Life After AREDS 2: What Should We Recommend to Patients With or at Risk of AMD?

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Abstract

PURPOSE
To establish a consensus on clinical recommendation of oral supplementation for patients with or at risk of developing age-related macular degeneration (AMD), from the perspective of the Age-Related Eye Disease Study 2 (AREDS 2) and other studies.

METHODS
Panel discussion based on a literature review of pertinent articles related to the prevention of AMD with oral supplementation.

RESULTS
On the basis of the findings, patients must first be encouraged to modify their diet and to eliminate modifiable risk factors before being recommended any type of oral supplementation. Then, recommendations must be customized on the basis of a patient's individual risk profile (i.e., age, gender, heredity, etc.) and severity of disease (i.e., category 1 to 4). Essential fatty acids (omega-3s) and vitamins may play a role, in a given clinical population, to prevent the occurrence or the progression of AMD disease. However, there is no single formula that can be applied to all patients with or at risk of AMD.

CONCLUSIONS
This group concluded that the full body of literature must be taken into consideration in order to justify clinical recommendations for patients. A single study such as AREDS 2 cannot, by itself, guide clinical practice. In all cases, recommendations must be individualized and patients should be monitored regularly.

KEY WORDS:
age-related macular degeneration, poly-unsaturated fatty acids, vitamins, AREDS 2

Sommaire

BUT
Établir des recommandations cliniques consensuelles quant à la gestion clinique des patients atteints ou à risque de développer une dégénérescence maculaire liée à l'âge (DMLA).

MÉTHODES
Discussion d'un panel d'experts basée sur l'analyse de divers articles scientifiques relatifs à la prise de suppléments vitaminiques et nutritionnels chez des patients atteints ou à risque de DMLA.

RÉSULTATS
Selon le panel, suite à l'analyse des articles, la première intervention devrait être d'inciter le patient à améliorer son hygiène de vie avant de recourir à des suppléments oraux.

Par la suite, les recommandations cliniques doivent tenir compte du profil de risque du patient, de sa nutrition, de sa condition systémique ainsi que de l'état de sa santé oculaire. Les omégas 3s et les vitamines peuvent jouer un rôle bénéfique auprès de populations cibles afin de prévenir l'apparition ou l'évolution de la DMLA. Comme il n'existe pas de recettes uniques, le tout doit être personnalisé selon les besoins du patient.

CONCLUSION
Le groupe conclut que l'ensemble de la littérature doit être prise en compte afin de justifier le recours à des suppléments oraux (omégas et vitamines) et que les recommandations doivent être personnalisées. Une seule étude, comme AREDS 2, bien que très importante, ne peut déterminer à elle-seule le comportement clinique des professionnels de la vue. L'importance du suivi régulier du patient doit également être comprise par tous.

Age-related macular degeneration (AMD) is the leading cause of irreversible vision loss in developed countries.[1,2] It is estimated that there are 17,000 new cases of neovascular (NV) AMD and 180,000 new cases of geographic atrophy (GA) AMD in Canada every year.[3] The disease has a substantial negative impact on patient quality of life and imposes a considerable burden on the economy.[3] Early and intermediate stages of AMD are prevalent in people older than 65 years of age,[4] and without intervention, the condition can evolve to advanced AMD[5] and result in significant loss of visual function.

Published 12 years ago, the Age-Related Eye Disease Study (AREDS) demonstrated that in persons with intermediate to severe AMD, a daily oral supplement containing vitamins and antioxidants reduced the risk of progression to advanced AMD by 25% versus placebo over a period of 5 years.[6] This "AREDS formula" consisted of 500 milligrams (mg) vitamin C, 400 international units (IU) of vitamin E, 15 mg beta-carotene, 80 mg zinc oxide, and 2 mg cupric oxide. Since then, observational studies have suggested that dietary intake of other carotenoids, particularly lutein and zeaxanthin, might play a role in protecting against AMD.[7,8] Moreover, the authors of AREDS[9,10] and others[8,11-13] highlighted the important role of dietary or supplemental forms of omega-3s, for preventing the development of AMD or its progression.

This is the context in which the AREDS 2 was published in May 2013.[14] This study, which was initiated in 2006, demonstrated that the addition of lutein, zeaxanthin, and omega-3s to the original AREDS formula, did not further reduce the risk of progression to advanced AMD

relative to the original formula.[14] However, several secondary and subgroup analyses in this study suggested a benefit to replacing beta-carotene, which is associated with an increased risk of lung cancer in current and former smokers, with other carotenoids such as lutein and zeaxanthin. These conflicting results, notably with regard to omega-3s, have led to confusion among health care professionals about how to counsel patients and their caregivers about dietary strategies to prevent the development and progression of AMD.

On November 1, 2013, a group of Quebec experts, consisting of eight optometrists and one ophthalmologist, gathered in Montreal to discuss the outcomes of the AREDS 2 from a clinical perspective, with the goal of guiding the optimal management of this disease. In order to consider the AREDS 2 in a more global context, a general critique was undertaken. Then, each participant was assigned to review and present the key findings of a published article related to the use of dietary supplements or dietary factors associated with AMD (see **Table 1** for a brief synopsis of the studies and key findings). A facilitated group discussion that ensued focused on synthesizing the data with the eventual goal of developing a clear and practical set of consensus-based, nonbinding clinical recommendations for patients with AMD.

GENERAL CRITIQUE OF THE AREDS 2

First, it is important to recognize that the AREDS 2 was founded on the original AREDS. A socioeconomic analysis of the patients enrolled in this latter study showed that they were, on average, more educated and better nourished at baseline than the average American[14] as well as those attending optometry practices in Canada. Moreover, a substantial proportion of patients were already taking vitamin and antioxidant supplements,[6,14] which suggested that their overall nutrition status was already supported by an external source of these nutrients. In this regard, there was no real placebo group in the AREDS 2. Moreover, 14% of patients were additionally taking "nonauthorized" supplements, which further increased their antioxidant intake.[14] Furthermore, the dosage and formulation of omega-3 supplements that were used in this study (eicosapentaenoic acid greater than docosahexaenoic acid [EPA>DHA] 1000 mg/day versus 2000 mg/day, as esters or triglycerides) were not optimal, considering the results of earlier studies on this subject. Finally, the AREDS 2 evaluated progression of AMD from moderate to advanced disease (NV and GA forms) without considering the effects of supplementation on the risk of development of the disease or its progression from mild to moderate disease.

The conclusions of the AREDS 2 can be applied to patients who were similar to those who were evaluated in the study, that is, patients with moderate to advanced AMD who are well nourished and well educated. Before extrapolating the study results to other patients, evidence derived from other studies must first be considered in order to appreciate the general context from which clinical recommendations can be formulated.

GENERAL RECOMMENDATIONS

After considering the outcomes of several studies that were presented and keeping a general context in mind, a consensus was reached by this group of experts—that recommendations should be based on the individual patient and their particular risk profile. Health care professionals should assess a patient's modifiable risk factors at the earliest opportunity to better counsel and categorize their risk of developing AMD or its progression to advanced AMD and to tailor advice about lifestyle, diet, and supplements. Tools are available to assist health care professionals in this regard. The results of the Macular Assessment Program (MAP), which aimed at evaluating the perceptions versus the realities of 290 Canadian optometrists, were recently reported and reviewed at this meeting.[15] This tool enables optometrists to categorize patients as having low, moderate, or high risk of AMD, on the basis of an evaluation of their modifiable and nonmodifiable risk factors. The literature suggests that the most important modifiable risk factors are smoking, alcohol consumption (>3 standard drinks/day), sun exposure (photostress), poor-quality diet, obesity, cardiovascular risk factors, and adherence to medication, whereas the most important nonmodifiable risk factors include age, gender, family history, ethnicity (Caucasians), and socioeconomic and educational status.

Therefore, all patients should be strongly encouraged to act on their modifiable risk factors

including smoking, diet, exercise, weight control, cholesterol, sun protection, and cardiovascular risk factors. This should constitute the foundation of counselling for all patients at risk of AMD or with AMD of any severity. Dietary advice should include information on food sources of lutein and zeaxanthin (e.g., green leafy vegetables and canned corn) and omega-3 fatty acids (e.g., wild fatty fish such as salmon, herring, and mackerel).

RECOMMENDATIONS STEMMING FROM THE AREDS 2

When a health care professional decides to recommend a vitamin supplement to a patient, the general consensus is that lutein and zeaxanthin should be preferred over beta-carotene. There is a growing body of evidence suggesting that high-dose beta-carotene supplementation (20–30 mg/day) is associated with a higher risk of lung cancer in smokers.[14,16] The AREDS 2 confirmed that any patient who actively smoked in the past must be considered a smoker, regardless of the duration since cessation. This is an important point because the prevalence of current and ex-smokers is higher in Quebec compared with the national average. According to the Canadian Tobacco Use Monitoring Survey, in 2012, 14.9% of the Quebec population aged 45 years and older identified themselves as current smokers and a further 44.7% were former smokers.[17]

RECOMMENDATIONS BASED ON CATEGORY OF AMD

Primary Prevention of AMD

Among the group of experts of the AREDS 2, it was felt that unaffected people with risk factors for the disease (e.g., family history or genetic risk) had been less well studied in randomized controlled trials and that the potential benefits of supplementation with antioxidants remains unclear for them. However, strong evidence from observational studies suggests that diets rich in omega-3 fats and fish intake are associated with protection against the development of AMD.[8,9,12,18] Consequently, eye health professionals may consider recommending omega-3 supplements or a diet rich in omega-3 sources in patients with risk factors for AMD (e.g., genetics), especially those who are poorly nourished, rather than recommending antioxidant supplements. Most of the experts also agreed that the safety and tolerability profile for omega-3 supplements was favourable and that supplementation did not appear to introduce unacceptable risks. There was stronger consensus among this group of experts that with regard to other modifiable risk factors, counselling that includes recommendation of regular exercise, sun protection, weight control, control of cardiovascular risk factors, and cessation of smoking, is very important and should not be neglected as a first step to prevent AMD occurrence.

Progression from Early AMD to Advanced AMD

The AREDS failed to demonstrate any significant benefit of supplementation in patients with less severe AMD (i.e., Category 1 or 2).[6] In this study, very few patients with Category 2 disease at baseline (i.e., patients with extensive small drusen, pigment abnormalities, or a few intermediate drusen) developed advanced AMD over the study period. On the basis of the available data, some clinicians therefore would not explicitly recommend antioxidant supplements to individuals with early AMD unless there was clear evidence of poor diet quality or dietary intake of carotenoids and omega-3s was insufficient. Dietary interventions may be of value in reducing the risk of progression in these patients.

Intermediate or Advanced AMD

For those patients who already have advanced AMD (i.e., defined by AREDS category), there may be some benefit in taking an antioxidant supplement with or without omega-3s, given that both the AREDS and the AREDS 2 showed a 25 to 30% reduction in the risk of progression from moderate to advanced AMD in the affected eye, as well as progression in the other eye.[6,14] Patients who are most likely to benefit from supplements are those who fit the profile of the patients studied in the AREDS and AREDS 2, that is, those with category 3 (many intermediate drusen or at least one large druse with abnormal pigmentation) or category 4 AMD (GA affecting the fovea or wet AMD with retinal fibrosis).[14]

Some experts still believe that patients with intermediate or advanced AMD could also benefit from omega-3 fatty acid supplementation despite the negative findings of the AREDS [2,14]

particularly older patients who often have comorbid conditions (cardiovascular disease, diabetes, etc.), in whom the beneficial effects of fatty acid supplementation have been more clearly demonstrated. However, at this time, given the available evidence from randomized controlled trials, the optimal dose of omega-3 supplements, duration of treatment, and the magnitude of potential benefit remain unclear. There is consistent evidence from observational studies that people who consume the highest amount of omega-3s, particularly in the form of triglycerides or fatty fish in their diet have a lower incidence of AMD or progression to advanced AMD compared with those with the lowest intake.[9,12,18] Moreover, supplementing the diet with omega-3s, through either diet or supplements, could offer ancillary benefits, notably in patients presenting with symptoms of dry eyes, which is often the case in patients with AMD.

It was acknowledged that many patients with AMD want to do something to try to improve their health and prevent the progression of their disease. Taking a supplement that offers a potential 25% reduction in the risk of progression[6] may offer them hope and a sense of control over their disease. Notably, evidence suggests that people with the lowest dietary intakes of antioxidants[14] and those under 75 years of age[7] may derive the greatest benefits from supplementation. These patients might therefore constitute the best group to target in terms of clinical recommendations around diet and supplements. This further underscores the importance of classifying patients according to their risk of advanced AMD in the clinical setting.

SHOULD WE RECOMMEND SUPPLEMENTS VERSUS DIETARY INTERVENTIONS?

This group of experts acknowledged that patients must first be counselled to modify their diet to include green vegetables (source of lutein and zeaxanthin), and carotenoids and vitamins (fruits and vegetables), as well as fatty fish, if possible from wild sources, several times a week. For example, some studies reported benefits of consuming four or more portions of fish weekly.[18] In addition to the quantity of fish, the type of fish may also be influential with respect to outcomes.[12] Moreover, clinicians should be cognizant of the tendency of patients to over-report or overstate adherence to dietary recommendations. The populations studied tended to be better nourished and more highly educated than the general population, particularly in the AREDS[6] and the AREDS 2.[14] This might have biased the results of studies. Consequently, it seems logical to recommend supplements to people with nutritional deficiencies and risk factors for AMD, as well as for people living alone (who are often less well nourished) in the hope that outcomes will be superior to those expected in well-nourished patients.

Once supplementation is recommended, it is essential to assess adherence during follow-up visits. One should not assume that patients are always adherent to their prescribed regimen. Factors that may limit patient adherence to dietary supplementation include lack of perceived benefit (e.g., no effects on vision), cost of supplements, size of pills, frequency of dosing, and potential problems with tolerability (e.g., gastrointestinal discomfort). Eye care professionals should be prepared to discuss the reasons for recommending supplements and help their patients set reasonable goals. From the start, it should be made clear to patients that supplements do not improve vision but that they are meant to reduce the risk of progression to more advanced disease. The AREDS suggested that in patients with category 3 or 4 AMD who are generally well nourished, the risk of progression to advanced disease may be reduced by 25 to 30% with antioxidant supplementation.[6]

INFORMATION FOR OTHER HEALTH CARE PROFESSIONALS

Vitamin and nutritional supplements can have an impact on a patient's medication regimen. When in doubt, eye care professionals should seek advice from the pharmacist to better evaluate the risk of potential drug–nutrient interactions. Although there have been some concerns about the use of supplements in patients with existing renal dysfunction, in the clinical experience of this group of advisors, such problems have been uncommon. Patients should also be reminded to inform their family physician about any intake of vitamins or omega-3s, notably when taking other medications such as warfarin or antidiabetic drugs, since the dosage of these might need to be adjusted based on the patient's response to omega-3s.

RECOMMENDATIONS FOR OPTIMAL FREQUENCY OF FOLLOW-UP

Timing of follow-up is an important consideration because the optometrist needs to see the intermediate AMD patient at the right time to see progression of the disease. Like recommendations for supplements and diet, the frequency of follow-up should ideally be individualized to the patient's risk profile and needs. It was generally agreed that patients with milder cases of AMD (i.e., category 2 or lower) should be seen at least annually. The majority of patients with category 3 AMD should be monitored every 6 months and, in some cases, more often. Patients with NV AMD should be seen more frequently by their ophthalmologist (i.e., three or four times annually). Self-report of symptoms using the Amsler grid does not substitute for clinic visits, although it can complement the tools used for assessing the progression of disease. Finally, clinical visits represent an opportunity for optometrists to educate patients about modifiable risk factors, the importance of following clinical recommendations, and to modify the treatment and follow-up plan as needed.

EXAMINATION OF THE PATIENT WITH AMD

In a perfect world, optical coherence tomography (OCT) would be used to test all patients with AMD to monitor for progression to neovascular disease. However, given the limited resources, judicious use is of this technology is necessary. It was suggested that a baseline OCT followed by annual testing might be appropriate in Category 3 or 4 patients with no new symptoms or complaints and without evidence of hemorrhage or exudate on clinical examination. OCT is not mandatory but is recommended in patients with dry AMD, especially if a visual acuity change occurs. Fundus photography is a good tool to document a patient's status and allow for easy evaluation of a patient's disease progression. In addition, it can be beneficial to show patients pictures of their eye examination, results of OCT, or both to help them understand their disease and its eventual progression and thereby promote greater adherence to the proposed treatment regimen.

For patients with category 1 or 2 AMD, use of the Amsler grid remains appropriate despite suboptimal sensitivity and specificity. This at-home test is particularly helpful for patients to self-evaluate the progression of their eye disease. Optometrists must remember to instruct patients to test one eye at a time.

CONCLUSION

The first step in the management of a patient with AMD is to identify the disease and determine its severity. Recommendations must be customized based on a patient's individual risk profile (i.e., age, gender, heredity, etc.) and severity of disease (i.e., category 1 to 4). There is no single formula that can be applied to all patients with or at risk of AMD.

Patients must, first and foremost, be encouraged to modify their diet and to eliminate modifiable risk factors such as smoking, sedentary lifestyle, excessive alcohol intake, and so on. The patient should be encouraged to exercise regularly. Medication adherence (for hypertension, hypercholesterolemia, diabetes, etc.) must be reinforced. Taking a supplement must not be a substitute for making healthy lifestyle changes.

Next, the optometrist should ensure that the patient's eyeware provides adequate protection against ultraviolet rays. Evidence to date supports the use of a daily high-dose antioxidant supplement consisting of vitamins C and E, carotenoids, and zinc (i.e., the AREDS 2 formula), to reduce the risk of progression from intermediate to advanced AMD. Optometrists should recommend this type of supplement to patients with category 3 or 4 AMD to mitigate the risk of disease progression. The benefits in patients with milder forms of AMD or in those who are at risk of developing the disease is less clear. In such cases, it could be beneficial to recommend an omega-3 supplement, and eventually vitamin supplements, based on the patient's diet quality. The results of observational studies, including those derived from the original AREDS study, suggest that omega-3 supplementation may help to prevent or slow the progression of disease in its early stage. This approach has biological plausibility, since omega-3 fatty acids are concentrated in the retina and have been shown to modulate retinal function.

On the basis of the recently reported AREDS 2 study, substitution of beta-carotene by lutein plus zeaxanthin seems reasonable, since these carotenoids have been shown to protect against AMD without the associated risk of lung cancer in smokers. Consequently, any patient who has previously been a smoker or been exposed to second-hand smoke should consider taking supplements that do not contain beta-carotene.

This group concluded that the full body of literature must be taken into consideration in order to justify clinical recommendations for patients. A single study cannot, by itself, guide clinical practice. In all cases, recommendations must be individualized and patients should be monitored regularly.

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Table 1. *Description of the Clinical Studies Discussed During the Round Table Meeting That Formed the Basis of Clinical Recommendations for Patients with AMD*

Study	Trial Design	Participants	Primary Objective	Results	Potential Biases	Conclusions
Dietary Intake Studies						
CAREDS: lutein and zeaxanthin[7]	Observational study; sub-study of the Women's Health Initiative (WHI)	1787 women aged 50 to 79 years with intake of lutein plus zeaxanthin above the 78th (high) and below the 28th (low) percentile at baseline	To evaluate the relationship between dietary lutein plus zeaxanthin and intermediate AMD during a 7-year follow-up	No significant association in the total group (odds ratio [OR] 0.96; 95% confidence interval [CI] 0.75–1.23). Protective effects in women aged <75 years (OR 0.57; 95% CI 0.34–0.95)	Food frequency questionnaire subject to recall bias 36% of eligible participants declined Unknown effects of intake of other nutrients Numerous confounders	A diet rich in lutein plus zeaxanthin may protect against intermediate AMD in healthy women younger than 75 years
CAREDS: dietary fats[11]	Observational study; sub-study of the Women's Health Initiative (WHI)	1787 women aged 50 to 79 years with high and low lutein intake at baseline	To evaluate the relationships between the amount and type of dietary fat and intermediate AMD	Intakes of omega-6 and omega-3 fatty acids were associated with a two-fold higher prevalence of intermediate AMD in high versus low quintiles Intake of monounsaturated fats was associated with a lower prevalence	Food frequency questionnaire subject to recall bias 36% of eligible participants declined Unknown effects of intake of other nutrients Numerous confounders	These results support a growing body of evidence suggesting that diets high in several types of fat may contribute to the risk of intermediate AMD Diets high in monounsaturated fats may be protective
Nurses' Health Study: dietary fat[18]	Prospective follow-up study of participants in the Nurses' Health Study and the Health Professionals Follow-up Study	42,743 women and 29,746 men aged ≥50 years with no diagnosis of AMD at baseline	To prospectively examine the association between fat intake and AMD	567 developed AMD during a follow-up of 10 to 12 years The relative risk for the highest versus the lowest quintile of total fat intake was 1.54 (95% CI 1.17–2.01) Other dietary fats: omega-6 (relative risk [RR] 1.49; 95% CI 1.15–1.94) DHA (RR 0.70; 95% CI 0.52–0.93) >4 servings of fish/wk (RR 0.65; 95% CI 0.46–0.91)	Food frequency questionnaire subject to recall bias Inaccurate classification of types of dietary fats	Total fat intake was positively associated with risk of AMD, which may have been caused by intakes of individual fatty acids such as omega-6, rather than to total fat intakes per se A high intake of fish may reduce the risk of AMD
Rotterdam Study: antioxidants[13]	Prospective cohort study	4120 adults aged 55 years or older in a middle-class suburb of Rotterdam at risk of AMD	To investigate whether regular dietary intake of antioxidants is associated with a lower risk of incident AMD	560 participants (13.4%) developed incident AMD after a mean follow-up of 8 years Dietary intake of both vitamin E and zinc was inversely associated with incidence AMD An above-median intake of beta-carotene, vitamins C and E, and zinc, was associated with a 35% reduced risk of AMD Exclusion of supplement users did not affect the results	Food frequency questionnaire subject to recall bias Questionnaire evaluated "typical" intake of nutrients only during the previous year	A high dietary intake of beta-carotene, vitamins C and E, and zinc was associated with a substantially reduced risk of AMD in older adults

Study	Trial Design	Participants	Primary Objective	Results	Potential Biases	Conclusions
Rotterdam Study: antioxidants, zinc and omega-3s[8]	Prospective, nested case-control study from the population-based Rotterdam Study	2,167 individuals aged 55 years and older with genetic risk factors for AMD.	To investigate whether dietary nutrients can reduce the genetic risk of early AMD conferred by the genetic variants CFH Y402H and LOC387715 A69S	517 participants developed early AMD during a median follow-up of 8.6 years High dietary intakes of zinc, beta-carotene, lutein/zeaxanthin, and EPA/DHA significantly reduced the risk of early AMD by 25% in carriers of genetic variants	Relatively fewer cases of incident AMD (fewer than expected) Only two genetic variants were studied—were they the right ones? Unknown effects of other environmental risk factors	High dietary intake of nutrients with antioxidant properties reduces the risk of early AMD in those at high genetic risk Clinicians should provide dietary advice to young susceptible individuals to postpone or prevent AMD
Christen Study: omega-3s and fish[12]	Large, prospective cohort study	38,022 female health care professionals with a mean age of 54.6 years without AMD at baseline	To examine whether intake of omega-3 fatty acids and fish affects the incidence of AMD in women	235 cases of AMD were confirmed during an average of 10 years of follow-up Women with the highest tertile of intake for DHA, compared with those in the lowest (RR 0.62; 95% CI 0.44–0.87) For EPA (RR 0.66; 95% CI 0.48–0.92) Intake of ≥1 fish servings/wk versus <1 (RR 0.58; 95% CI 0.38–0.87) Higher ratio of DHA to EPA offers protection against the negative effects of high dietary intake of omega-6 fatty acids	Low number of early stage AMD cases Women with a history of cardiovascular or cerebrovascular disease, cancer, or other major chronic diseases were excluded Generalizability? Numerous confounders	Regular consumption of DHA and EPA and fish was associated with a significantly decreased risk of incidence AMD and may be of benefit in primary prevention of AMD
Dietary Supplement Studies: The AREDS Studies						
AREDS 8: antioxidants[6]	Multicentre, double-masked, randomized clinical trial with four treatment groups: vitamins C (500 mg), E (400 IU) and beta-carotene (15 mg); zinc (80 mg)/ copper (2 mg); antioxidants plus zinc / copper; placebo	3640 participants aged 55 to 80 years with AMD of Categories 1 to 4	To evaluate the effect of high-dose vitamins C and E, beta-carotene and zinc supplements on AMD progression and visual acuity	Significant odds reduction for the development of advanced AMD over an average follow-up of 6.3 years for antioxidants + zinc (OR 0.72; 99% CI 0.52–0.98) Participants with Category 3 or 4 AMD had a 25% relative risk reduction for the progression to advanced AMD	Mortality rate was 50% lower in the population studied versus the general population—generalizability to other populations? Colour fundus photography underestimates the true incidence of advanced AMD compared to fluorescein angiography 67% of participants took a multivitamin supplement (e.g., Centrum) during the study Relatively well-nourished population	Persons older than 55 years with Category 3 or 4 AMD and without contraindications such as smoking should consider taking a supplement of antioxidants plus zinc such as that used in this study

Study	Trial Design	Participants	Primary Objective	Results	Potential Biases	Conclusions
AREDS 20: dietary lipid intake[9]	Prospective case control study; part of the AREDS randomized controlled trial	4519 participants in the AREDS study aged 60 to 80 years at enrollment provided estimates of habitual nutrient intake through a self-administered semiquantitative food frequency questionnaire.	To evaluate the association of lipid intake with baseline severity of AMD in the AREDS	Dietary omega-3 fatty acid intake was inversely associated with neovascular (NV) AMD (OR 0.61; 95% CI 0.41–0.90) Higher fish consumption was also inversely associated with NV AMD Dietary omega-6 was directly associated with NV AMD prevalence (OR 1.54; 95% CI 1.04–2.29) No statistically significant relationships existed for incidence of geographic atrophy (GA) AMD.	Potential selection of non-nutritional factors associated with risk of NV AMD Food frequency questionnaire subject to recall bias Participant selection bias Dietary intakes could be influenced by other socioeconomic and demographic factors	Higher intake of omega-3 fatty acids and fish was associated with decreased likelihood of having NV AMD The ratio of dietary omega-3/omega-5 intakes may be important
AREDS 30: dietary intake of omega-3s during 12 years of follow-up[10]	Nested cohort study within the AREDS multicentre phase 3 clinical trial	1,837 participants at moderate to high risk of AMD.	To investigate whether omega-3 fatty acid intake was associated with a reduced likelihood of developing central GA AMD and NV AMD	364 cases of GA and NV AMD were reported during 12 years of follow-up (19.8 %) Participants who reported the highest omega-3 intake were 30% less likely to develop GA AMD (OR 0.65; 95% CI 0.45–0.92) and NV AMD (OR 0.68; 95% CI 0.49–0.94)	Observational study therefore effects of other risk factors unknown High intakes of omega-3 rich foods could be linked with a generally healthier lifestyle Dietary intake of omega-3s was reported relative to total caloric intake rather than total quantity in grams	The 12-year incidence of GA and NV AMD in participants at moderate-to-high risk of these outcomes was lowest for those reporting the highest consumption of omega-3 fatty acids
AREDS 2: lutein + zeaxanthin and omega-3s[14]	Phase 3 multicentre, randomized, double-masked, placebo-controlled study with a 2 × 2 factorial design Treatment groups (primary randomization) : lutein (10 mg) + zeaxanthin (2 mg), DHA (350 mg) + EPA (650 mg), both, or placebo. Secondary randomization: elimination of beta-carotene, reduction of zinc dose, both, or placebo (AREDS formula)	4,203 participants aged 50 to 85 years (mean age 73.1 years) at risk of progression to advanced AMD	To determine whether adding lutein + zeaxanthin, DHA + EPA, or both to the AREDS formulation decreases the risk of developing advanced AMD and to evaluate the effect of eliminating beta-carotene, lowering zinc doses, or both in the AREDS formulation	1608 participants progressed to advanced AMD during a median follow-up of 5 years There was no significant difference between treatment groups in the primary analyses and no apparent effect of beta-carotene elimination or lower-dose zinc on progression to advanced AMD Secondary analysis: 10% risk reduction in participants receiving lutein + zeaxanthin versus no lutein + zeaxanthin ($p = 0.05$). Subgroup analysis: participants with the lowest quintile of dietary lutein + zeaxanthin had a 26% lower risk of progression with lutein + zeaxanthin supplementation vs no lutein + zeaxanthin ($p = 0.01$). Lutein + zeaxanthin reduced the risk of NV AMD by 10% ($p = 0.05$) There was a higher rate of lung cancer in former smokers receiving beta-carotene versus no beta-carotene	The dose of omega-3s was based on cardiovascular studies—is this the optimal dose to prevent progression to advanced AMD? Was the study duration adequate to observe protective effects? 44% of participants were taking a statin—could this interfere with absorption of DHA + EPA?	Addition of lutein + zeaxanthin, DHA + EPA, or both to the AREDS formulation in primary analyses did not further reduce risk of progression to advanced AMD However, because of potential increased incidence of lung cancer in former smokers, lutein + zeaxanthin could be an appropriate carotenoid substitute in the AREDS formulation