Secondary Outcomes in a Clinical Trial of Carotenoids with Coantioxidants versus Placebo in Early Age-related Macular Degeneration

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Purpose: To report the secondary outcomes in the Carotenoids with Coantioxidants in Age-Related Maculopathy trial.

Design: Randomized double-masked placebo-controlled clinical trial (registered as ISRCTN 94557601).

Participants: Participants included 433 adults 55 years of age or older with early age-related macular degeneration (AMD) in 1 eye and late-stage disease in the fellow eye (group 1) or early AMD in both eyes (group 2).

Intervention: An oral preparation containing lutein (L), zeaxanthin (Z), vitamin C, vitamin E, copper, and zinc or placebo. Best-corrected visual acuity (BCVA), contrast sensitivity (CS), Raman spectroscopy, stereoscopic colour fundus photography, and serum sampling were performed every 6 months with a minimum follow-up time of 12 months.

Main Outcome Measures: Secondary outcomes included differences in BCVA (at 24 and 36 months), CS, Raman counts, serum antioxidant levels, and progression along the AMD severity scale (at 12, 24, and 36 months).

Results: The differential between active and placebo groups increased steadily, with average BCVA in the former being approximately 4.8 letters better than the latter for those who had 36 months of follow-up, and this difference was statistically significant ($P = 0.04$). In the longitudinal analysis, for a 1-log-unit increase in serum L, visual acuity was better by 1.4 letters (95% confidence interval, 0.3–2.5; $P = 0.01$), and a slower progression along a morphologic severity scale ($P = 0.014$) was observed.

Conclusions: Functional and morphologic benefits were observed in key secondary outcomes after supplementation with L, Z, and coantioxidants in persons with early AMD.

Financial Disclosure(s): The author(s) have no proprietary or commercial interest in any materials discussed in this article. *Ophthalmology 2013;120:600–606 © 2013 by the American Academy of Ophthalmology.*

There is scientific support for the hypothesis that increased oxidative stress in the macular tissues of the eye is involved in the pathogenesis of early age-related macular degeneration (AMD) and progression to its late-stage manifestations of neovascularization (neovascular AMD), geographic atrophy (GA), or both.[1–3] There is a strong consensus of existing opinion that has developed over the last decade that a lack of the macular pigments lutein (L) and zeaxanthin (Z) plays an etiologic role in the development of AMD.[4] The Age-Related Eye Disease Study (AREDS), a large placebo-controlled trial, demonstrated a reduction in progression in persons with stage 3 and 4 AMD after long-term supplementation with high doses of vitamins C and E, β-carotene, and zinc.[5]

We hypothesized that inclusion of L and Z to the preparation used in AREDS could result in discernible functional benefits within 1 year that represent a shorter follow-up time than that of AREDS. Therefore, a randomized controlled clinical trial (the Carotenoids with Coantioxidants in Age-Related Maculopathy [CARMA] study) was undertaken of supplementation with L and Z with coantioxidant vitamins and minerals versus placebo using a parallel group design. Only those persons judged to be at highest risk of progression to advanced AMD were selected. Participants underwent tests of macular function and morphologic features at baseline and at 6-month intervals. The detection of differences in the groups in the rate of deterioration in visual function in response to the antioxidant cocktail, it was contended, would strengthen the argument for screening for early AMD, for the use of combined antioxidant supplementation to prevent progression of AMD, and also would help in the understanding of the role of carotenoids in the maintenance of macular health. The primary outcome was best-corrected visual acuity (BCVA) after all participants

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Published by Elsevier Inc.
ISSN 0161-6420/13/$–see front matter
http://dx.doi.org/10.1016/j.ophtha.2012.08.040

had completed 1 year (Beatty S, et al, manuscript in press, 2012). No difference was found between placebo and treatment groups (data in press). However, a number of secondary outcomes also were collected that included BCVA for participants who had more than 12 months of follow-up, contrast sensitivity (CS), fundus morphologic grading, macular pigment estimates using Raman spectroscopy, and serum levels of the constituent antioxidants. This report presents the detailed findings from the secondary outcomes.

Patients and Methods

Study Design

Details of the study design and methods already have been published, and the CARMA trial is registered on the ISRCTN database (number 94557601).[6] The study was conducted at 2 sites, one in Northern Ireland (Belfast, United Kingdom), and the other in the south of Ireland (Waterford, Republic of Ireland). Both study sites are hospitals that are regional tertiary referral centers for their respective locations with provision for specialist retinal services. Ethics approval was obtained in each site separately, and the study was conducted in accordance with the tenets of the Declaration of Helsinki regarding research into human volunteers. In brief, the CARMA trial is a randomized controlled trial of oral supplementation with an antioxidant preparation versus placebo. The study was designed so that all participants would have a minimum follow-up of 1 year. The active preparation consisted of a tablet taken twice daily to deliver a daily dose of 12 mg L, 0.6 mg Z, 15 mg d-α-tocopherol (vitamin E), 150 mg ascorbic acid (vitamin C), 20 mg zinc oxide (Zn), and 0.4 mg copper gluconate. The preparation is commercially available under the trademark Ocuvite (Bausch and Lomb, Berlin, Germany). The placebo consisted of cellulose, lactose, and magnesium stearate and was manufactured to be indistinguishable from the active preparation in size, color, smell, and taste. The study preparations (active and placebo) were packaged in identical containers that bore only the participant information and study label and were indistinguishable in all respects from each other.

Study Population

The first participant was enrolled on June 14, 2004, and the last participant was enrolled on April 3, 2008. The minimum follow-up time was 12 months. Participants recruited in the early phases of the study had the opportunity to be followed up for up to 3 years.

Inclusion and Exclusion Criteria

These criteria have been described in detail,[6] but briefly, participants fell into 1 of 2 groups. Group 1 included persons with late AMD in 1 eye and with any severity of early AMD in the fellow eye. The sole study eye in this group was the eye free of late-stage AMD and with a visual acuity of 0.3 logarithm of the minimum angle of resolution units or better (70 letters or better on the Early Treatment Diabetic Retinopathy Study chart; equivalent to Snellen 20/40). Group 2 included persons with features of early AMD in at least 1 eye when both eyes were free of late-stage AMD. The minimum severity level was 20 soft distinct or indistinct drusen in the central macular field; if there were fewer than 20 drusen, focal hyperpigmentation was required to be present. Because eligibility was clinically determined, the size of drusen was not specified. Visual acuity had to be 0.3 logarithm of the minimum angle of resolution units or better (equivalent to Snellen 20/40) in the eye(s) selected to be study eyes in group 2 participants. Thus, group 2 participants had both eyes as study eyes unless visual acuity or some other reason precluded the use of one of the eyes as a study eye. Although all fundus images were graded in a reading center, there was no prerandomization eligibility determination.

Study Procedures

Participants underwent a full general physical examination at baseline and collection of demographic information at the baseline visit. These included measurement of height, weight, sitting blood pressure with the random zero sphygmomanometer, and completion of a set of questionnaires that included information on diet and lifestyle.[6] A complete set of ocular examinations was undertaken at study visits, which occurred at 6-month intervals and included visual acuity, photopic interferometry, contrast sensitivity, shape discrimination testing, fundus photography, and Raman spectroscopy. Blood samples were collected at every study visit.

Best-Corrected Distance Visual Acuity

Best-corrected distance visual acuity (BCVA) after refraction was measured in CARMA trial participants at every visit in each eye separately and was recorded as letters read.[7]

Contrast Sensitivity

Contrast sensitivity was measured on the Pelli-Robson chart placed at 1 m with the participant wearing the appropriate refractive correction. As with BCVA, CS also was analyzed as letters read, allowing it to be treated as a continuously distributed variable.

Raman Spectroscopy

The Raman spectroscope was used to record macular carotenoid signals (Spektrotec, Salt Lake City, UT) applying the method described by Bernstein et al.[8] In brief, after pupillary dilation with the participant seated comfortably with the chin on the chin rest, and after appropriately aligning the spectroscope on the pupil, 5 readings were captured from the study eyes, with the highest 3 used for analysis.

Photographic and Fundus Grading Procedures

All participants underwent color fundus photography of both eyes at every visit with digitally captured 35° stereoscopic pairs centered on the optic disc and the central macula.[9] All images were anonymized and sent to the fundus photographic and angiographic reading center at Queen's University of Belfast, where grading was performed by trained graders. Stereoscopic pairs were displayed on screen using a customized grading platform (EyeQPro; Digital Healthcare Ltd, Cambridge, UK). The definitions for grading were based on the Wisconsin Age-Related Maculopathy Grading System.[9] For the determination of size of the various graded characteristics, circle areas of predefined size could be displayed on the screen and superimposed onto the features of interest.

Serum Antioxidant Measurements

Blood samples were acquired at baseline and at each follow-up visit. Serum was extracted and high-performance liquid chromatography with diode array detection was used to measure α-tocopherol, L, and Z.[10] The interassay and intra-assay coefficient of variation for each of the lipid-soluble antioxidants were less than 10%. The detection limit for tocopherol was 0.05 μmol/l, and

0.005 μmol/l for L and Z. Vitamin C was measured by an automated fluorometric assay. Serum Zn was measured by inductively coupled plasma mass spectrometry. Standard reference materials and quality controls were included at intervals throughout each analytical batch, and the assays were included in quality assurance schemes where possible.

Randomization

A block randomization design was used with stratification by center and by group status, and separate block randomized lists were provided to each site. After ensuring informed consent and after the clinical examination, the study clinician at each site determined whether a participant fulfilled the criteria for study entry and assigned the participant to group 1 or group 2 status (i.e., only 1 study eye or 2 study eyes). Participants then were assigned consecutively to the next available study number. Participants and study staff were masked to treatment assignment, and to ensure the robustness of masking procedures, the study preparations were indistinguishable from each other and were supplied in appropriately labeled containers by the hospital pharmacy at each of the 2 clinical sites. Any unused tablets were returned in their containers to the hospital pharmacy.

Of the 433 participants who were eligible for study entry and were enrolled, 216 were assigned to treatment and 217 to placebo. After grading, a single participant in group 1 who was assigned to the placebo group was deemed ineligible because the reading center judged that choroidal neovascularization (CNV) was present in the sole study eye. However, the participant remained in the study and was retained in the analysis because of the intention-to-treat study design.

Outcome Measures

The primary outcome of BCVA at 1 year was reported elsewhere, but in brief, no difference in BCVA was seen between treatment and placebo groups at 1 year. Secondary outcome measures fell into 2 broad categories. The first included ocular parameters of interest in study eyes and included CS and shape discrimination testing, Raman counts (RC), and extent and severity of the macular early AMD features (AMD grade). The second set of parameters was person related and consisted of serum levels of L, Z, vitamin E, vitamin C, and Zn. Interferometric measurements of retinal acuity also were made at every visit, but were deemed unreliable in more than half of the participants, and thus these data were not analyzed.

Statistical Analysis

After completion of consistency checks, statistical analysis was performed with the Statistical Packages for Social Sciences version 15 (SPSS, Inc, Chicago, IL). The outcomes from both eyes of group 2 individuals were not treated as independent observations.[11] A method similar to that of generalized estimating equations and imposed weights that were inversely proportional to the variance of each individual were used. The weights were computed based on the correlation between the changes in BCVA in study eyes at the primary outcome point of 12 months within participants belonging to group 2 who contributed 2 eyes to the analysis. These weights were applied in all the main analyses.

The 13 AMD severity grades assigned by the reading center first were collapsed into 6 stages,[12] which formed a graded categorical scale of severity (Table 1 available at http://aaojournal.org). The separation of the thresholds between the 6 severity stages indicated that the 2 least severe should be collapsed to yield 5 levels. The macular characteristics that constituted each level of the final severity staging also are shown.

Serum values of L, Z, vitamin E, vitamin C, and Zn were found to be skewed and heterogenous (high levels in the active arm and low levels in the placebo arm), and therefore data were log transformed for the main analyses. Prespecified secondary outcomes of (1) change in BCVA at all visits beyond 12 months, (2) change in CS and RC in study eyes at all study visits, and (3) change in AMD severity grading were tested with arm of study as the grouping variable

The study design did not permit assessment of each antioxidant separately for its beneficial effect. However, serum was sampled at each visit and data were obtained on the levels of L, Z, vitamin C, vitamin E, and Zn, and thus a series of analyses to examine the relationships between these and the 2 most clinically meaningful outcomes of BCVA and AMD severity stage could be undertaken. In 12% of the samples, Zn concentrations were more than 20 μmol/l and were excluded from the analysis, because these were considered to reflect artifactual Zn accumulation during sample handling and did not represent normal physiologic concentrations in response to the dose of supplement used.[13]

A general linear model was used to assess the longitudinal effects of individual serum analytes. The dependent variable was BCVA in study eyes. Time on study was entered as a linear effect, and the patient was entered as a fixed block effect. A sequence of models was run in which each of the following serum covariates were tested: L, Z, vitamin C, vitamin E, and Zn. To examine the effect of serum covariates on morphologic change, an ordinal regression model was used with the computed AMD grade as the dependent variable, the person as a fixed factor, and each of the serum factors and time on study as covariates.

Results

In total, 433 participants were enrolled in the 2 study sites: 200 in Belfast and 233 in Waterford (Table 2). Randomization resulted in 216 participants assigned to receive the active preparation, whereas 217 were assigned to placebo. There were 252 participants who contributed only 1 study eye (group 1) and 181 who contributed 2 study eyes (group 2) to the analysis. In all, there were 7908 person-months of follow-up, with an average of 18.3 months. Patient demographics at baseline by study site and by treatment assignment are shown in Table 2. There were no imbalances in any of the measured baseline variables by treatment assignment. There were no significant differences between the study sites in any of

Table 2. Baseline Characteristics of Study Participants by Site and Treatment Assignment

	Belfast Center, n (%)		Waterford Center, n (%)	
	Treatment (n = 100)	*Placebo (n = 100)*	*Treatment (n = 116)*	*Placebo (n = 117)*
Gender				
Male	48 (48)	41 (41)	44 (38)	52 (44)
Female	52 (52)	59 (59)	72 (62)	65 (56)
Age (yrs)				
50–64	9 (9)	4 (4)	13 (11)	21 (18)
65–74	34 (34)	37 (37)	55 (47)	43 (37)
75–84	46 (46)	53 (53)	44 (38)	49 (42)
≥85	11 (11)	6 (6)	4 (3)	4 (3)
Smoking history				
Never	41 (41)	41 (41)	40 (35)	52 (45)
Ever	46 (46)	40 (40)	62 (54)	48 (41)
Current	12 (12)	19 (19)	13 (1)	16 (14)

Table 3. Mean Best-Corrected Visual Acuity in Study Eyes at Each Visit by Treatment Assignment

Visit	Treatment Group (n = 216)		Placebo Group (n = 217)	
	Study Eyes (n)	*Mean Best-Corrected Visual Acuity (Standard Deviation)*	*Study Eyes (n)*	*Mean Best-Corrected Visual Acuity (Standard Deviation)*
Baseline	304	79.7 (6.6)	310	79.9 (6.5)
6 mos	269	79.4 (9.2)	278	80.1 (8.3)
12 mos	243	79.7 (8.9)	250	80.4 (9.8)
18 mos	171	79.1 (11.0)	183	79.7 (10.7)
24 mos	125	78.7 (11.7)	135	79.2 (11.4)
30 mos	77	79.7 (11.1)	73	78.7 (11.8)
36 mos	30	83.1 (6.7)	28	79.5 (11.7)

Best-corrected visual acuity was recorded as the number of letters read at 4 m on the Early Treatment Diabetic Retinopathy Study chart. Beyond 12 months, the number of study eyes available for analysis at each visit fell markedly because the minimum follow-up in the trial was 1 year.

the measured baseline variables. The CONSORT (Consolidated standards of reporting trials) diagram of the flow of participants during the study (Fig 1, available at http://aaojournal.org) shows that 88 participants (20%) exited the study before the 12-month visit and that these participants were distributed equally between the 2 arms. Most exits were self-withdrawals for personal reasons. By 12 months, there were 5 withdrawals because of gastrointestinal disturbances and 7 as a result of death. Six participants demonstrated late AMD in the sole study eye and exited the study because this was prespecified in the protocol. All of these events were distributed equally across the 2 study arms. For those participants who remained in the trial up to its prespecified end point of 12 months, there were no missing data on the primary outcome variable.

Functional Outcomes

By 24 months, a steadily increasing differential was observed in BCVA that favored the active group by 1.4 letters ($P = 0.04$; Table 3 and Fig 2). Change in contrast sensitivity marginally favored the active group, but no statistically significant differences were observed (Table 4 and Fig 3, available at http://aaojournal.org).

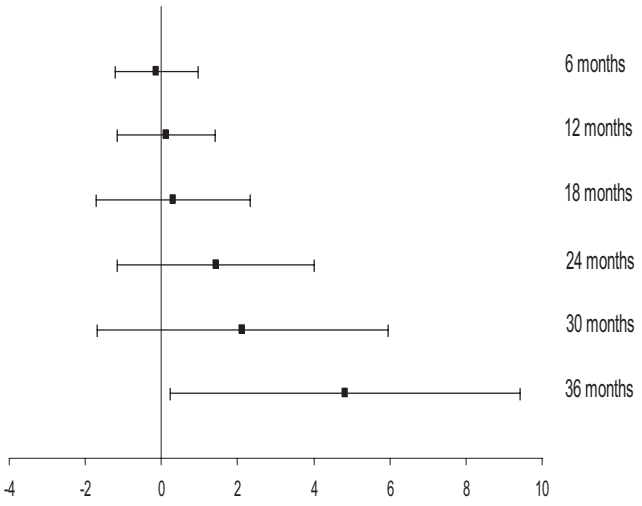

Figure 2. Point estimate showing the mean differential in the change in best-corrected visual acuity in the treatment and placebo groups (x-axis) at each study visit (y-axis), with the bars representing the 95% confidence limits.

Morphologic Outcomes

There were no statistically significant differences in the distribution of severity stage in study eyes when categorized by treatment assignment at any of the follow-up time points (Tables 5 and 6, available at http://aaojournal.org). On examining progression, which was defined as a change in at least 1 stage from a lower level to a higher level of severity from the baseline visit to a follow-up visit, proportionately fewer eyes in the active group demonstrated progression compared with the placebo group. This is reflected in the Kaplan Meier 1-survival graph (Fig 4), which shows that eyes of participants in the active group progressed at a slower rate. Thus, for example, at 12 months, 47.4% of eyes in the placebo arm (108/228) had demonstrated progression compared with 41.7% of eyes in the active arm (96/230). There was no statistically significant difference between the event rates at any of the time points when analyzed by arm of study. On testing for progression to late AMD only (i.e., a conversion from an early AMD stage to either central GA or CNV), 39 such conversions occurred in the placebo group and 33 in the active group. This difference was not statistically significant.

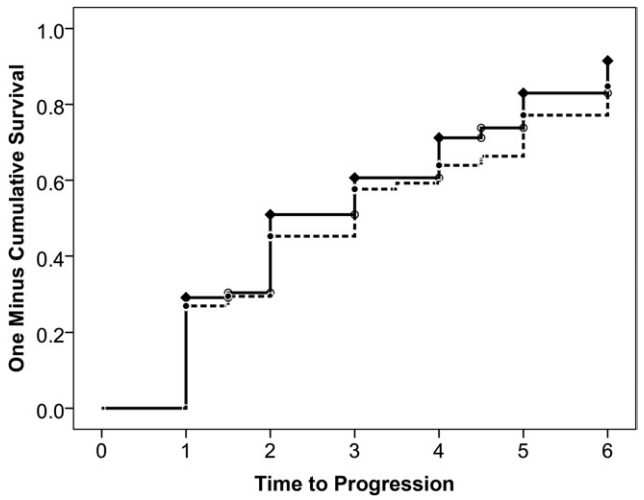

Figure 4. Kaplan-Meier graph of progression on the age-related macular degeneration severity scale. The intervals on the x-axis are 6 months apart. The eyes of participants in the active treatment arm (dashed line) progressed at a slower rate than the placebo arm (solid line). There were no statistically significant differences between event rates by arm of study at any of the time points.

Table 7. Mean Raman Counts by Treatment Assignment

Visit	Active		Placebo		Differential Change between A and P (95% Confidence Interval)	P Value
	No. of Eyes	*Mean Raman Count*	*No. of Eyes*	*Mean Raman Count*		
Baseline	246	433	249	398		
6 mos	197	464	200	369	84 (31–137)	0.002
12 mos	142	443	139	343	87 (25–149)	0.006
18 mos	93	487	105	372	83 (18–147)	0.013
24 mos	63	535	80	317	168 (86–249)	0.000
30 mos	70	486	62	335	104 (15–194)	0.021
36 mos	28	494	28	278	67 (–113 to 248)	0.454

A = active; P = placebo.
Mean Raman counts are shown by treatment assignment. Statistical significance was tested using the *t* test. The differential change in Raman count during time in study by treatment assignment is shown. Statistically significant differences in Raman count are seen between the 2 treatment groups at all time points except 36 months.

Macular Pigment

Average RC in study eyes of participants in the active group demonstrated a small increase with time, whereas that of the placebo group showed a steady decline (Table 7). Highly statistically significant differences were observed between treatment and placebo groups for absolute values of average RC at each study visit after the baseline visit (data not shown). The differential change over time (Table 7) between active and placebo groups was highly statistically significant at all time points except at the 36-month visit, when numbers were small.

Serum Analytes

At baseline, serum concentrations of L and Z were highly similar between the active and placebo groups (log L, 0.159 μmol/l and 0.141 μmol/l, active vs. placebo, respectively; and for serum Z, 0.025 μmol/l and 0.022 μmol/l, active vs. placebo, respectively). In the group that received the active preparation, serum levels of L (Table 8) and Z (Table 9, available at http://aaojournal.org) had risen markedly by the 6-month visit. Serum levels of vitamin C, vitamin E, and Zn also increased by the 6-month visit (Tables 10 and 11, available at http://aaojournal.org). The differences in serum analytes were highly statistically significant between the active and placebo groups for all time points.

Longitudinal Analysis at 12 Months

The relationships between serum analytes and visual acuity are shown in Table 12. The only analyte that showed statistical significance was serum L, for which a 10-fold rise resulted in a benefit of 1.4 letters (95% confidence interval, 0.3–2.5; $P = 0.01$). The removal of a single outlier reduced this effect to 0.9 letters (95% confidence interval, −0.2 to 1.9) with loss of significance. Similar models with all other serum analytes of Z, vitamin C, vitamin E, and Zn showed no statistically significant relationships.

When change in AMD severity stage was included as the dependent variable, serum L as the covariate, and person as the fixed factor, the model showed that a 1-log unit increase in serum L was associated with a slower progression along the AMD severity scale by approximately 0.2 of an AMD stage ($P = 0.014$). A model with log serum Z produced an effect of similar size, but failed to reach statistical significance ($P = 0.053$).

Discussion

This article reports the secondary outcomes that were collected in the CARMA study, which is a double-masked, randomized controlled clinical trial of oral antioxidant supplementation versus placebo in persons with early AMD in at least 1 eye. The prespecified primary outcome was that supplementation would result in either preserved or improved retinal function in those randomized to the active arm when compared with the placebo group by 12 months. Although the mean change in BCVA marginally favored the supplemented group, this did not reach statistical significance, and this result has been reported elsewhere (Beatty S, et al, manuscript in press, 2012).

Table 8. Log Serum Lutein by Treatment Assignment

Visit (mos)	Treatment Group		Placebo Group	
	No. of Participants	*Change in Log Lutein in μmol/l (95% Confidence Interval)*	*No. of Eyes*	*Change in Log Lutein in μmol/l (95% Confidence Interval)*
6	178	0.677 (0.629–0.725)	179	–0.009 (–0.031 to 0.013)
12	163	0.672 (0.618–0.726)	161	0.009 (–0.014 to 0.032)
18	115	0.705 (0.640–0.769)	122	0.036 (–0.007 to 0.079)
24	83	0.710 (0.637–0.769)	92	0.008 (–0.022 to 0.039)
30	52	0.609 (0.484–0.733)	49	–0.018 (–0.069 to 0.032)
36	18	0.730 (0.526–0.935)	16	0.031 (–0.031 to 0.092)

The mean change in log serum lutein from baseline to each study visit is shown by treatment assignment. Marked increases in serum lutein are seen in the group that received the active supplement, whereas serum lutein in the placebo group remained unchanged.

Table 12. Longitudinal Analysis on the Effect of Serum Analytes on Best-Corrected Distance Visual Acuity

Analyte	Estimate	95% Confidence Interval	*P* Value
Lutein	1.44	0.32–2.55	0.012
Zeaxanthin	0.66	–0.92 to 2.25	0.41
Vitamin E	2.61	–1.21 to 6.42	0.18
Vitamin C	0.50	–0.09 to 1.09	0.095
Zinc	0.42	–3.23 to 4.08	0.82

General linear model of the effect of serum analytes on best-corrected visual acuity. The model showed a statistically significant benefit on best-corrected visual acuity for lutein, but not for other serum analytes.

One of the secondary outcome measures in the CARMA study was the change in BCVA beyond 12 months. Over time, the differential in BCVA between active and supplemented groups increased and was reflected in statistically significant differences at 2 years and beyond. Small differences were observed in favor of the supplemented group for CS,[14] but these did not reach statistical significance.

Macular pigment (MP), as measured by Raman spectroscopy, declined steadily over time in the placebo group, whereas a rise in MP was observed in the intervention group. The differences between the 2 arms of the study reached statistical significance at all points of follow-up during the study. This prospectively observed decline in MP over time in eyes with AMD has not been reported previously and is consistent with loss of photoreceptors in association with this disease, because MP is housed in the photoreceptors and their axons.[15]

Although the CARMA study was not powered to detect differences in the development of late features of AMD, some 16.5% of eyes progressed to either GA or CNV. Overall, eyes in the actively supplemented group progressed along the AMD severity scale at a slower rate when compared with the placebo group. Of the 72 eyes in which late-stage AMD (either CNV or GA) developed during the study, the split favored the active group (33 conversions in the active vs. 39 in the placebo). This difference was not statistically significant.

Cross-sectional studies have suggested that AMD is associated with a relative lack of macular carotenoids in the serum.[16,17] Higher serum concentrations of L were associated with retardation of AMD progression and with an improvement in BCVA. It is notable that L is converted to meso-zeaxanthin within retinal tissue, whereas Z is not.[18] Meso-zeaxanthin is thought to be a more powerful antioxidant than either L or Z, and data indicate that it is dominant in the central fovea.[18] Therefore, it is hypothesized that augmentation with L could have resulted in a rise of meso-zeaxanthin with consequent protection against progression to more severe levels of AMD.

Macular pigments optical and anatomic properties have prompted the so-called optical hypotheses of this pigment, which is based on its potential to enhance visual function and comfort by attenuation of the effects of chromatic aberration and light scatter, via its light-filtering properties.[19] Several studies have suggested a beneficial role for MP in visual acuity and contrast sensitivity, glare sensitivity, photostress recovery, critical flicker fusion frequency, and color vision.[20–22] Recent trials have added to the body of knowledge on the complex role of L in improving visual function in disease.[23–28] The Lutein Antioxidant Supplementation Trial demonstrated an increase in mean MP optical density associated with an improvement in visual acuity, CS, glare recovery, and visual distortion in the actively supplemented groups.[27] However, legitimate criticisms include the small number of patients recruited into each arm of the investigation and the short follow-up (i.e., only 12 months).

The supplement used in the CARMA study was different in composition to that used in AREDS.[5] The CARMA study excluded β-carotene, reduced the daily dose of Zn from 80 mg to 20 mg, and reduced that of vitamin C from 500 mg to 150 mg because these levels are not permitted within the European Union. Also, L and Z were included, which were not part of the original AREDS formulation. In AREDS, the benefit in terms of a reduced progression from early to late AMD was mainly attributed to Zn, because the intervention group that received this mineral alone had the better reduction in risk. However, AREDS also found that there was better preservation of visual acuity in persons who were supplemented with both antioxidants and Zn.[5]

The smaller sample size in the CARMA study and constraints in terms of resources did not permit the use of a factorial design, and instead the active preparation, which consisted of antioxidant vitamins and carotenoids combined with Zn, merely was compared with a placebo. Nonetheless, the longitudinal model that tested the effect of all of the included antioxidants suggested that only L was associated with a small benefit in terms of maintained BCVA.

Weaknesses of the CARMA study include a loss to follow-up of some 20% of participants in the first year of the trial. However, 7 of these were because of death and a further 6 were the result of the development of either CNV or GA in the sole study eye, necessitating prespecified withdrawal of these participants. Set against this weakness, the CARMA study was a double-masked, randomized, controlled clinical trial that collected a wide range of functional and morphologic outcomes in a standardized manner across 2 clinical sites and measured robust biomarkers of supplementation through serial blood sampling.

In summary, these findings of differences in psychophysical measures that favored the supplemented group is in accord with other recent reports of benefits that were observed in much smaller clinical trials of antioxidant supplementation.[26–28] These findings are of relevance and will inform the design of future studies.

Acknowledgments. The authors thanks the Data and Safety Monitoring Committee, comprising Professor Astrid Fletcher (chairperson), Professor Frank Holz, and Professor Erik VanKuijk.

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Footnotes and Financial Disclosures

Originally received: August 15, 2011.
Final revision: August 20, 2012.
Accepted: August 23, 2012.
Available online: December 6, 2012. Manuscript no. 2011-1230.

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Financial Disclosure(s):
The author(s) have no proprietary or commercial interest in any materials discussed in this article.

Supported by a grant from Bausch and Lomb, Dr. Mann Pharma, Berlin, Germany. The data set was managed and analyzed by the independent statistician (MRS) and his team. The senior corresponding author (UC) had full access to the data outputs. The funders had no access to the data, were not involved in the data analysis, and had no role in the construction of the manuscript, except in the approval of the final draft.

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