects but no differences were seen for the other conditions of concern before the study.

Hospitalizations—Hospitalizations were assigned *International Classification of Diseases, Ninth Revision (ICD-9)*⁴⁵ codes based on discharge summaries. Participants in the antioxidant arms were hospitalized less frequently for mild/moderate symptoms, eg, chest pain or discomfort, vasovagal episode, fever (7.4% vs 10.1%; $P=.005$), and more frequently for infections (1.6% vs 0.8%; $P=.04$). Genitourinary hospitalizations (eg, unspecified urinary tract infection and prostatic hyperplasia in men and stress incontinence in women) were more frequent in participants randomized to the zinc arms (7.5% vs 4.9%; $P=.001$ for men and women combined, and 8.6% vs 4.4%; $P=.001$ for men alone). Hospitalizations for mild/moderate symptoms were also more frequent in participants randomized to zinc arms (9.7% vs 7.8%; $P=.04$).

Adverse Experiences—Reported adverse experiences were assigned *ICD-9* codes. Circulatory adverse experiences were less frequent in the antioxidant arms than the nonantioxidant arms (0.3% vs 0.8%; $P=.04$) and more frequently reported in the zinc arms than the nonzinc arms (0.9% vs 0.3%; $P=.01$). Skin and subcutaneous tissue conditions were more frequent in the antioxidant arms (2.2% vs 1.0%; $P=.003$); most participants with these conditions also self-reported yellow skin.

Conditions Reported at Follow-up—Participants in the antioxidant arms less frequently reported chest pains (20.2% vs 23.1%; $P=.03$) when asked at a follow-up visit. Participants assigned to zinc arms more frequently reported difficulty swallowing the study tablets (17.8% vs 15.3%; $P=.04$) compared with participants taking formulations without zinc.

Mortality—Table 11 presents the RR estimates from the Cox proportional hazards model for each treatment. Figure 9 shows Kaplan-Meier estimates of the probability of death for each treatment. For the AMD clinical trial, none of the individual treatments, when

compared with placebo, statistically significantly reduced or increased the risk of mortality ($P \geq .14$ for all treatments). An analysis of zinc vs no zinc suggested a benefit (RR, 0.79; 99% CI, 0.61–1.02). An analysis restricted to participants in Categories 3 and 4 showed similar results (data not shown).

The effect of treatment on mortality stratified by baseline smoking status (current smoker, former smoker, never smoked) found no significant effect of the use of antioxidants alone on mortality for current smokers (RR, 0.99; 99% CI, 0.45–2.17) and a nonsignificant reduction in mortality for the combination arm (RR, 0.61; 99% CI, 0.24–1.56). Relative risks for former smokers were similar to current smokers. For participants who had never smoked, the RR of death for those taking antioxidants alone was increased (RR, 1.57; 99% CI, 0.82–3.02) and suggested no effect on the combination arm (RR, 1.12; 99% CI, 0.56–2.24). The small number of deaths from lung cancer (29 [0.8%]) showed no statistically significant difference by treatment.

COMMENT

Data from AREDS demonstrate that treatment with zinc alone or in combination with antioxidants reduced the risk of progression to advanced AMD in participants in Categories 3 and 4. These categories are defined by extensive intermediate drusen, large drusen, or noncentral GA in 1 or both eyes, or advanced AMD or visual acuity $<20/32$ attributable to AMD in 1 eye. Estimates of RR derived from ORs suggest risk reductions for those taking antioxidants alone or zinc alone of 17% and 21%, respectively. The risk reduction for those taking antioxidants plus zinc was 25%. The probability of developing advanced AMD by 5 years among participants assigned to receive placebo varied within Category 3 from about 27% for those with large drusen in both eyes or with GA not involving the center of the macula in at least 1 eye, to about 6% for the remaining participants in that category. Participants in Category 4 had the highest probability of progression, with an estimated probability of 43% at 5 years.

Too few advanced AMD events occurred in Category 2 participants to assess whether any treatment tested in this study could slow the progression to advanced AMD for participants with milder drusen and retinal pigment epithelial abnormalities. This predefined group of participants adds virtually no information to the treatment comparisons. Removing this group provides more appropriate estimates of odds reductions within participants at risk for development of advanced AMD. There was no statistically significant evidence of a benefit in delaying the progression of Category 2 eyes to more severe drusen pathology (eg, moving from Category 2 at baseline to Categories 3 or 4 during follow-up). One of the original and continuing goals of AREDS is to develop severity scales for AMD similar to those for diabetic retinopathy, and to use such scales to assess whether treatment slows the progression from earlier to more advanced stages of AMD.

The apparent treatment benefit of antioxidants plus zinc and zinc alone was present for each of the events predefined in the study protocol to be signs of advanced AMD (development of signs of neovascular AMD, accounting for 70%–80% of events, and development of central GA). There was a nonstatistically significant trend for an increase in the risk of developing GA away from the center of the macula in the zinc and antioxidant plus zinc treatment groups compared with the placebo-treated group. Because the increase is not statistically significant and is contrary to the primary outcome of development of GA at the center, its explanation and importance are unclear.

The clinical importance of the reduction in the development of advanced AMD is enhanced by a corroborating effect on visual acuity. Compared with the placebo group, only the

participants in Categories 3 and 4 assigned to antioxidants plus zinc had a statistically significant reduction in the odds of a 15-letter or greater visual acuity decrease ($P=.008$). Findings of AREDS suggest that the estimated 27% odds reduction in the visual acuity outcome for the combination arm may be the combined benefit of the zinc component (odds reduction of 17%) and the antioxidant component (odds reduction of 15%). The visual acuity benefit observed for the combination arm remains consistent for other, more severe, visual acuity outcomes, such as visual acuity worse than 20/100 or a decrease in visual acuity of 6 lines or more.

Although not a predefined outcome, a composite event was created to estimate risk reduction when advanced AMD and a loss of at least 15 letters in visual acuity were observed concurrently. This event definition resulted in estimates of odds reductions of about 25% for zinc and 37% for zinc plus antioxidants for participants in Categories 3 and 4 combined. Odds reductions for the antioxidants plus zinc treatment were 24% for Category 3 participants and 48% for Category 4 participants. This analysis suggests that the reduction in risk of visual acuity loss observed with the antioxidant plus zinc formulation may be a result of the reduction in risk of progression to advanced AMD. The AREDS clinical trial of cataract found no effect of treatment on the development of lens opacity,⁴⁶ and the proportion of participants with cataract surgery in 1 or both eyes during the study was balanced across treatment groups. It is unlikely that differential treatment effects on lens opacity are affecting this visual acuity result.

Two other trials assessed supplementation for patients with AMD. A small randomized trial, completed before AREDS began, suggested a benefit of large doses of zinc on visual acuity in persons with AMD.²⁷ For zinc alone, AREDS did not find a statistically significant reduction in the odds of a 15-letter visual acuity loss. The proportion of participants in the zinc arm with a visual acuity loss of at least 15 letters draws closer to the placebo arm by 7 years. Results from another randomized trial reported that after 4 years of supplementation, 500 IU per day of vitamin E had little benefit in reducing the risk of development or progression of AMD in a population of 1193 volunteers.⁴⁷ There were few advanced AMD events in the latter study. Their results may be consistent with the AREDS finding of little or no treatment effect in slowing the progression of AMD in Category 2 participants.

Fifty-seven percent of AREDS participants were using a multivitamin or at least 1 ingredient found in the AREDS formulation at the time of their AREDS screening examination. About half of those supplementing were taking RDA doses rather than the 5- to about 15-fold higher doses of the AREDS ingredients. To accommodate these persons within the AREDS clinical trial and to standardize the use of nonstudy supplements, Centrum without lutein, a widely available multivitamin/mineral preparation with RDA-level dosages, was provided to each participant who wanted to take or continue to take a daily multivitamin. Approximately 67% of participants chose to take Centrum (about 13% of the AREDS participants who were not taking vitamins at the start of the study decided to take a multivitamin along with the study medication, perhaps because they were enrolling in this long-term study assessing the effects of vitamins and minerals). Thus, in addition to their dietary intake of vitamins C and E, beta carotene, and zinc, these persons had an increase in their intake by approximately 100% of the RDA for each of the study ingredients whether assigned to placebo or active intervention. Any increase in serum levels resulting from this intake was negligible compared with serum increases from the use of the study supplements. The statistical power of the study to test its primary hypothesis about high doses of the study ingredients might have been reduced to the extent that prior use or the continued use of RDA doses of these nutrients or other nutrients in the Centrum formulation affect the risk of AMD development. The treatment effect of the study formulations was in the beneficial direction for both AMD and visual acuity outcomes both in the group of participants choosing to supplement with

Centrum at baseline and in the group not choosing Centrum at baseline (data not shown). However, these comparisons are underpowered and the choice to use Centrum was confounded by the presence of AMD at study entry.

Estimated pill counts showed that most patients took 75% or more of the assigned medications and adherence was balanced by treatment. These estimates suggest good adherence to the medication regimens, and this is supported by data showing that serum levels of each of the vitamins or minerals in the assigned study formulations in participants enrolled in the 3 AREDS clinics collecting specimens were elevated throughout the study. Tissue levels of the vitamins and minerals studied were not measured.

Possible differences between treatment groups and the placebo group were assessed for approximately 100 adverse events. The limited number of imbalances in the incidence of adverse events that were observed could be real or due to chance. The following 3 imbalances are notable ($P < .01$): an increase in hospitalization for genitourinary symptoms and an increase in self-reported anemia in persons assigned to receive zinc formulations; and an increase in yellowing of skin in persons assigned to receive antioxidants. A subset of participants was monitored for lipid and copper levels and the entire cohort was monitored for hematocrit because of potential concerns about the high doses of zinc given. Although there was an increase in self-reported anemia, no statistically significant effect of zinc supplements on hematocrit or serum levels of lipids or copper was observed. We have followed participants for an average of 6.3 years and have observed no serious consequence but we do not know the longer-term health effects of supplementation with these high doses of vitamins and minerals. Following the unmasking of study participants, all consenting participants will be followed for at least another 5 years.

Mortality in AREDS is about half that of the comparable general population.⁴⁸ Early in the trial, a nonstatistically significant increase in mortality was observed among participants assigned to the antioxidants-alone arm. Results from 2 other randomized clinical trials suggested increased risk of mortality among smokers supplementing with beta carotene. The data and safety monitoring committee recommended that smokers discontinue study medications containing beta carotene. At the time of study enrollment, only 8% of AREDS participants were smokers and 49% were former smokers. Early imbalances in mortality were observed regardless of smoking status. Results to date find no statistically significant deleterious effect of antioxidants on mortality, although the RR estimate remains in the direction of harm for participants who had never smoked. Whether there is a true increase in risk cannot be confirmed by AREDS. The observation of a reduction in mortality associated with zinc arms compared with nonzinc arms may be somewhat exaggerated by the apparent nonstatistically significant increase in mortality observed for the antioxidants-alone arm. Comparison of zinc or zinc plus antioxidants with placebo was not significant ($P \geq .14$). Mortality risk in the antioxidants plus zinc arm was lower than in the placebo arm but this difference is also not statistically significant.

The antioxidant formulation included only 3 antioxidants: beta carotene, vitamin E, and vitamin C. Individual effects of each of these components cannot be evaluated. Two carotenoids, lutein and zeaxanthin, were considered for inclusion in the formulation during the planning phase because they are concentrated in the macula.⁴⁹ However at AREDS initiation, neither carotenoid was readily available for manufacturing in a research formulation. Beta carotene, another carotenoid with antioxidant potential, was included because it was readily available and under investigation in clinical trials of heart disease and cancer. The dose of beta carotene used in this study was 15 mg/d. Other studies using similar doses of beta carotene in persons at high risk for lung cancer (cigarette smokers and asbestos workers) have demonstrated an increased incidence of cancer and mortality in

persons assigned to beta carotene supplementation.⁴²⁻⁴³ Persons who smoke are at increased risk for both AMD⁵⁰ and lung cancer. Whether the benefits of a formulation that contains beta carotene for AMD outweigh the increased risk of lung cancer cannot be determined from this study and it may be prudent for smokers to avoid taking beta carotene. Lutein and zeaxanthin may be beneficial to macular health⁵¹ but whether they can be substituted for beta carotene cannot be answered by AREDS. The dose of vitamin C (500 mg) used in the formulation is about 5 times what the general population receives from diet alone.⁴⁴ The 400-IU dose of vitamin E is about 13 times the RDA and the dose of zinc as zinc oxide is about 5 times the RDA. These levels of zinc and vitamins C and E generally can be obtained only by supplementation.

When interpreting AREDS data, several factors should be considered. First, as is often the case in prevention studies, the population participating in this study may differ from the general population. The AREDS participants were relatively well-nourished compared with the general population, and the effect of this and other differences on the generalizability of AREDS findings is unknown. Second, the AREDS retinal outcomes are based on color fundus photography rather than on fluorescein angiography or clinical examinations. Using fundus photographs without fluorescein angiography to identify advanced AMD may delay the identification of advanced AMD events and may underestimate the absolute incidence. Most cases are identified with long-term follow-up and the assessment of the outcome is identical in each randomized treatment group. Third, for data in this study OR reductions are greater than estimates of RR reductions. Finally, it is not known how long someone at risk for advanced AMD should use supplements. Data from AREDS suggest that the combination therapy confers a treatment benefit for AMD and visual acuity outcomes that is maintained through 7 years of follow-up in participants at risk for progression to advanced AMD. The treatment benefit is modest and participants in all treatment arms continue to progress to advanced AMD and lose vision over time.

AREDS was designed to assess whether active treatment with antioxidants and/or zinc could reduce the risk of developing advanced AMD. The results are consistent in demonstrating that, compared with the placebo group, participants in Categories 3 and 4 assigned to receive antioxidants plus zinc had the largest reduction of the risk of developing advanced AMD or visual acuity loss. Participants assigned to receive either zinc or antioxidants seem to have a lesser benefit from the study medication. The study was not powered to assess whether there were differences between apparently effective treatments.

Who should consider long-term supplementation with zinc and antioxidants? The results of AREDS to date demonstrate no benefit of the study formulations for persons in Categories 1 or 2. For Americans older than age 70, approximately 80% fall in these low-risk groups.³⁷ In AREDS, persons in these categories had low rates of progression to advanced AMD (1.3% in 5 years for Category 2 and <1% for Category 1) and therefore the study has very low power to assess the effect of these treatments on the development of advanced AMD. With these low rates it seems reasonable to defer consideration of supplementation until the risk of progression is higher, especially because analyses to date do not show that treatment is effective in slowing the progression of AMD from Category 2 to Categories 3 or 4. Whether supplementation benefits persons who already have advanced neovascular AMD in both eyes is not clear and this study was not designed to address this question. There is limited evidence from AREDS that supplements may delay further visual acuity loss in some of these more advanced eyes (Table 7) but further study of this outcome is needed.

Although both zinc and antioxidants plus zinc significantly reduce the odds of developing advanced AMD for participants in Categories 3 and 4, the only statistically significant reduction in rates of at least moderate visual acuity loss occurred in persons assigned to

antioxidants plus zinc. When considering long-term supplementation, some people may have reason to avoid 1 or more of the ingredients evaluated in AREDS. Persons who smoke cigarettes should probably avoid taking beta carotene, and they might choose to supplement with only some of the study ingredients. The effect of using zinc supplementation alone can be estimated from these data but the effect of using only some of the antioxidants or substituting other antioxidants, such as lutein, cannot be determined.

Based on data from AREDS, persons older than 55 years should have dilated eye examinations to determine their risk of developing advanced AMD. Those with extensive intermediate size drusen, at least 1 large druse, or noncentral GA in 1 or both eyes or those with advanced AMD or vision loss due to AMD in 1 eye, and without contraindications such as smoking, should consider taking a supplement of antioxidants plus zinc such as that used in this study.

PARTICIPANTS AND METHODS

STUDY POPULATION

Details of the study design and methods presented elsewhere³² are briefly summarized here. Eleven retinal specialty clinics enrolled participants aged 55 to 80 years from November 13, 1992, through January 15, 1998, and followed them in the clinical trial until April 16, 2001. Potential participants were identified from the following sources: medical records of patients being seen at AREDS clinics, referring physicians, patient lists from hospitals and health maintenance organizations, public advertisements, friends and family of study participants and clinical center staff, and screenings at malls, health fairs, senior citizen centers, and other gathering places.

All participants had a best-corrected visual acuity of 20/32 or better in at least 1 eye (the study eye[s]). Visual acuity was assessed by certified examiners using the ETDRS logMAR chart and a standardized refraction and visual acuity protocol (*AREDS Manual of Operations*; The EMMES Corporation, Rockville, Md). Persons were enrolled in 4 AMD categories determined by the size and extent of drusen and retinal pigment epithelial abnormalities in each eye,³³ the presence of advanced AMD (each determined by evaluation of color photographs at a reading center³⁴), and visual acuity as presented in Table 1. Briefly, persons in Category 1 were essentially free of age-related macular abnormalities, with a total drusen area less than 5 small drusen (<63 μm), and visual acuity of 20/32 or better in both eyes. Category 2 participants had mild or borderline age-related macular features (multiple small drusen, single or nonextensive intermediate drusen [63–124 μm], pigment abnormalities, or any combination of these) in 1 or both eyes, and visual acuity of 20/32 or better in both eyes. Category 3 required absence of advanced AMD in both eyes and at least 1 eye with visual acuity of 20/32 or better with at least 1 large druse (125 μm), extensive (as measured by drusen area) intermediate drusen, or geographic atrophy (GA) that did not involve the center of the macula, or any combination of these. Category 4 participants had visual acuity of 20/32 or better and no advanced AMD (GA involving the center of the macula or features of choroidal neovascularization) in the study eye, and the fellow eye had either lesions of advanced AMD or visual acuity less than 20/32 and AMD abnormalities sufficient to explain reduced visual acuity as determined by examination of photographs at the reading center. Persons aged 55 to 59 years were eligible only if they were in Category 3 or 4. Figure 1 shows photographic examples of eyes of persons in Categories 2 and 3.

Individuals were not enrolled unless the ocular media were sufficiently clear, as determined by reading center review, to obtain adequate quality stereoscopic fundus photographs of the macula in all potential study eyes. At least 1 eye of each participant had to be free from any

eye disease that could complicate assessment of AMD, lens opacity progression, or visual acuity (eg, optic atrophy, acute uveitis), and that eye could not have had previous ocular surgery (other than cataract surgery). Potential participants were excluded for illness or disorders (eg, history of cancer with a poor 7-year prognosis, major cardiovascular or cerebrovascular event within the last year, or hemochromatosis) that would make long-term follow-up or compliance with the study protocol unlikely or difficult.

Of the 4757 study participants, all but 3 met the study eligibility and exclusion criteria. The 3 exceptions, all in AMD Category 1, were found postrandomization to be technically ineligible because 2 were aged 58 years and 1 exceeded by 2 weeks the 4-month allowable time between qualification and randomization visits. All 3 participants remained in the trial and in their assigned treatment group.

Prior to study initiation, the protocol was approved by an independent data and safety monitoring committee and by the institutional review board for each clinical center. Written informed consent was obtained from all participants before enrollment.

STUDY DESIGN

Interventions—The clinical trial component of AREDS consists of 2 trials—AMD and cataract—generally sharing 1 pool of participants (Figure 2). The 4 treatment interventions were double-masked and given as an oral total daily supplementation of antioxidants (500 mg of vitamin C, 400 IU of vitamin E, and 15 mg of beta carotene), or zinc (80 mg of zinc as zinc oxide and 2 mg of copper as cupric oxide to prevent potential anemia), or the combination of antioxidants and zinc, or placebo.

As in all vitamin products, some ingredients degrade somewhat during the life of the product (ie, prior to expiration date). The manufacturer formulated each product with slightly different amounts of ingredients than listed above in an effort to achieve appropriate potency at the expiration date.*

Two study medication tablets were to be taken each morning and 2 each evening to meet the total daily dose requirement. Tablets were to be taken with food to avoid potential irritation of an empty stomach by zinc.

Randomization—Simple randomization, stratified by clinical center and AMD category, was used to assign treatment. Participants in Categories 2, 3, and 4 were assigned with probability one quarter to each treatment group: placebo, antioxidants, zinc, and antioxidants plus zinc. Participants in Category 1 were assigned with probability one half to placebo or antioxidants. These study participants were at low risk for vision loss from AMD and there was no reason to suspect that zinc use would reduce the risk of progression of lens opacities. Because there was no apparent reason for these participants to supplement their diets with zinc, it seemed inappropriate to subject them to the possible consequences of high levels of zinc supplementation; thus, they were not enrolled in the clinical trial of zinc and are not included in analyses of AMD progression. Persons in Categories 2, 3, and 4 were randomized to the 4 interventions (Figure 2). Multiple unique bottle codes were randomly assigned to each of the 4 treatments for Categories 2, 3, and 4, and also to each of the 2 treatments for participants in Category 1. A bottle code corresponding to the assigned treatment was randomly selected for each participant.

*Tablets used in the active treatment arms of these trials were manufactured to have the following minimum contents throughout the shelf life of the product: 7160 IU of vitamin A (beta carotene), 113 mg of vitamin C (ascorbic acid), 100 IU of vitamin E (dl-alpha tocopheryl acetate), 17.4 mg of zinc (zinc oxide), and 0.4 mg of copper (cupric oxide).

Masking—Study medication tablets for the 4 treatment groups were identical in external appearance and similar in internal appearance and taste. The coordinating center was custodian of the treatment code. Information documenting unmasking was collected during the study.

Procedures—General physical and ophthalmic examinations at baseline and at annual intervals included standardized measurement of the participant's height, weight, blood pressure, manifest refraction, best-corrected visual acuity, and intraocular pressure. Slitlamp biomicroscopy and ophthalmoscopy were performed at each examination. Stereoscopic fundus photographs of the macula were taken at baseline and annually beginning 2 years after randomization and graded centrally using standardized grading procedures.³⁴ Demographic information, history of smoking and sunlight exposure, medical history, history of specific prescription drug and nonprescription medication use, and history of vitamin and mineral use were obtained at baseline.

Following determination of participant eligibility by the coordinating center and reading center and successful participation in a 1-month run-in with placebo, to demonstrate compliance with the treatment regimen (at least 75% of the run-in medication taken according to pill count), participants were randomly assigned to 1 of the 4 treatment groups and then evaluated every 6 months. The run-in aspect of the study was considered important for 2 reasons. Participants had to be willing to take 2 fairly large tablets 2 times per day for up to 8 years and they had to agree that, for the duration of the study, the only other supplement they might take that contained any of the study medications would be Centrum (Whitehall-Robins Healthcare, Madison, NJ), a multivitamin and mineral supplement with RDA-level doses. Fifty-seven percent of the study participants were supplementing with zinc or antioxidant vitamins prior to joining the study and 95% of this group chose to take Centrum, which the study provided. In addition, although not encouraged, an additional 13% who were not taking vitamin supplements prior to the start of the study chose to take Centrum. Among other differences, persons in the study who chose to take Centrum during the course of the study were somewhat more likely to be in the higher-risk AMD categories and therefore may differ from persons who did not choose to take Centrum with regard to their risk of AMD progression.

At each visit, participants returned their used study medication bottles and any unused tablets, and received new bottles of their study medication. They received an ophthalmic examination every 6 months. In addition to the scheduled fundus photography, photographs were also taken when a decrease in visual acuity score of 10 or more letters from baseline was first observed at a nonannual visit or at the first annual visit. If any submitted photographs were inadequate to assess lens or AMD status, requests were made for these photographs to be taken again. Best-corrected visual acuity was measured according to the ETDRS protocol (*AREDS Manual of Operations*) at every annual visit and whenever a decrease from baseline of 10 or more letters was observed at a nonannual visit using the participant's previous refraction. Special questionnaires were administered to all or a subset of participants at various times during participant follow-up: a modified Block Food Frequency Questionnaire, a 24-hour dietary recall questionnaire, and cognitive function tasks (*AREDS Manual of Operations*); an ocular sunlight-exposure questionnaire derived from the Melbourne study³⁵; and the National Eye Institute Visual Function Questionnaire (NEI VFQ-25).³⁶

Four clinical centers (The Johns Hopkins Medical Institutions [Baltimore, Md], Devers Eye Institute [Portland, Ore], National Eye Institute Clinical Center [Bethesda], and the Associated Retinal Consultants [Royal Oak, Mich]) collected blood samples at baseline, which were analyzed at the central laboratory (Centers for Disease Control and Prevention,

Atlanta, Ga) for total cholesterol, high-density lipoprotein cholesterol, triglycerides, vitamins A, C, and E, beta carotene, zinc, copper, alpha carotene, lutein and zeaxanthin, β -cryptoxanthin, and lycopene. The first 3 centers also collected blood samples annually during follow-up for estimation of adherence to the study medication regimen and to assess the effect of the study medications during the course of the study on serum levels of the parameters measured at baseline. Hematocrit was measured at all centers on all participants at baseline and annually thereafter to monitor the possible development of anemia. Safety outcomes included serum levels, adverse events, hospitalizations, and mortality. Participants also were asked to report at each annual visit if they had experienced any 1 of 19 conditions since the last follow-up visit. These included anemia, gastrointestinal conditions, kidney stones, fatigue, skin conditions, cardiovascular conditions, and thyroid abnormalities. Although individuals could have multiple occurrences of a condition or safety outcome, analyses compared the frequency of those who ever had the event with those who never had the event. The data and safety monitoring committee monitored safety outcomes annually. A network of collaborating physicians from non-AREDS clinics was formed to assist in obtaining follow-up visual acuity, fundus photographs, and ophthalmic examinations from participants who could not return to an AREDS clinic.

Sample Size and Power—A total sample size of 4600 was selected. For the AMD trial, with an estimated 3600 participants in Categories 2, 3, and 4, power was calculated assuming 5 years of follow-up, 15% of participants lost to follow-up prior to experiencing an event, 10% discontinuing study medication (and thereafter assuming the placebo event rate), and 10% beginning a nonstudy supplement containing study medication ingredients (and thereafter assuming the full treatment [antioxidants plus zinc] event rate). The placebo 5-year rate of progression to advanced AMD was assumed to be 17% based on the information available.^{5,37} After adjusting for non-compliance, for 2-sided $\alpha=.05$, a projected sample size of 3600 would provide at least 80% power to detect treatment effects of 25% to 50% on progression to advanced AMD depending on possible interactions between zinc and antioxidants.

OUTCOMES

At the start of the study, 2 primary outcomes were defined for study eyes in the AMD trial: (1) progression to advanced AMD and (2) at least a 15-letter decrease in visual acuity score.

Advanced AMD—Progression to advanced AMD (an “AMD event”) for a study eye was defined as follows: photocoagulation or other treatment for choroidal neovascularization (based on clinical center reports), or photographic documentation of any of the following (based on reading center reports)³⁴: GA 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, and/or sub-retinal fibrosis.

In AREDS, the retinal outcomes are based on color fundus photography rather than on fluorescein angiography or clinical examination.

Visual Acuity Loss—A decrease in best-corrected visual acuity score from baseline of 15 or more letters in a study eye (equivalent to a doubling or more of the initial visual angle, eg, 20/20 to 20/40 or worse, or 20/50 to 20/100 or worse) was the primary visual acuity outcome. Visual acuity was measured every 6 months.

Secondary Outcomes—Secondary AMD outcomes analyzed as part of the clinical trial included development of neovascular AMD, incidence of GA (not necessarily in the center of the macula), progression to advanced AMD with an associated visual acuity decrease of

at least 15 letters, and worsening of AMD classification in Category 2 participants to Category 3 or 4 during follow-up. Secondary visual acuity outcomes included a decrease in the best-corrected visual acuity score from baseline of 30 or more letters in a study eye (≥ 6 lines or a quadrupling of the initial visual angle) and progression to a visual acuity score worse than 20/100 in 1 or both eyes.

STATISTICAL ANALYSES

All comparisons were made on an intention-to-treat basis. Photographic AMD events were determined from photographs taken at annual visits beginning at year 2. Events of treatment for choroidal neovascularization from clinical reports at nonannual visits were attributed to the next annual visit. Primary comparisons for the development of advanced AMD and for a visual acuity decrease were the overall (main) effects of zinc (treatments 1 and 2) vs no zinc (treatments 3 and 4) and antioxidants (1 and 3) vs no antioxidants (2 and 4) on persons in Categories 2, 3, and 4. The 2×2 factorial design (Table 2) also permits comparisons of each of the 3 active treatment strategies with the placebo. Because persons are the units of analysis, no adjustment for correlation between paired eyes is needed.

Only 15 participants in Category 2 (3 in the placebo arm) developed an AMD event by 5 years of follow-up. Therefore, assessment of treatment effect of the size seen in Categories 3 and 4 was not possible in this group. Consequently, analyses limited to Categories 3 and 4 were performed. Primary analysis of treatment effect was done by repeated-measures logistic regression using the SAS procedure GENMOD (SAS Institute, Cary, NC), a generalized estimating equations method that allows for determining events at each visit for each participant. The annual probability estimates of event occurrence for each treatment that are derived from this model take into account the variability as well as the correlation of observations at follow-up visits for a given participant. This model was adopted because study events (either visual acuity loss or photographic evidence of lesions of advanced AMD) can come and go during study follow-up. We found that in approximately 8% of the identified cases of advanced AMD, based on central grading of color stereo photographs, the AMD lesions were not seen on subsequent yearly photographs. Possible reasons for this disappearance include grading error, problems in photographic quality, and actual disappearance of the lesions. Because some of the lesions that define the study outcome are apparently transient, a life-table technique such as Kaplan-Meier to estimate the probability of progression is problematic; in this method an event remains an event despite evidence of reversal during follow-up. Cox proportional hazards survival analyses for the AMD outcomes and repeated-measures analysis of variance of mean change in visual acuity were used for comparison with the findings of repeated-measure logistic regression to check for consistency of treatment effects. Cox proportional hazards survival analysis, an extension of life-table analysis, is a regression model of the effect of explanatory variables on time to first occurrence of an event. This method was given secondary importance because it is more appropriate for irreversible and error-free events like death, where subsequent observations are not relevant.

Repeated-measures logistic regression provides estimates of odds ratios (ORs) for specified outcomes. Relative risk (RR) may be further estimated from the algebraic relation $RR = OR / [(1 - P_o) + (P_o \times OR)]$, where P_o is the incidence of the outcome of interest in the nonexposed or control group.³⁸ For P_o we use the estimated probability of the outcome from the repeated-measures analysis in the placebo group at 7 years. Analyses are unadjusted and also adjusted for the following baseline covariates: age (55–64, 65–69, and 70–80 years), sex, race, AMD category, and smoking status.

STATISTICAL MONITORING

A data and safety monitoring committee monitored 5 end points from the 2 trials (AMD and cataract) simultaneously for both safety and efficacy.³² Sequential monitoring of end points assumed no interaction between the antioxidant formulation and the zinc formulation, so that only main effects were analyzed. An α -spending function group-sequential method³⁹ was extended to address multiple time-to-event outcome variables by a Bonferroni adjustment distributing the type I error among the multiple end points. Log-rank tests were used to compare the response distributions of the 2 treatment groups with an O'Brien-Fleming boundary.⁴⁰ A separate monitoring of mortality used a Pocock-type boundary.⁴¹ Comparisons were made with spending of α when requested by the data and safety monitoring committee. Treatment effects at the end of the trial that are significant at $P=.01$ can be considered statistically significant at $\alpha=.05$ after adjustment for multiple outcomes and interim analyses. Nominal P values greater than .01 but less than .05 should not be considered statistically significant and should only be considered as suggestive, owing to the multiple outcomes and interim analyses performed.

CHANGE IN TREATMENT

In 1994 and 1996, AREDS participants were informed of the results of 2 studies suggesting potential harmful effects of beta carotene among smokers.^{42,43} Participants who were current cigarette smokers at the time of enrollment were contacted in 1996 and offered the option of continuing or discontinuing their masked AREDS study medication. Participants in Categories 2, 3, and 4 who were current or former smokers at baseline were also given the opportunity to be reassigned to a masked study medication that excluded any antioxidant component. As a result, 72 participants (2.0% of all participants and 18% of smokers) stopped taking medications (15 or 1.7% in the placebo arm) and 84 participants (2.3%) were reassigned from a study medication containing beta carotene to one without beta carotene. The original treatment group assignments were retained for all analyses.

AREDS Research Group

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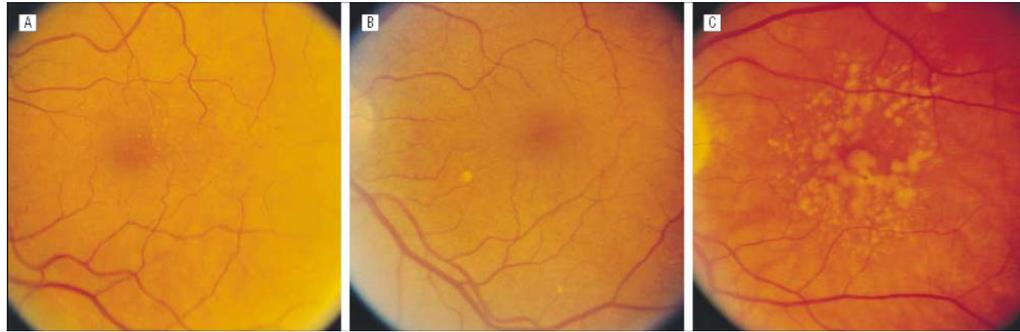


Figure 1.

Fundus photographs from participants in the Age-Related Eye Disease Study (AREDS) illustrating eyes in age-related macular degeneration Categories 2 and 3. A, Left eye in Category 2 shows nonextensive intermediate drusen, mostly located superotemporal to the center of the macula. No druse is 125 μm or greater in diameter, although some are 63 μm 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 druse (≥ 125 μm 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.

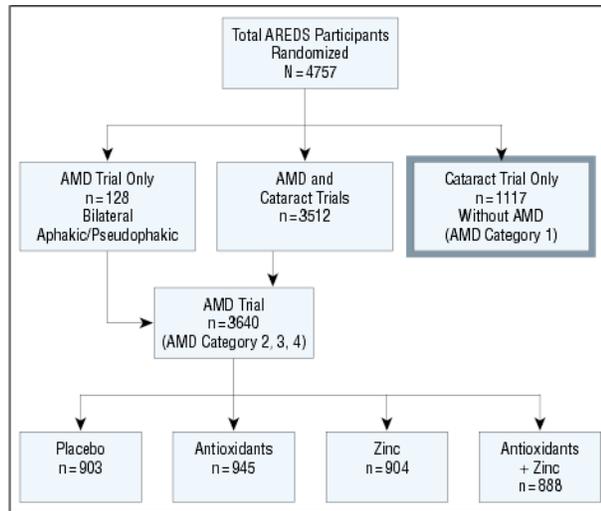


Figure 2. Age-Related Eye Disease Study (AREDS) randomization schema. AMD indicates age-related macular degeneration.

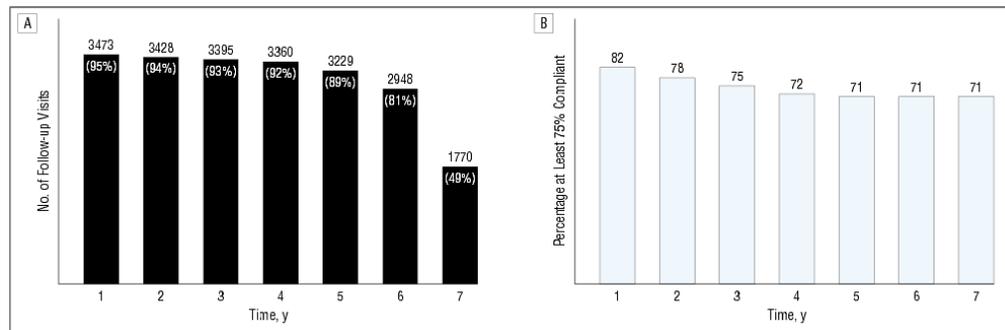


Figure 3. Participant follow-up and adherence by year in study. A, Number of participants with follow-up visits and percentage of total enrolled (n = 3640). B, Percentage of participants taking at least 75% of their study tablets.

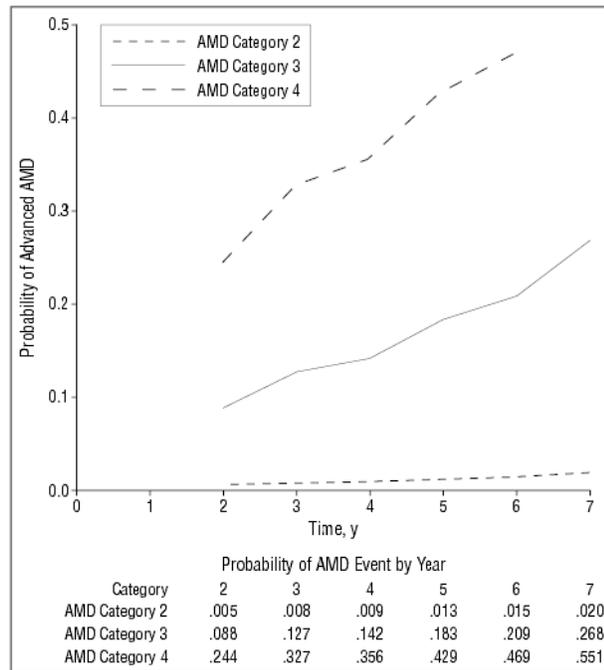


Figure 4. Repeated-measures estimates of the probability of the development of advanced age-related macular degeneration (AMD) in at least 1 eye of participants assigned to placebo by baseline AMD category. Events before year 2 reflect only photocoagulation.

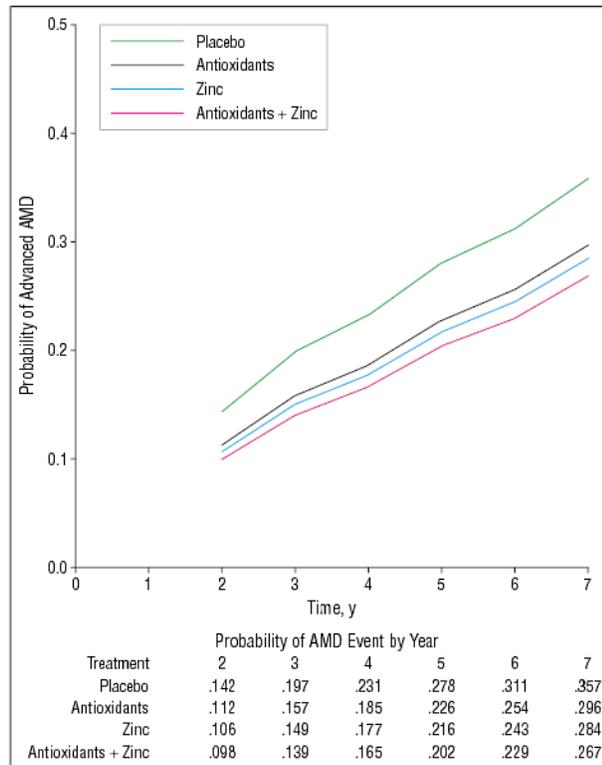


Figure 5. Repeated-measures estimates of the probability of development of advanced age-related macular degeneration (AMD) in at least 1 study eye of participants in Categories 3 and 4 by treatment group. The study eye is an eye without disqualifying lesions or evidence of advanced AMD, and with a visual acuity score of greater than 73 letters (20/32 or better) at baseline. Events before year 2 reflect only photocoagulation.

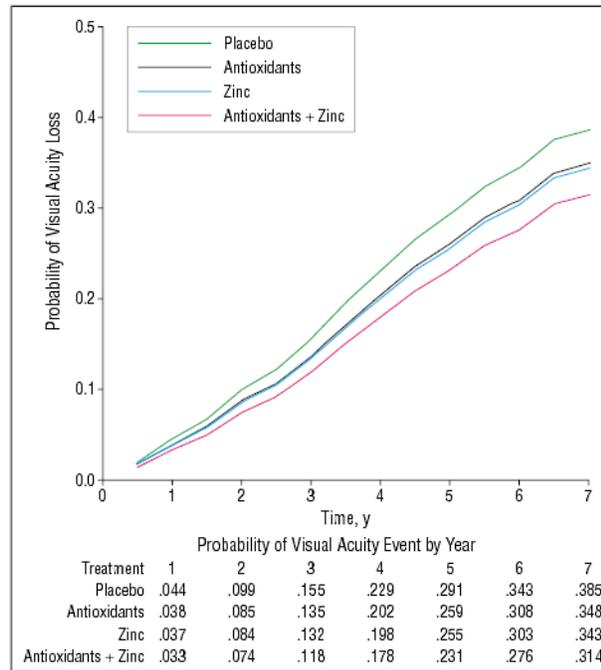


Figure 6. Repeated-measures estimates of the probability of a loss in the visual acuity score of at least 15 letters in at least 1 study eye of participants in age-related macular degeneration (AMD) Categories 3 and 4 by treatment group. The study eye is an eye without disqualifying lesions or evidence of advanced AMD and with a visual acuity score greater than 73 letters (20/32 or better) at baseline.

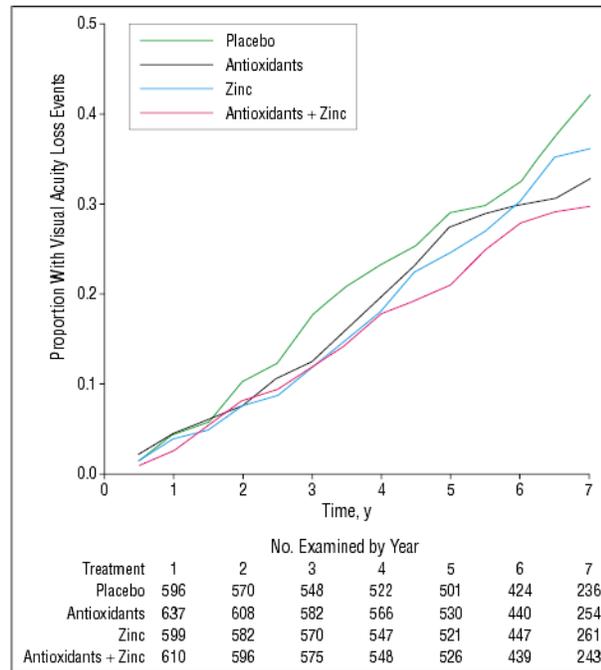


Figure 7. Proportion of participants with visual acuity loss of 15 letters or more in at least 1 study eye by treatment group and follow-up time among participants in age-related macular degeneration (AMD) Categories 3 and 4.

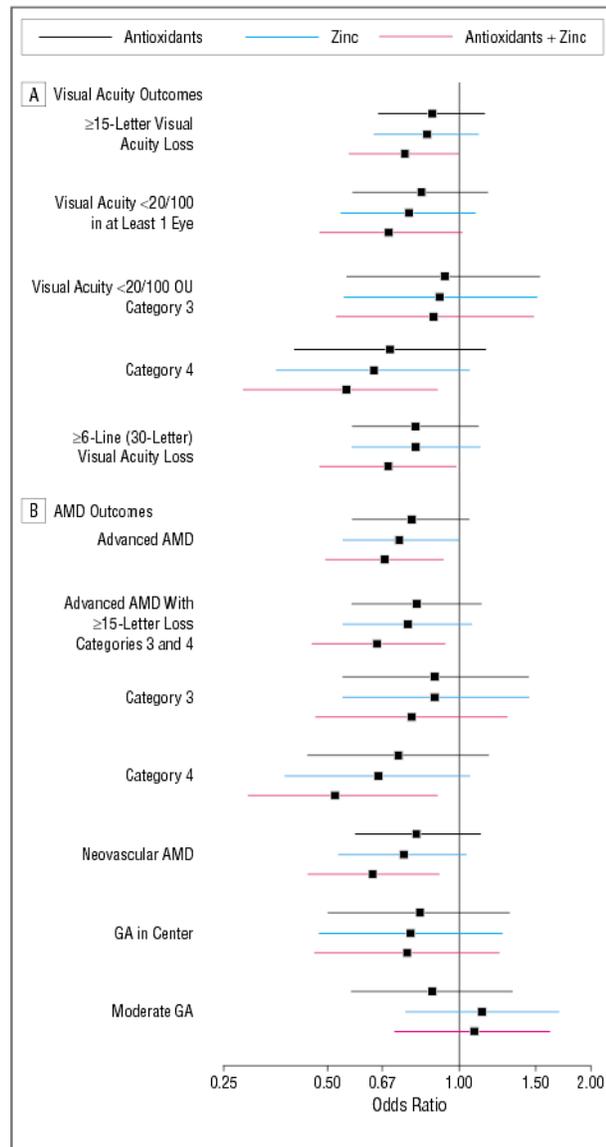


Figure 8. Odds ratios (squares) and 99% confidence intervals (colored bars) for each treatment compared with placebo for participants in age-related macular degeneration (AMD) Categories 3 and 4. A, Visual acuity outcomes. B, AMD outcomes. GA indicates geographic atrophy.

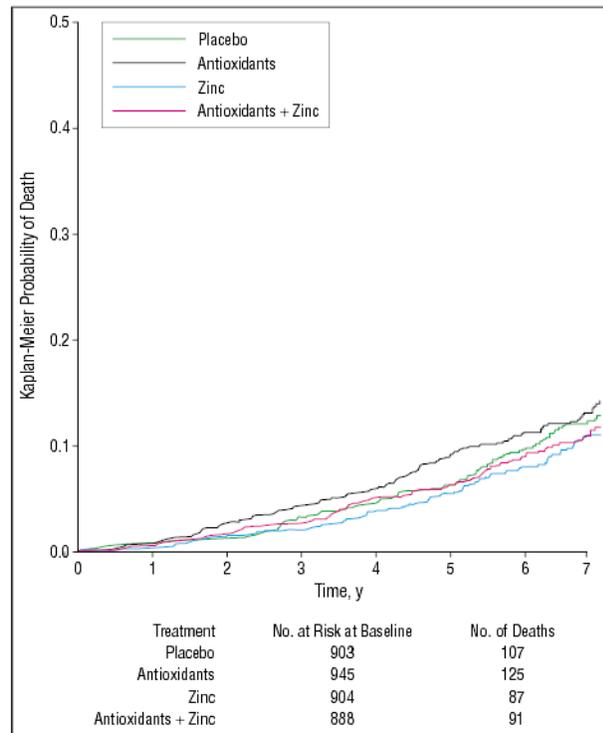


Figure 9. Kaplan-Meier estimates of the probability of death among all participants in the age-related macular degeneration trial by treatment group. $P = .08$, unadjusted comparison across treatments.

Table 1

AMD Eligibility Categories

AMD Category	First Eye*			Second Eye
	Drusen Size [†]	Drusen Area [‡]	Pigment Abnormalities [‡]	
1	None or small (<63 μm)	<125 μm diameter circle (≈5–15 drusen) small	None	Same as first eye
2	Small (<63 μm) Or intermediate (≥63, <125 μm) Or none required if pigment abnormalities present	≥125 μm diameter circle (about 1/150 disc area) At least 1 druse	Absent or present, but GA absent	Same as first eye or Category 1
3a	Intermediate (≥63, <125 μm) Or none required if noncentral GA [‡] is present	≥360 μm diameter circle (about 1/16 disc area) if soft indistinct drusen are present (≈20 intermediate drusen) ≥656 μm diameter circle (about 1/5 disc area), if soft indistinct drusen are absent (≈65 intermediate drusen) At least 1 druse	Absent or present, but central GA [‡] absent	Same as first eye or Category 1 or 2
3b	Or large (≥125 μm) Or none required, if noncentral GA [‡] is present			
4a	First eye same as Category 1, 2, or 3a			VA <20/32 not due to AMD [§] , or unioctular disqualifying disorder is present ^{//}
4b	First eye same as Category 1, 2, or 3a			Advanced AMD [¶] VA <20/32 due to AMD, but advanced AMD [¶] not present [§]

* Must have visual acuity (VA) ≥20/32, no advanced age-related macular degeneration (AMD), and no disqualifying lesions.

[†] Drusen and geographic atrophy (GA) are assessed within 2 disc diameters (3000 μm)³³ of the center of the macula.

[‡] Pigment abnormalities (increased pigmentation or depigmentation) within 1 disc diameter of the center of the macula.

[§] Eye not eligible for VA event.

^{//} Eye not eligible for AMD event.

[¶] The GA involving center of macula or signs of choroidal neovascularization (presence beneath the retinal pigment epithelium or sensory retina of fluid, blood, or fibrovascular or fibrous tissue).

Table 2

Treatment Design

	Antioxidants	No Antioxidants
Zinc	1: Antioxidants + zinc	2: Zinc
No Zinc	3: Antioxidants	4: Placebo

Table 3

Baseline Characteristics by Treatment Group*

Participant Characteristic	Placebo (n = 894)	Antioxidants (n = 936)s	Zinc (n = 897)	Antioxidants + Zinc (n = 882)	Total (n = 3609)
<i>Age, y</i>					
55–59	3	4	2	3	3
60–64	16	16	18	17	17
65–69	32	34	29	33	32
70–74	31	29	34	30	31
75–80	18	16	18	17	17
Median age, y	69	69	70	69	69
Females	56	55	57	56	56
<i>Race</i>					
White	96	97	96	97	96
Black	4	2	3	3	3
Other	<1	1	1	<1	1
<i>AMD Category</i>					
2	30	28	30	28	29
3a, 3b	40, 4	39, 5	41, 4	41, 5	40, 4
4a, 4b	21, 5	23, 5	22, 4	22, 4	22, 4
<i>Marital status</i>					
Married	70	71	73	71	72
Divorced/separated	7	6	6	6	6
Widowed	19	18	16	18	18
Never married	4	4	5	4	4
<i>Primary lifetime occupation</i>					
Managerial/professional	34	35	36	37	35
Technical, sales, administrative	29	26	24	25	26
Other	37	40	40	38	39
<i>Current annual household income, \$</i>					
<15 000	15	13	11	13	13
15 000–50 000	58	62	63	62	61
>50 000	24	22	22	21	22

Participant Characteristic	Placebo (n = 894)	Antioxidants (n = 936)s	Zinc (n = 897)	Antioxidants + Zinc (n = 882)	Total (n = 3609)
Refused to answer	3	3	4	4	3
Bachelor's degree or higher	33	31	34	32	32
Currently smoking	8	9	8	8	8
Former smoker	47	50	51	46	49
Chose to take Centrum [†] at enrollment	69	66	67	66	67
Taking multivitamins or a supplement containing a study ingredient	58	53	59	57	57
Taking insulin or pills for diabetes mellitus	6	7	6	6	6
Taking medication to control cholesterol/lipids	10	7	8	10	9
Taking aspirin or anti-inflammatory medication	39	38	40	38	39
Taking antacids	12	10	14	12	12
Taking medication for hypertension	32	32	33	35	33
Arthritis	48	47	48	47	48
Diagnosis of angina	9	10	12	11	11
Prior diagnosis of cancer	18	17	17	19	18

* Data are given as percentage unless otherwise indicated. AMD indicates age-related macular degeneration.

[†]A multivitamin and mineral supplement manufactured by Whitehall-Robins Healthcare, Madison, NJ.

Table 4

Effect of Treatment on Risk of Progression to Advanced AMD*

Treatment	Participants in AMD Categories 2, 3, and 4 (n = 3609)		Participants in AMD Categories 3 and 4 (n = 2556)	
	OR (99% CI)	PValue	OR (99% CI)	PValue
Antioxidants vs no antioxidants	0.87 (0.70–1.09)	.12	0.83 (0.66–1.06)	.05
Zinc vs no zinc	0.82 (0.66–1.03)	.02	0.79 (0.62–0.99)	.009
Antioxidants vs placebo	0.80 (0.59–1.09)	.07	0.76 (0.55–1.05)	.03
Adjusted	0.77 (0.56–1.05)	.03 [†]	0.76 (0.54–1.05)	.03 [†]
Zinc vs placebo	0.75 (0.55–1.03)	.02	0.71 (0.52–0.99)	.008
Adjusted	0.71 (0.51–0.98)	.005 [†]	0.70 (0.50–0.97)	.005 [†]
Antioxidants + zinc vs placebo	0.72 (0.52–0.98)	.007	0.66 (0.47–0.91)	.001
Adjusted	0.68 (0.49–0.93)	.002 [†]	0.66 (0.47–0.93)	.001 [†]
Total No. of participants with events	803		775	

* Advanced age-related macular degeneration (AMD) indicates photocoagulation or other treatment for choroidal neovascularization, central geographic atrophy, nondrusenoid retinal pigment epithelial detachment, serous or hemorrhagic retinal detachment, hemorrhage under the retina or pigment epithelium, or subretinal fibrosis; OR, odds ratio; and CI, confidence interval. Analysis by repeated-measures logistic regression, unadjusted. $P \leq .01$ is considered statistically significant.

[†] Adjusted for age, sex, race, AMD category, and baseline smoking status.

Table 5Effect of Treatment on Risk of Loss of Visual Acuity Score of ≥ 15 Letters From Baseline*

Treatment	Participants in AMD Categories 2, 3, and 4 (n = 3597)		Participants in AMD Categories 3 and 4 (n = 2549)	
	OR (99% CI)	PValue	OR (99% CI)	PValue
Antioxidants vs no antioxidants	0.90 (0.74–1.09)	.14	0.86 (0.70–1.07)	.07
Zinc vs no zinc	0.88 (0.73–1.07)	.09	0.84 (0.68–1.04)	.04
Antioxidants vs placebo	0.88 (0.67–1.15)	.22	0.85 (0.63–1.14)	.16
Adjusted	0.87 (0.67–1.15)	.20 [†]	0.87 (0.65–1.17)	.23 [†]
Zinc vs placebo	0.87 (0.66–1.13)	.17	0.83 (0.62–1.11)	.10
Adjusted	0.82 (0.63–1.08)	.07 [†]	0.82 (0.61–1.09)	.07 [†]
Antioxidants + zinc vs placebo	0.79 (0.60–1.04)	.03	0.73 (0.54–0.99)	.008
Adjusted	0.77 (0.58–1.03)	.02 [†]	0.75 (0.55–1.02)	.017 [†]
Total No. of participants with events	1197		1022	

* AMD indicates age-related macular degeneration; OR, odds ratio; and CI, confidence interval. Analysis by repeated-measures logistic regression, unadjusted. $P \leq .01$ is considered statistically significant.

[†] Adjusted for age, sex, race, AMD category, and baseline smoking status.

Table 6

Effect of Treatment on Risk of Loss of Visual Acuity Score of ≥ 15 Letters Coincident With Progression to Advanced AMD*

Treatment	Participants in AMD Categories 3 and 4 (n = 2516)		Participants in AMD Category 3 (n = 1588)		Participants in AMD Category 4 (n = 928)	
	OR (99% CI)	PValue	OR (99% CI)	PValue	OR (99% CI)	PValue
Antioxidants vs no antioxidants	0.82 (0.63–1.06)	.04	0.87 (0.60–1.26)	.34	0.76 (0.53–1.11)	.06
Zinc vs no zinc	0.77 (0.60–1.00)	.011	0.87 (0.60–1.26)	.34	0.69 (0.47–0.99)	.009
Antioxidants vs placebo	0.79 (0.55–1.13)	.09	0.87 (0.52–1.46)	.49	0.71 (0.43–1.17)	.08
Zinc vs placebo	0.75 (0.53–1.07)	.04	0.87 (0.52–1.46)	.49	0.64 (0.38–1.06)	.02
Antioxidants + zinc vs placebo	0.63 (0.44–0.92)	.001	0.76 (0.45–1.30)	.19	0.52 (0.31–0.89)	.002
Total No. of participants with events	585		270		315	

* Unadjusted analysis by repeated-measures logistic regression. AMD indicates age-related macular degeneration; OR, odds ratio; and CI, confidence interval. $P \leq .01$ is considered statistically significant.

Table 7

Effect of Treatment on Risk of Loss of VA Score of ≥ 15 Letters From Baseline in AMD Category 4 Eyes With Advanced Neovascular AMD*

Treatment	Baseline VA 20/100 or better (n = 260)		Baseline VA 20/200 or better (n = 352)	
	OR (99% CI)	PValue	OR (99% CI)	PValue
Antioxidants vs no antioxidants	0.54 (0.30–0.95)	.005	0.66 (0.40–1.07)	.03
Zinc vs no zinc	0.99 (0.56–1.74)	.96	1.10 (0.67–1.79)	.62
Antioxidants vs placebo	0.35 (0.15–0.81)	.001	0.56 (0.27–1.13)	.03
Zinc vs placebo	0.65 (0.28–1.50)	.18	0.93 (0.46–1.89)	.79
Antioxidants + zinc vs placebo	0.53 (0.23–1.24)	.05	0.72 (0.36–1.46)	.24
Total No. of participants with events	167		206	

* Eyes with geographic atrophy at baseline are excluded. Unadjusted analysis by repeated-measures logistic regression. VA indicates visual acuity; AMD, age-related macular degeneration; OR, odds ratio; and CI, confidence interval. $P \leq .01$ is considered statistically significant.

Table 8

Effect of Treatment on Risk of Development of Neovascular AMD and Central Geographic Atrophy*

Treatment	Neovascular AMD (n = 2556)		Central Geographic Atrophy (n = 2124)	
	OR (99% CI)	PValue	OR (99% CI)	PValue
Antioxidants vs no antioxidants	0.83 (0.64–1.07)	.06	0.88 (0.62–1.26)	.37
Zinc vs no zinc	0.76 (0.58–0.98)	.005	0.84 (0.59–1.21)	.22
Antioxidants vs placebo	0.79 (0.56–1.13)	.09	0.80 (0.48–1.32)	.25
Zinc vs placebo	0.73 (0.51–1.04)	.02	0.76 (0.46–1.27)	.17
Antioxidants + zinc vs placebo	0.62 (0.43–0.90)	.001	0.75 (0.45–1.24)	.13
Total No. of participants with events	592		257	

* Age-related macular degeneration (AMD) Category 3 and 4 participants. Unadjusted analysis, by repeated-measures logistic regression. Neovascular AMD indicates photocoagulation or other treatment for choroidal neovascularization, nondrusenoid retinal pigment epithelial detachment, serous or hemorrhagic retinal detachment, hemorrhage under the retina or pigment epithelium, or subretinal fibrosis; for central geographic atrophy, eyes of participants with prior neovascular AMD are excluded. OR indicates odds ratio; CI, confidence interval. $P \leq .01$ is considered statistically significant.

Table 9
Serum Values at Baseline and Median Percent Change at Follow-up Years 1 and 5

Specimen	n	Baseline Median				Median % Change at Year 1				Median % Change at Year 5			
		Placebo	Antioxidants	Zinc	Antioxidants + Zinc	Placebo	Antioxidants	Zinc	Antioxidants + Zinc	Placebo	Antioxidants	Zinc	Antioxidants + Zinc
Vitamin C, mg/dL ^{††}	695	1.1	1.1	1.1	1.0	-8	30	-10	21	-7	14	-12	12
Vitamin E-cholesterol ratio [‡]	715	6.6	6.2	6.6	6.4	0	80	-3	84	6	78	6	81
Beta carotene, µg/dL	715	25	28	25	26	4	516	0	452	4	388	0	303
Zinc, µg/dL [*]	677	83	82	82	85	1	1	18	17	3	1	16	19
Copper, µg/dL [*]	675	117	115	116	117	2	-2	-2	-1	2	0	-3	2
Lutein + zeaxanthin, µg/dL	714	24	24	24	25	-2	-14	-7	-19	-13	-23	-21	-33
Vitamin A, µg/dL [*]	716	64	62	64	62	3	4	0	2	8	9	4	7
β-Cryptoxanthin, µg/dL	714	11	12	11	11	-3	0	0	0	-18	-21	-16	-14
Lycopene, µg/dL	716	19	20	20	18	-2	-5	0	-4	-20	-23	-20	-12
α-Carotene, µg/dL	713	6.0	6.0	6.0	6.0	0	48	0	38	-17	0	-20	0
Total cholesterol, mg/dL [§]	719	220	216	226	222	-1	3	-2	-1	-2	-2	-4	-3
Triglycerides, mg/dL [§]	719	134	116	132	128	0	7	0	11	-2	6	-5	-2
HDL-C, mg/dL [§]	698	50	52	53	51	3	0	0	-2	6	-2	2	0
LDL-C, mg/dL ^{§//}	697	137	139	142	139	-6	6	-11	-5	-5	-5	-6	-5
Hematocrit, % [¶]	2708	42	42	41	41	0	0	0	-2	-2	-2	-2	-2

* To convert to micromoles per liter in Système International Units, multiply by the following conversion factors: vitamin C, 56.78; beta carotene, 0.0186; zinc, 0.153; copper, 0.1574; vitamin A, 0.0349.

† Value is the total ascorbate level.

‡ Value is the ratio of vitamin E and total cholesterol levels, which adjusts for potential differences in vitamin E.

§ To convert to millimoles per liter in Système International Units, multiply by the following conversion factors: triglycerides, 0.01129; total cholesterol, 0.02586; high-density lipoprotein cholesterol (HDL-C), 0.02586; and low-density lipoprotein (LDL-C), 0.02586.

// Value calculated as total cholesterol level - HDL-C - (triglycerides/5).

¶ Hematocrit was measured at all clinical centers.

Table 10

Participants Reporting at Least 1 Hospitalization, Adverse Experience, or Condition During Follow-up, by Treatment*

	No. (%)		
	No Antioxidants (n = 1798)	Antioxidants (n = 1823)	Total (n = 3621)
Primary hospitalization cause ⁴⁵			
Infections [†]	15 (0.8)	29 (1.6)	44 (1.2)
Mild/moderate symptoms [‡]	181 (10.1)	135 (7.4)	316 (8.7)
Primary adverse experience cause ⁴⁵			
Circulatory [†]	15 (0.8)	6 (0.3)	21 (0.6)
Skin, subcutaneous tissue [‡]	18 (1.0)	41 (2.2)	59 (1.6)
Follow-up condition [§]			
Change in skin color [‡]	108 (6.0)	151 (8.3)	259 (7.2)
Chest pain [†]	415 (23.1)	368 (20.2)	783 (21.6)

	No. (%)		
	No Zinc (n = 1838)	Zinc (n = 1783)	Total (n = 3621)
Primary hospitalization cause ⁴⁵			
Genitourinary [‡]	90 (4.9)	134 (7.5)	224 (6.2)
Males [‡]	36 (4.4)	66 (8.6)	102 (6.4)
Females	54 (5.3)	68 (6.7)	122 (6.0)
Mild/moderate symptoms [†]	143 (7.8)	173 (9.7)	316 (8.7)
Primary adverse experience cause ⁴⁵			
Circulatory [†]	5 (0.3)	16 (0.9)	21 (0.6)
Follow-up condition [§]			
Anemia [‡]	187 (10.2)	236 (13.2)	423 (11.7)
Difficulty swallowing pills [†]	281 (15.3)	318 (17.8)	599 (16.5)

* Of nearly 100 comparisons, only causes and conditions significantly different by treatment are presented.

[†] $P < .05$.

[‡] $P < .01$.

[§] Self-reported in response to predefined list of signs and symptoms suggesting an adverse event.

Table 11

Effect of Treatment on Risk of Mortality*

Treatment	RR (99% CI)	PValue
Antioxidants vs no antioxidants	1.10 (0.85–1.42)	.35
Zinc vs no zinc	0.79 (0.61–1.02)	.02
Antioxidants vs placebo	1.12 (0.80–1.57)	.39
Zinc vs placebo	0.81 (0.56–1.17)	.14
Antioxidants + zinc vs placebo	0.87 (0.60–1.25)	.32
Total participants with events	410	

* Analysis by Cox survival analysis. RR indicates relative risk; CI, confidence interval.