



# AREDS2: what does it mean for eye care?

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## **John Nolan, Stephen Beatty (both pictured) and Jim Stack discuss the results of the AREDS2 study and what it means for the future of eye care**

In 2001, the landmark Age-Related Eye Disease Study (AREDS), conducted by the National Eye Institute, provided level 1 evidence that supplementation with a formulation of dietary antioxidants and zinc, which included vitamin C 500mg, vitamin E 400 IU,  $\beta$ -carotene 15mg, zinc 80mg and copper 2mg, but which was devoid of the macular carotenoids, was associated with a 27% risk reduction for visual loss and a 25% risk reduction for disease progression in patients with at least intermediate AMD. The AREDS, therefore, furnished the scientific and medical communities with proof of principle that supplemental dietary antioxidants are of benefit in AMD, and somewhat paradoxically, generated interest in the role that macular pigment might play, given its exquisite biological relevance to the tissue affected by this condition.

The AREDS2 report has recently been published, with important implications for those afflicted with early stage AMD. In summary, AREDS2 recruited 4,203 volunteers with the non-advanced form of AMD, into a five-year study. All patients received the AREDS1 formulation, or variations thereof, with either placebo (treatment one), macular pigment's constituent carotenoids (lutein and zeaxanthin [L+Z]; treatment two), omega-3 fatty acids (docosahexanoic acid and eicosapentaenoic acid [DHA+EPA]; treatment three) or with L, Z and omega-3 fatty acids (treatment four). Dietary habits were also assessed for each patient.

### **The 'primary' analysis**

The AREDS2 report distinguishes between 'primary' and 'secondary' analyses of the study data. In the primary analysis, the placebo group (treatment group one) consisted of 1,695 eyes of 1,012 patients who received some variation of the original AREDS1 formulation, but no additional treatment (no L or Z, or omega 3). The other three treatment groups also received an original AREDS1 formulation, but in addition received either L+Z (1,714 eyes, 1,044 patients), DHA+EPA (1,753 eyes, 1,068 patients) or

L+Z+DHA+EPA (1,754 eyes, 1,079 patients). Allocation to treatment groups was random, except where some patients (mostly at their own request) were allocated to a specific AREDS1 formulation.

The purpose of the primary analysis was to decide which, if any, of the three treatments led to improved AMD outcomes (reduced progression of AMD), compared with the reference (placebo) group. "Improved" outcomes in the primary analysis were assessed by length of time before progression to advanced AMD.

The analysis revealed a 10% lower risk of progression to advanced AMD for the L+Z only group compared with the reference subgroup, but this difference in risk was not statistically significant. This was also the case for treatment group four (11% reduction in risk of progression, but not statistically significant), the other group to receive L+Z. The reduction in risk for treatment group three, not receiving any L or Z, was only 3%.

It is worth reiterating here that the control group in this study is not a true placebo group, but rather a group receiving some form of AREDS1 supplement. Therefore, it would be incorrect to conclude from this study that none of the three treatments is shown to reduce risk of progression to advanced AMD. Such an analysis would not have been possible with this study, as no subject received a true placebo. The correct conclusion from this primary analysis is that, controlling for baseline AMD status, none of the treatments (two, three and four) were shown to significantly further reduce the risk of AMD progression relative to the group who received the AREDS1 supplement only (treatment one).

### **The 'secondary' analyses**

The primary analysis described above was complemented in AREDS2 with a secondary analysis, where treatment and control groups were re-defined as follows: treatment group = L+Z and L+Z+DHA+EPA groups, combined (3,451 eyes) and a control group = all other patients (3,440 eyes). Thus the control group now consists of patients who did not receive supplemental L+Z at all; it includes the reference subgroup from the primary study but also patients who received DHA+EPA only.

Therefore, all patients supplemented with L+Z were compared with all other patients (those not supplemented with L+Z) with respect to progression to advanced AMD.

The crucial difference, statistically, between this secondary analysis and the primary analysis, is that only two groups are now being compared and hence there are far more patients/eyes in each group. The actual reduction in risk for L+Z patients (9%) is similar to the reduction in the primary analysis (10-11%), but (because of the larger sample sizes), this reduction is now statistically significant. Based on statistical significance, the conclusion from the study is now that supplementing with L+Z does indeed reduce the risk of progression to advanced AMD compared to not supplementing with these macular pigments.

The evidence is even stronger when dietary intake of patients is included in the analysis. Quintile groups were formed on the basis of dietary intake of L+Z. Quintile group one, therefore, consists of patients in the lowest 20% when ranked according to dietary intake of these carotenoids (median = 696 µg/1000Kcal per day). In this group, the risk for progression is 26% lower for the L+Z treatment group than the secondary analysis reference subgroup.

This represents robust evidence that L+Z supplementation reduces the risk of progression to advanced AMD for patients with low dietary intake of these carotenoids. In the manuscript of the AREDS2 paper, it is stated that similar results were obtained when tertiles were used instead of quintiles to define the subgroups of dietary intake of L and Z. Thus, the study evidence is that the lowest third of patients, based on dietary intake of L+Z, will have a reduced risk of progression to advanced AMD when supplemented with L+Z.

Furthermore, a statistically significant reduction of 18% in risk of progression to advanced AMD for patients receiving lutein and zeaxanthin in the absence of beta-carotene, when compared with patients receiving an AREDS formulation with beta-carotene (and not receiving lutein and zeaxanthin), was reported.

## **Conclusion**

As a result of AREDS2, the eye care professional is now furnished with firm evidence that patients with established non-advanced AMD will benefit from supplementation with broad spectrum antioxidants that include the constituents of macular pigment, and that the formulation should not contain  $\beta$ -carotene or omega-3 fatty acids.

## **AREDS2 summary**

There are many important results emanating from AREDS2. The list below summarizes the main findings from the study:

1. There was no statistically significant benefit (reduction in risk of progression to advanced AMD) for any of the treatments two to four compared to reference subgroup (treatment one)
2. A statistically significant reduction of 9% in risk of progression to advanced AMD was observed for patients receiving lutein and zeaxanthin when compared with patients not receiving these macular pigments
3. Participants with the lowest dietary intake of lutein and zeaxanthin showed a statistically significant reduction of 26% in risk of progression to advanced AMD, when compared with patients not receiving lutein and zeaxanthin
4. A statistically significant reduction of 18% in risk of progression to advanced AMD was found for patients receiving lutein and zeaxanthin in the absence of beta-carotene, when compared with patients receiving an AREDS formulation with beta-carotene (and not receiving lutein and zeaxanthin)
5. A statistically significant reduction of 26% in risk of profound visual loss (i.e. neovascular AMD) was found for patients receiving lutein and zeaxanthin (plus an AREDS formulation) in the absence of beta-carotene, when compared with patients receiving an AREDS formulation with beta-carotene (and not receiving lutein and zeaxanthin)
6. Beta-carotene was associated with poor absorption of lutein and zeaxanthin, with consequentially reduced serum bioavailability of these carotenoids
7. The inclusion of beta-carotene in the formulation was associated with increased risk of lung cancer amongst current and past smokers
8. There was no evidence that supplementation with omega-3 fatty acids was of benefit in any of the analyses reported in this study
9. Supplementation with omega-3 fatty acids or beta carotene had no statistically significant effect on visual acuity
10. Supplementation with lutein and zeaxanthin, omega-3 fatty acids or beta carotene had no statistically significant effect on mortality.

## **About the authors**

John Nolan, Stephen Beatty and Jim Stack Macular are all members of the Macular Pigment Research Group based at the Vision Research Center at the Waterford Institute of Technology in Ireland.