Published in final edited form as:

Curr Ophthalmol Rep. 2015 March ; 3(1): 34–39. doi:10.1007/s40135-014-0059-z.

Nutritional Supplements for Age-Related Macular Degeneration

Ninel Z. Gregori, M.D.,

Bascom Palmer Eye Institute, Department of Ophthalmology, Miller School of Medicine, University of Miami, 900 NW 17th St., Miami, FL 33136, USA, Miami Veterans Affairs Medical Center, 1201 NW 16th, Miami, FL 33126, USA

Raquel Goldhardt, M.D.

Bascom Palmer Eye Institute, Department of Ophthalmology, Miller School of Medicine, University of Miami, 900 NW 17th St. Miami, FL 33136, Miami Veterans Affairs Medical Center, 1201 NW 16th, Miami, FL 33126, USA

Abstract

The Age-Related Eye Disease Study (AREDS) and The Age-Related Eye Disease Study 2 (AREDS2), are the only large-scale, long-term, randomized controlled trials to demonstrate a role of nutritional supplements in reducing risk of progression to advanced forms of age-related macular degeneration (AMD). This review summarizes the study design, main results, and implications of these trials in the clinical care of nonexudative AMD patients. In addition, it discusses other recent prospective studies focusing on efficacy of nutritional supplementation for prevention or slowing progression of AMD as well as briefly discusses possible effect of genotypes on response to AREDS supplementation.

Keywords

Nutritional supplements; age-related macular degeneration; Age-Related Eye Disease Study; vitamins; age-related macular degeneration

Introduction

Age-related macular degeneration (AMD) is the leading cause of blindness among white persons and the third most common cause of blindness and visual impairment worldwide, [1–3] and its visual impact on society is growing. [2] While there have been recent advances in the pharmacologic treatment of exudative AMD, treatments for nonexudative AMD are lacking. Epidemiological studies have provided information on the risk factors associated with AMD, including advancing age, female gender, cigarette smoking, obesity, red meat intake, and beneficial effects of fish, fruit, low glycemic index, moderate alcohol consumption, and high intake of omega-3 long-chain polyunsaturated fatty acids

(corresponding author) TEL: 305-326-6000, FAX: 305-326-6417, ngregori@med.miami.Edu.

Human and Animal Rights and Informed Consent:

This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest:

Dr. Gregori and Dr. Goldhardt do not have any conflicts of interests to disclose.

(LCPUFAs) and macular xanthophylls. [4–6] The Age-Related Eye Disease Study (AREDS) was the landmark prospective, large-scale, randomized controlled trial which provided level 1 evidence that a combination of vitamin C, vitamin E, beta-carotene, zinc, and copper significantly reduced the risk of visual loss and disease progression in patients with at least intermediate AMD, thereby establishing the role of nutritional supplements in the care of nonexudative AMD patients. The extension of the AREDS trial, the AREDS2 study was completed and the findings were recently published.[7] This study looked at the potential added benefit of omega-3 fatty acids and macular xanthophylls (lutein and zeaxanthin) supplementation and the effect of beta-carotene elimination as well as zinc content reduction in the original AREDS formulation. [8] These prospective trials represent the best evidence available to date to guide clinicians' recommendations of nutritional supplementation in patients at risk of advanced forms of AMD.

The aim of the current review is to summarize the results of AREDS and AREDS2 trials and their implication in the clinical care of nonexudative AMD patients, and to briefly overview other recent prospective studies that have investigated efficacy of nutritional supplementation for prevention or slowing progression of AMD. This article does not contain any studies with human or animal subjects performed by any of the authors.

Possible role of nutrition in the pathogenesis of AMD

The pathogenesis of AMD is complex and multifactorial involving genetic and environmental factors.[9] Pathological findings in AMD include degeneration of the retinal photoreceptors, retinal pigment epithelium (RPE), Bruch's membrane, as well as choroidal capillaries. [9] Aging is associated with alterations in RPE cellular size and shape as well as thickening of Bruch's membrane and the internal limiting membrane. Glycoproteins and lipids accumulate between the RPE and the Bruch's membrane and within Bruch's membrane forming drusen. [9] Immunohistochemical analyses have shown various molecular constituents, such as apolipoproteins B and E, different immunoglobulins, factor X, amyloid P component, amyloid β , complement C5 and C5b-9 terminal complexes, fibrinogen, vitronectin, and others, to be present in all phenotypes of hard and soft drusen. [9] Drusen has also been shown to contain proteins associated with inflammation including complement components and inflammatory cells such as the antigen-presenting dendritic cells, suggesting the involvement of the immune system in AMD pathogenesis. [10] Potential targets for treatment include prevention of oxidative damage, lipofuscin accumulation, complement activation, chronic inflammation, mitochondrial damage, and increased bone morphogenetic protein-4 in the RPE and extracellular matrix of eyes with drusen as well as those with geographic atrophy. [9] Not all may be addressed by nutrition, but it is well known that nutrition plays a role in oxidative damage and inflammation, both of which are important in AMD. For example, it has been shown that antioxidants plus zinc, offer a protective effect on progression to advanced AMD in individuals homozygous for non-risk phenotype (Y402Y/Y402Y) of the major AMD-susceptibility gene, complement factor H, which is identified in normal RPE and choroid. [11] The National Eye Institute-funded Age-Related Eye Disease Study (AREDS) clinical trial program was designed to gain insight into AMD (and cataract) as well as evaluate the role of vitamins and minerals on progression of these diseases.

Pivotal Prospective Clinical Trials on Nutritional Supplements for AMD

The Age-Related Eye Disease Study (AREDS)—Although a number of epidemiologic studies have suggested the role of various antioxidants in AMD, AREDS was the first randomized controlled trial to evaluate the effect of combination antioxidants (500 mg vitamin C, 400 IU vitamin E, 15 mg β -carotene, 80 mg zinc, 2 mg copper) on visual acuity and progression of AMD.[12] A total of 3609 participants were randomized to receive placebo, antioxidants, zinc, or antioxidants plus zinc. Subjects were also allowed to take Centrum (Whitehall-Robins Healthcare, Madison, NJ), a multivitamin and mineral supplement. Subjects were divided into several categories based on the location and extend of drusen and geographic atrophy within 2 disc diameters of the center of the macula and pigment abnormalities within 1 disc diameter of the center of the macula as seen on the fundus photographs examined at the University of Wisconsin reading center. [12] Category 1 participants had none or 5–15 small drusen ($<63\ \mu\text{m}$), no pigment abnormalities, and visual acuity of 20/32 or better in both eyes. Category 2 participants had multiple small drusen, single or nonextensive intermediate drusen ($63\text{--}124\ \mu\text{m}$) with or without pigment abnormalities, or no drusen if pigment abnormalities are present, and visual acuity of 20/32 or better in both eyes. Category 3 required absence of advanced AMD in both eyes and at least one eye with visual acuity of 20/32 or better with at least one large druse ($\geq 125\ \mu\text{m}$), extensive intermediate drusen (approximately 20 intermediate drusen if soft drusen are present or at least 65 intermediate drusen if soft drusen are absent), or geographic atrophy (GA) that did not involve the center of the macula, or any combination of these (Figure 1). 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 due to AMD. [12]

The primary outcomes were progression to (1) advanced AMD and (2) 15-letters decrease in visual acuity from baseline to 5 years. Secondary outcomes included development of neovascular AMD, incidence of GA (not necessarily in the center of the macula), progression to advanced AMD with an associated VA decrease of 15-letters, and worsening of AMD classification in Category 2 participants to Category 3 or 4 during follow-up. Secondary VA outcomes included a decrease in the best-corrected visual acuity (BCVA) score from baseline of 30-letters in a study eye and progression to a BCVA score worse than 20/100 in one or both eyes.[12]

Overall, AREDS demonstrated that the combination of vitamin C, vitamin E, beta-carotene, zinc, and copper, reduced the 5-year risk of developing advanced AMD by 25% in eyes with at least intermediate AMD, i.e. Category 3 and Category 4. At 5 years, the probability of moderate visual loss was 29% for those in placebo group, 26% for those in the oxidants group, 25% for the zinc group, and 23% for the antioxidants plus zinc group. [12] Only participants in Categories 3 and 4 assigned to antioxidants plus zinc had a significant reduction in the risk of moderate visual loss at 5-years. [12] Based on these results, it was reasonable to recommend that those patients with extensive intermediate size drusen, at least one large druse, noncentral geographic atrophy in one or both eyes (Figure 1), or advanced AMD or vision loss due to AMD in one eye, and without contraindications such as smoking,

should consider taking a supplement of antioxidants plus zinc such as that used in this study. [12] The effect of the AREDS formulation on primary prevention of AMD is uncertain, therefore AREDS formulation is not recommended for patients without AMD or with early stages of AMD (less than Category 3 or 4 characteristics).

Potential adverse effects of the AREDS supplements are as follows: 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). The incidence of potential side effects was reported low and insignificant. [12]

In relation to cataract progression, the AREDS study did not show a significant effect on the 7-year risk of development or progression of age-related lens opacities.[13] One caveat, however, is that the AREDS population was comprised of relatively well-nourished older adults, thus the effects of vitamin supplementation may be different in other populations.

The Age-Related Eye Disease 2 Study (AREDS2)—Observational studies suggest that higher dietary intake of macular carotenoids and omega-3 long-chain polyunsaturated fatty acids (LCPUFAs) maybe associated with lower risk of developing late AMD. A recent meta-analysis reported that a high dietary intake of omega-3 fatty acids was associated with a 38% reduction in the risk of late AMD. [14] Lutein and zeaxanthin are selectively concentrated in the macula of the eye. Lutein and zeaxanthin have been shown to modulate inflammatory responses in cultured RPE cells in response to photo-oxidation, and it has been hypothesized that they might protect against AMD by reducing oxidative stress within the retina and by blocking harmful blue light. [15, 16] At the molecular level this may occur via modulation of oxidation-induced alterations in expression of inflammation-related genes and attenuation of oxidation-induced inactivation of the ubiquitin-proteasome pathway which is involved in stress responses.[16] Recently published results of a randomized, double-masked, placebo-controlled trial of lutein and zeaxanthin supplementation in individuals with early AMD significantly improved macular pigment optical densities and multifocal electroretinogram parameters. [17]

The AREDS2 is a multicenter, randomized, double-masked, placebo-controlled phase 3 study, which enrolled 4203 participants, 50 to 85 years of age. The Age-Related Eye Disease Study 2 (AREDS 2) was designed to evaluate whether the addition of oral lutein/zeaxanthin and/or omega-3 fatty acids (eicosapentaenoic (EPA) acid and docosahexaenoic (DHA) acid) to the original AREDS formula would further decrease the risk of progression to late AMD. In addition, AREDS2 assessed the effect of eliminating beta-carotene, which increases risk of lung cancer in cigarette smokers, [18] and lowering the dose of zinc from 80 mg, which is above the tolerable upper level of daily zinc intake of 40 mg, to 25 mg. [8] All participants were randomly assigned to take one of the following daily: placebo (n = 1012); lutein plus zeaxanthin (10 mg/2 mg; n = 1044); omega-3 fatty acids EPA plus DHA (650 mg/350 mg; n = 1069), or the combination of lutein plus zeaxanthin (10 mg/2mg) and EPA plus DHA (650 mg/350 mg) (n = 1078). All participants were offered a secondary randomization to 1 of 4 variations of the original AREDS formulation keeping vitamins C (500 mg) and E (400 IU) and copper (2 mg) unchanged. Of those who opted to take the AREDS formulation, 3036

were randomized a second time as follows: keep zinc at the original level (80 mg), lower zinc to 25 mg, omit beta-carotene, or lower zinc to 25 mg and omit beta-carotene. Because beta-carotene increases risk of lung cancer in cigarette smokers,[8] participants who were current smokers or former smokers who had stopped smoking within the year before enrolling in AREDS2 were assigned to the no beta-carotene arms with 25 mg or 80 mg zinc oxide.

The primary analyses of AREDS2 data showed that the rate of progression to advanced AMD was similar among the study groups compared to placebo after a median follow-up of 5 years: 31% for placebo, 29% for lutein-zeaxanthin, 31% for DHA plus EPA, and 30% for lutein plus zeaxanthin and DHA plus EPA.[7] Further subgroup analysis stratifying participants by dietary lutein/zeaxanthin intake showed protective effect of lutein/zeaxanthin in the lowest quintile (the lowest dietary intake of these carotenoids) with a Hazard Ratio of 0.74 (95% CI, 0.59–0.94; $P=0.01$) for progression to late AMD.[7] This protective effect was not seen for higher quintiles of lutein/zeaxanthin intake. Primary, secondary, and subgroup analyses demonstrated no beneficial or harmful effects of DHA with EPA for progression to late AMD. Moreover, there was no effect of beta-carotene elimination or lower dose zinc formulation on progression to advanced AMD. None of the nutrients affected development of moderate visual loss defined as a reduction of 15 letters. More lung cancers were noted in the beta-carotene versus no beta-carotene group (23 [2.0%] vs 11 [0.9%], $P=0.04$); and 91% of participants who developed lung cancer were former smokers. No significant differences in serious adverse events or mortality were found among the different groups.

Secondary head-to-head analyses of lutein/zeaxanthin versus beta-carotene (both given with the AREDS formulation consisting of Vitamin C, E, zinc, and copper) revealed significantly better protective effect of lutein/zeaxanthin for progression to late AMD, particularly neovascular AMD but not to central geographic atrophy. [19] Secondary analysis comparing lutein/zeaxanthin versus no lutein/zeaxanthin in terms of progression to late AMD and particularly neovascular AMD in eyes with bilateral large drusen versus eyes with advanced AMD in one eye revealed significantly better protective effect of lutein/zeaxanthin only in the eyes with bilateral large drusen. It was also shown that beta-carotene did not contribute a synergistic effect to lutein/zeaxanthin in these comparisons. [19]

No significant difference was found in terms of progression to central geographic atrophy in either category of participants, which may be partly due to lower rates of development of central geographic atrophy in AREDS2 limiting statistical power. [19] AREDS trial has previously reported no statistically significant benefit of antioxidants or zinc on the progression of atrophic AMD or the development of any or central GA. [20] Median time to progression from GA to central GA was 2 years. [20]

Based on the analyses described, the authors concluded that despite lack of beneficial effect of adding lutein plus zeaxanthin, DHA plus EPA, or both to the original AREDS formulation, lutein and zeaxanthin could be substituted for beta-carotene in the AREDS formulation to eliminate the potential increased risk of lung cancer in former smokers. [7]

Other Recent Prospective Trials

Other significant recent trials are two trials out of Ireland, the CARMA and the CREST. The CARMA study (Carotenoids with Coantioxidants in Age-Related Maculopathy study) was a randomized, double-blind, placebo-controlled clinical trial of lutein (12 mg) and zeaxanthin (0.6 mg) in combination with co-antioxidants (vitamin C, E, and zinc) versus placebo administered to 433 persons with either early AMD in at least one eye (the minimum severity level was 20 soft distinct or indistinct drusen in the central macula) or any level of AMD in one eye with late AMD (neovascular AMD or central geographic atrophy) in the fellow eye. [21] No difference in best-corrected visual acuity (BCVA) was found between the active and placebo groups at 12 months, however the average BCVA was significantly better in the active group at 36 months.[22, 23] Retinal and serum levels of lutein and zeaxanthin were significantly higher in the active group, however no clear correlation was found between serum levels of the carotenoids or antioxidants and the visual acuity at 12 months.[23] A 1-log unit increase in serum lutein levels was associated with a 1.4 letter increase in BCVA (although statistical significance was questionable) and significantly slower progression along the AMD severity scale.[23]

The CREST trial (Central Retinal Enrichment Supplementation Trial) is an ongoing single-center, double-blind, randomized trial, which is recruiting 120 normal subjects and 150 patients with AMD to investigate change in visual function, namely contrast sensitivity (primary outcome measure), visual acuity, glare disability, photostress recovery, light scatter, cognitive function, foveal architecture by spectral-domain optical coherence tomography and color photography, retinal macular pigment density, serum carotenoid concentrations, reading speed and National Eye Institute Visual Functioning Questionnaire 25 following supplementation with three macular carotenoids, lutein (10 mg), zeaxanthin (2 mg), and *meso*-zeaxanthin (10 mg) for 12 months in the normal subjects and 24 months in the AMD patients. AMD patients will also be receiving 500 mg vitamin C, 400IU vitamin E, 25 mg zinc and 2 mg copper. [24]

Genetics and Risk of AMD progression

Recent studies looking at association between known AMD genetic risk markers and progression to advanced AMD in patients with available DNA analysis in AREDS trial were published with conflicting results. In 2013, Awh et al reported that among white patients enrolled in the AREDS trial with Category 3 AMD in at least one eye, those with no complement factor H (CFH) risk alleles and with 1 or 2 age-related maculopathy sensitivity 2 (ARMS2) risk alleles obtained maximum benefit from zinc-only supplementation during average follow-up of 10.1 years.[25] Patients with one or two CFH risk alleles and no ARMS2 risk alleles derived maximum benefit from antioxidant-only supplementation; while treatment with zinc was associated with increased progression to advanced AMD. [25] In 2014, a subgroup analysis of 989 white patients from the AREDS study with category 3 or 4 AMD and available DNA reported that patients with 2 CFH risk alleles and no ARMS2 risk alleles progressed more with zinc-containing treatment compared to placebo.[26] The 7-year rates of progression were 17.0% for placebo, 43.2% for zinc, and 40.2% for the AREDS formulation with zinc. [26] Patients with 0 or 1 CFH risk alleles and 1 or 2 ARMS2 risk alleles benefited from zinc-containing treatment compared with placebo, with 7-year rates of

progression 43.3% for placebo, 25.2% for zinc, and 27.3% for the AREDS formulation with zinc. Patients with 0 or 1 CFH risk alleles and no ARMS2 risk alleles, did not benefit from zinc-containing treatment more than the placebo, but treatment with antioxidants decreased progression.[26] However, AREDS report number 38 showed that among 1237 genotyped AREDS patients of white ethnicity, the AREDS supplements reduced progression to advanced AMD across all genotype groups defined by the CFH and ARMS2 loci during a mean follow-up of 6.6 years. [27] Chew et al concluded that genetic testing does not seem to provide benefit in managing nutritional supplements for patients at risk for AMD progression. [27] Future research should help clarify whether certain genetic markers are associated with the effects of nutritional supplements in AMD, and whether genetic testing would be useful in generating an individualized treatment plan for patients.

Conclusions

AREDS and AREDS2 are the only large-scale, long-term follow-up, randomized controlled trials to demonstrate that a high-dose combination of vitamin C, vitamin E, beta-carotene, and zinc significantly reduced the risk of advanced AMD. Moreover, lutein and zeaxanthin could be substituted for beta-carotene in the AREDS formulation to eliminate the increased risk of lung cancer in former smokers. The effect of genotype on response to AREDS supplementation remains controversial at this time. Based on these results, the AREDS and AREDS2 formulations are the nutritional standard of care in AMD.

References

Papers of particular interest, published recently, have been highlighted as:

•Of importance

••Of outstanding importance

1. Congdon N, O'Colmain B, Klaver CC, Klein R, Munoz B, Friedman DS, Kempen J, Taylor HR, Mitchell P, Eye Diseases Prevalence Research G. Causes and prevalence of visual impairment among adults in the United States. *Arch Ophthalmol* 2004;122(4):477–485. [PubMed: 15078664]
2. Jonas JB. Global prevalence of age-related macular degeneration. *Lancet Glob Health*. 2014;2(2):e65–66. [PubMed: 25104656]
3. Bourne RR, Stevens GA, White RA, Smith JL, Flaxman SR, Price H, Jonas JB, Keeffe J, Leasher J, Naidoo K, Pesudovs K, Resnikoff S, Taylor HR, Vision Loss Expert G. Causes of vision loss worldwide, 1990–2010: a systematic analysis. *Lancet Glob Health*. 2013;1(6):e339–349. [PubMed: 25104599]
4. Ersoy L, Ristau T, Lechanteur YT, Hahn M, Hoyng CB, Kirchhof B, den Hollander AI, Fauser S. Nutritional risk factors for age-related macular degeneration. *Biomed Res Int* 2014;2014:413150.
5. • Cong R, Zhou B, Sun Q, Gu H, Tang N, Wang B. Smoking and the risk of age-related macular degeneration: a meta-analysis. *Ann Epidemiol* 2008;18(8):647–656. [PubMed: 18652983] This meta-analysis provides evidence for significant association between smoking, especially current smoking, and increased risks of age-related macular degeneration.
6. • Chew EY, Clemons TE, Agron E, Sperduto RD, Sangiovanni JP, Davis MD, Ferris FL 3rd, Age-Related Eye Disease Study Research G. Ten-year follow-up of age-related macular degeneration in the age-related eye disease study: AREDS report no. 36. *JAMA Ophthalmol* 2014;132(3):272–277. [PubMed: 24385141] This article provides long-term follow-up of Age-Related Eye Disease Study (AREDS) participants. Risk factors, visual acuity, and 10-year progression rates to intermediate and advanced age-related macular degeneration are outlined.

7. •• Age-Related Eye Disease Study 2 Research G. Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. *JAMA*. 2013;309(19):2005–2015. [PubMed: 23644932] This article outlines main results of The Age-Related Eye Disease Study 2 (AREDS2). The addition of lutein and zeaxanthin, omega-3 fatty acids, or both to the original AREDS formulation did not further reduce the risk of age-related macular degeneration progression.
8. • Group AR, Chew EY, Clemons T, SanGiovanni JP, Danis R, Domalpally A, McBee W, Sperduto R, Ferris FL. The Age-Related Eye Disease Study 2 (AREDS2): study design and baseline characteristics (AREDS2 report number 1). *Ophthalmology*. 2012;119(11):2282–2289. [PubMed: 22840421] This article presents AREDS2 study design and the participants' baseline demographics.
9. Ding X, Patel M, Chan CC. Molecular pathology of age-related macular degeneration. *Prog Retin Eye Res* 2009;28(1):1–18. [PubMed: 19026761]
10. Hageman GS, Luthert PJ, Victor Chong NH, Johnson LV, Anderson DH, Mullins RF. An integrated hypothesis that considers drusen as biomarkers of immune-mediated processes at the RPE-Bruch's membrane interface in aging and age-related macular degeneration. *Prog Retin Eye Res* 2001;20(6):705–732. [PubMed: 11587915]
11. Klein ML, Francis PJ, Rosner B, Reynolds R, Hamon SC, Schultz DW, Ott J, Seddon JM. CFH and LOC387715/ARMS2 genotypes and treatment with antioxidants and zinc for age-related macular degeneration. *Ophthalmology*. 2008;115(6):1019–1025. [PubMed: 18423869]
12. •• Age-Related Eye Disease Study Research G. 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. *Arch Ophthalmol* 2001;119(10):1417–1436. [PubMed: 11594942] This article presents results of The Age-Related Eye Disease Study (AREDS). The article demonstrates that certain patients with age-related macular degeneration (AMD) should consider taking a supplement of antioxidants plus zinc to reduce rates of progression to advanced AMD.
13. Age-Related Eye Disease Study Research G. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E and beta carotene for age-related cataract and vision loss: AREDS report no. 9. *Arch Ophthalmol* 2001; 119(10):1439–1452. [PubMed: 11594943]
14. Chong EW, Kreis AJ, Wong TY, Simpson JA, Guymer RH. Dietary omega-3 fatty acid and fish intake in the primary prevention of age-related macular degeneration: a systematic review and meta-analysis. *Arch Ophthalmol* 2008;126(6):826–833. [PubMed: 18541848]
15. Barker FM 2nd, Snodderly DM, Johnson EJ, Schalch W, Koepcke W, Gerss J, Neuringer M. Nutritional manipulation of primate retinas, V: effects of lutein, zeaxanthin, and n-3 fatty acids on retinal sensitivity to blue-light-induced damage. *Invest Ophthalmol Vis Sci* 2011;52(7):3934–3942. [PubMed: 21245404]
16. Bian Q, Gao S, Zhou J, Qin J, Taylor A, Johnson EJ, Tang G, Sparrow JR, Gierhart D, Shang F. Lutein and zeaxanthin supplementation reduces photooxidative damage and modulates the expression of inflammation-related genes in retinal pigment epithelial cells. *Free Radic Biol Med* 2012;53(6):1298–1307. [PubMed: 22732187]
17. Ma L, Dou HL, Huang YM, Lu XR, Xu XR, Qian F, Zou ZY, Pang HL, Dong PC, Xiao X, Wang X, Sun TT, Lin XM. Improvement of retinal function in early age-related macular degeneration after lutein and zeaxanthin supplementation: a randomized, double-masked, placebo-controlled trial. *Am J Ophthalmol* 2012;154(4):625–634 e621. [PubMed: 22835510]
18. Goodman GE, Thornquist MD, Balmes J, Cullen MR, Meyskens FL Jr., Omenn GS, Valanis B, Williams JH Jr. The Beta-Carotene and Retinol Efficacy Trial: incidence of lung cancer and cardiovascular disease mortality during 6-year follow-up after stopping beta-carotene and retinol supplements. *J Natl Cancer Inst* 2004;96(23):1743–1750. [PubMed: 15572756]
19. •• Age-Related Eye Disease Study 2 Research G, Chew EY, Clemons TE, SanGiovanni JP, Danis RP, Ferris FL 3rd, Elman MJ, Antoszyk AN, Ruby AJ, Orth D, Bressler SB, Fish GE, Hubbard GB, Klein ML, Chandra SR, Blodi BA, Domalpally A, Friberg T, Wong WT, Rosenfeld PJ, Agron E, Toth CA, Bernstein PS, Sperduto RD. Secondary analyses of the effects of lutein/zeaxanthin on age-related macular degeneration progression: AREDS2 report No. 3. *JAMA Ophthalmol*

- 2014;132(2):142–149. [PubMed: 24310343] This article outlines evidence from AREDS2 study that lutein and zeaxanthin are more appropriate than beta carotene in AREDS formulation.
20. Lindblad AS, Lloyd PC, Clemons TE, Gensler GR, Ferris FL 3rd, Klein ML, Armstrong JR, Age-Related Eye Disease Study Research G. Change in area of geographic atrophy in the Age-Related Eye Disease Study: AREDS report number 26. *Arch Ophthalmol* 2009;127(9):1168–1174. [PubMed: 19752426]
21. Neelam K, Hogg RE, Stevenson MR, Johnston E, Anderson R, Beatty S, Chakravarthy U. Carotenoids and co-antioxidants in age-related maculopathy: design and methods. *Ophthalmic Epidemiol* 2008;15(6):389–401. [PubMed: 19065432]
22. Beatty S, Nolan JM, Muldrew KA, Woodside J, Stevenson MR, Chakravarthy U. Visual outcome after antioxidant supplementation. *Ophthalmology*. 2013;120(3):645. [PubMed: 23714607]
23. Beatty S, Chakravarthy U, Nolan JM, Muldrew KA, Woodside JV, Denny F, Stevenson MR. Secondary outcomes in a clinical trial of carotenoids with coantioxidants versus placebo in early age-related macular degeneration. *Ophthalmology*. 2013;120(3):600–606. [PubMed: 23218821]
24. Akuffo KO, Beatty S, Stack J, Dennison J, O'Regan S, Meagher KA, Peto T, Nolan J. Central Retinal Enrichment Supplementation Trials (CREST): design and methodology of the CREST randomized controlled trials. *Ophthalmic Epidemiol* 2014;21(2):111–123. [PubMed: 24621122]
25. Awh CC, Lane AM, Hawken S, Zanke B, Kim IK. CFH and ARMS2 genetic polymorphisms predict response to antioxidants and zinc in patients with age-related macular degeneration. *Ophthalmology*. 2013;120(11):2317–2323. [PubMed: 23972322]
26. Awh CC, Hawken S, Zanke BW. Treatment Response to Antioxidants and Zinc Based on CFH and ARMS2 Genetic Risk Allele Number in the Age-Related Eye Disease Study. *Ophthalmology*. 2014.
27. Chew EY, Klein ML, Clemons TE, Agron E, Ratnapriya R, Edwards AO, Fritsche LG, Swaroop A, Abecasis GR, Age-Related Eye Disease Study Research G. No Clinically Significant Association between CFH and ARMS2 Genotypes and Response to Nutritional Supplements: AREDS Report Number 38. *Ophthalmology*. 2014.

Figure 1.

Fundus photographs representative of various patients falling into Category 3 of the AREDS study. These patients had vision of at least 20/32 in both eyes and no center involving geographic atrophy or exudative lesion in either eye. These patients benefit from the AREDS formulation.

A. The lower limit of Category 3, at least one large druse ($\geq 125 \mu\text{m}$ in diameter) if located within 2 disc diameters of the center of the macula.

B. Extensive intermediate (63–124 μm) drusen (at least 65 if no soft drusen are present)

C. Extensive intermediate (63–124 μm) drusen and few large drusen with pigment abnormalities

D. Multiple large ($\geq 125 \mu\text{m}$) soft drusen

E. Multiple intermediate (63–124 μm) and several large ($\geq 125 \mu\text{m}$), hard and soft, drusen

F. Multiple large ($\geq 125 \mu\text{m}$) hard drusen

G. Non-center involving geographic atrophy (drusen are not required if geographic atrophy is present)

H. Center involving geographic atrophy present in 1 eye (this is a Category 4 patient which is defined as advanced AMD, i.e. center involving geographic atrophy or exudative AMD in one eye)