Results from the Age-Related Eye Disease Study 2

Lutein/Zeaxanthin and Omega-3 Fatty Acids for Age-related Macular Degeneration & Cataract

National Eye Institute/National Institutes of Health
Age-Related Eye Disease Study 2 (AREDS2)

Research Group

LLUSM APC, March 8, 2014

Presenter:

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Disclosure
Clement K. Chan

• Genentech
  – Grant, research support
  – Investigator

• NEI
  – Investigator
  – Grant

• Acucela
  – Investigator

• Sequenom
  – Research support

• Regeneron
  – Advisory board
  – Grant, research support
  – Investigator

• ThromboGenics
  – Advisory board

• Allergan
  – Advisory board
  – Honorarium
AREDS2 Study Design

- Multi-center--Academic and Community Centers (82)
- Randomized
- Parallel
- Double-masked
AREDS2 Clinical Sites

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Univ. of Alabama at Birmingham

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Jones Eye Institute – UAMS

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Colorado Retina Associates, PC
Age-Related Eye Disease Study 2 (AREDS2)

Background Information and Study Design
AREDS 1 Formulation

- Vitamin C (500 mg)
- Vitamin E (400 IU)
- Beta Carotene (15 mg)
- Zinc (80 mg zinc oxide)
- Copper (2 mg cupric oxide)
Rates to Advanced AMD

AMD Categories 3 and 4 by Treatment Group

- Placebo
- Antioxidants
- Zinc
- Antioxidants + Zinc

Estimated Probability

- 0%
- 10%
- 20%
- 30%
- 40%

Years

- 0
- 1
- 2
- 3
- 4
- 5
- 6
- 7

P vs. A+Z – p<0.01
P vs. Z – p<0.01

25% Risk Reduction

20%

28%
Long-Term Rates to Advanced AMD

AMD Categories 3 and 4 by Treatment Group

- Placebo
- Antioxidants
- Zinc
- Antioxidants + Zinc

Estimated Probability

27% Risk Reduction

- P vs. A+Z – p<0.01
- P vs. A – p<0.01
Development of Advanced AMD
AREDS Categories 3 & 4

- Antioxidants
- Zinc
- Antioxidants + Zinc

Advanced AMD
Neovascular AMD
Central GA

Protective  Odds Ratio (95%CI)  Harmful
The Age-Related Eye Disease Study 2

Lutein/Zeaxanthin

Spinach, Kale and Collard Greens

Omega-3 Long-chain Polyunsaturated Fatty Acids (LCPUFAs) (DHA/EPA)
Self-reported Dietary Lutein/Zeaxanthin Association with Baseline AMD Status

Highest Intake vs. Lowest Intake (Quintile)

Odds Ratio (95%CI)

Favors High  Favors Low

Large Drusen
Geographic Atrophy
Neovascular AMD

0.2  0.4  0.6  0.8  1.2  1.6  2

Odds Ratio (95%CI)
Self-reported Dietary Omega-3 Fatty Acids Association with Baseline AMD Status

Highest Intake vs. Lowest Intake (Quintile)

Baseline
Neovascular AMD

Incident
Central GA
Advanced AMD

Favors High
Favors Low

Odds Ratio (95%CI)
To evaluate the effect of dietary xanthophylls (lutein and zeaxanthin) and/or omega-3 long chain polyunsaturated fatty acids (DHA and EPA) on progression to advanced AMD.
Dietary Supplements

• Carotenoids:
  - Lutein 10 mg/Zeaxanthin 2 mg

• Omega-3 Long Chain Polyunsaturated Fatty Acids (LCPUFA) ~ 1 gm
  - 350 mg Docosahexaenoic Acid (DHA)
  - 650 mg Eicosapentaenoic Acid (EPA)
AREDS2 Study Design

Ocular Characteristics

- Bilateral large drusen
- Advanced AMD in one eye and large drusen in the fellow eye

A study eye may have definite GA not involving the center of the macula without evidence of drusen
Inclusion Criteria

Bilateral large drusen (large drusen is defined as at least one large druse $\geq 125\mu$)
Inclusion Criteria

Large drusen in one eye and advanced AMD in the fellow eye

Neovascular AMD

Central GA
Run-In Period

- Qualification Visit
- Participants received a 1-month supply of placebo tablets (30 tablets and 60 soft-gels)
- Eligible for randomization if at least 75% of run-in supplements was consumed (estimated pill count)
Run-In Period

- Participants received a **1-month** supply of AREDS-type supplements (**60 soft-gels**)

- Grand total = 5 pills (1 tablet and 4 soft-gels) daily during run-in period

- Centrum Silver to be offered following randomization (final total=potentially 6 pills)
Inclusion Criteria

- Age 50 to 85 years at Qualification
- Study eye(s) with fundus photographs assessed by the Reading Center to be of adequate photo quality
- Pupillary dilation $\geq 5$ mm in each eye for all participants, except for pseudo/aphakic eye with adequate quality fundus photographs
- Randomization within 3 months
- Taking at least 75% of run-in medication
Inclusion Criteria

- Ability and willingness to sign informed consent
- Willingness to stop taking any supplements containing study nutrients
- Likely to be available, willing, and able to undergo examinations at yearly intervals for at least 5 years
Exclusion Criteria

- Ocular disease in *either eye* which may confound assessment of the retina, other than AMD
- Previous retinal or other ocular surgical procedures (other than cataract surgery)
- Systemic or ocular medication known to be toxic to the lens, retina, or optic nerve
Exclusion Criteria

- Supplementation with $\geq 2$ mg of lutein and/or $\geq 500$ mg of omega-3 LCPUFAs for a period of 1 year or more prior to the date of randomization
- Intraocular pressure $\geq 26$ mm Hg, or evidence of glaucoma
- Cataract surgery within 3 months or capsulotomy within 6 weeks prior to qualification
- History of lung cancer
Exclusion Criteria

- Any systemic disease with a poor five-year survival prognosis
- Hemochromatosis, Wilson’s Disease, or history of oxalate kidney stones
- Any condition that would make adherence or follow-up difficult or unlikely
- Participation in other studies likely to affect adherence with AREDS2 follow-up schedule
- Treatment with systemic anti-angiogenics for treatment of CNV or cancer
Primary and Secondary Outcomes

Evaluate the effects of dietary supplements:

- Progression to advanced AMD
- Progression to moderate vision loss
- Disease progression on the AMD scale
- Time to cataract surgery
- Progression of lens opacity
Primary and Secondary Outcomes

Evaluate the effects of dietary supplements:

- Cardiovascular Morbidity and Mortality
- Cognitive function status
Primary Randomization

Randomized Participants

- Control* 1000
- Lutein/Zeaxanthin 1000
- DHA/EPA 1000
- L/Z + DHA/EPA 1000

*No placebo group because AREDS treatment considered standard care
### AREDS 1-Type Supplement

<table>
<thead>
<tr>
<th>Vitamin C</th>
<th>Vitamin E</th>
<th>β-carotene</th>
<th>Zinc Oxide</th>
<th>Cupric Oxide</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>500 mg</td>
<td>15 mg</td>
<td>80 mg</td>
<td>2 mg</td>
</tr>
<tr>
<td>2*</td>
<td>500 mg</td>
<td>0 mg</td>
<td>80 mg</td>
<td>2 mg</td>
</tr>
<tr>
<td>3</td>
<td>500 mg</td>
<td>15 mg</td>
<td>25 mg</td>
<td>2 mg</td>
</tr>
<tr>
<td>4*</td>
<td>500 mg</td>
<td>0 mg</td>
<td>25 mg</td>
<td>2 mg</td>
</tr>
</tbody>
</table>

*Smokers were randomized to one of two arms without beta-carotene.*
If a participant was a current smoker or a former smoker who has quit within the last year he or she was randomized to one of the two arms without beta-carotene. Smokers were not given the original AREDS-type supplement.
AREDS2-2nd Randomization
Modification of AREDS formulation

Randomized Participants

- AREDS Formulation
- AREDS minus Beta-Carotene
- AREDS + Low Zinc
- AREDS minus Beta-Carotene + Low Zinc
Secondary Randomization

Randomized Participants

- Placebo
- L/Z
- DHA/EPA
- L/Z + DHA/EPA

No AREDS-I Supplements

AREDS-I Type Supplements

- AREDS
- No β-C
- Low Zn
- No β-C & Low Zn

AREDS2
Age-Related Eye Disease Study 2
Study Design

Randomized Participants
n=4203

Control
1012

Lutein and Zeaxanthin
1044

DHA and EPA
1068

Lutein/Zeaxanthin + DHA/EPA
1079

No AREDS
19

AREDS
3036

AREDS minus β-Carotene
863

AREDS + Low Zinc
689

AREDS minus β-Carotene + Low Zinc
825

Primary Randomization
Study Design

Randomized Participants
n=4203

Secondary Randomization

Control
Lutein and Zeaxanthin
DHA and EPA
Lutein/Zeaxanthin + DHA/EPA

Non-Randomized

AREDS
AREDS minus β-Carotene
AREDS + Low Zinc
AREDS minus β-Carotene + Low Zinc

Non-Randomized

AREDS 659
AREDS minus β-Carotene 863
AREDS + Low Zinc 689
AREDS minus β-Carotene + Low Zinc 825
Statistical Analysis

- Assumed majority of AREDS2 participants would take some form of AREDS formulation
- Assumed an additional 25% reduction for the progression to AAMD ($\alpha = 0.013$)

Intention-to-Treat Analyses
- Unit of analysis was by eye
- Time-to-event analyses (Cox Proportional Hazards)
Hazard Ratio Tree

Favors Treatment

Not Statistically Significant

Favors Placebo

95% CI

Hazard Ratio

Hazard Ratio (95% CI)

Favors Treatment

Favors Placebo

0.6 0.8 1 1.2 1.4 1.6

Favors Treatment

Favors Placebo
Lutein + Zeaxanthin and Omega-3 Fatty Acids for Age-Related Macular Degeneration: The Age-Related Eye Disease Study 2 (AREDS2) Randomized Clinical Trial

The Age-Related Eye Disease Study 2 (AREDS2) Research Group

Lutein + Zeaxanthin and Omega-3 Fatty Acids for Age-Related Macular Degeneration: The Age-Related Eye Disease Study 2 (AREDS2) Randomized Clinical Trial

Published online May 5, 2013
AREDS2 Enrollment and Study Conduct

- 5178 Screened
- 4203 Enrolled (2006-2008)
  - 3% Lost to Follow-up
  - 6% Died
- Median Follow-up: ~5 Years
- Study End: October 2012
Participant Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race</td>
<td>97% White/ 1% Black</td>
</tr>
<tr>
<td>Age</td>
<td>74 yrs (median)</td>
</tr>
<tr>
<td>Female</td>
<td>57%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>13%</td>
</tr>
<tr>
<td>Smoking Status</td>
<td>50% Former / 7% Current</td>
</tr>
</tbody>
</table>
Ocular Characteristics

AMD Status

Large Drusen – Bilateral  65 %
Advanced AMD – 1 eye   35 %
Ocular Characteristics

Lens Characteristics

Phakic – Bilateral  68%
Pseudophakic/Aphakic – 1 Eye  7%
Pseudophakic/Aphakic – Bilateral  25%
AREDS2 Adherence to Study Compliance with Study Supplements

Discontinued Study Medications – Continued FU

- 7% – Primary Randomization Supplements
- 6% – Secondary Randomization Supplements

Continued Study Medications – Continued FU

- 84% – Took ≥75% of Study Supplements
AREDS2 Adherence
“Drop-Ins” with Non-Study Supplements

• 3% – Took Lutein/Zeaxanthin on their own
• 11% – Took DHA/EPA on their own
AREDS2 Dietary Intake and Serum Levels of Study Nutrients

- Harvard Dietary Assessment
  - Baseline administration
  - Highly nourished cohort
- Serum levels at baseline, 1, 3, & 5 years
  - Compared with National Health and Nutrition Examination Survey (NHANES)
    - Statistically significantly higher in AREDS2
Competitive Absorption of Carotenoids

- Administered Two Carotenoids Simultaneously
  - Beta-Carotene
  - Lutein/Zeaxanthin
- Serum Levels of Lutein
  - Increased 2-fold in L/Z supplement group
  - Increased less when given with beta-carotene (p=.02)
Estimated Probability

Probability of Progression to AAMD

- Placebo - AREDS
- L/Z
- DHA/EPA
- L/Z & DHA/EPA

Years

0 1 2 3 4 5
Primary Randomization

Randomized Participants
4203

Placebo (Control)

Lutein/Zeaxanthin

DHA/EPA

Lutein/Zeaxanthin DHA/EPA

Three Primary Analyses
Primary Outcome Analyses
Progression to Advanced AMD

![Graph showing hazard ratios for different treatments.]

- **Lutein/Zeaxanthin**
- **DHA/EPA**
- **Lutein/Zeaxanthin + DHA/EPA**
- **Placebo (reference)**

Hazard Ratio (98.7% CI)

- **Favors Treatment**
- **Favors Placebo**

Values: 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3
Randomized Participants
4203

Primary Randomization

Analyses of Main Effects of Lutein/Zeaxanthin vs. No Lutein/Zeaxanthin
Post-Hoc exploratory analysis of effects of Lutein/Zeaxanthin

Secondary Analyses of the Effects of Lutein/Zeaxanthin on Age-Related Macular Degeneration Progression
AREDS2 Report No. 3

The Age-Related Eye Disease Study 2 (AREDS2) Research Group

Original Investigation | CLINICAL TRIAL

Secondary Analyses of the Effects of Lutein/Zeaxanthin on Age-Related Macular Degeneration Progression
AREDS2 Report No. 3

The Age-Related Eye Disease Study 2 (AREDS2) Research Group

**Importance.** The Age-Related Eye Disease Study (AREDS) formulation for the treatment of age-related macular degeneration (AMD) contains vitamin C, vitamin E, beta carotene, and zinc with copper. The Age-Related Eye Disease Study 2 (AREDS2) assessed the value of substituting lutein/zeaxanthin in the AREDS formulation because of the demonstrated risk for lung cancer from beta carotene in smokers and former smokers and because lutein and zeaxanthin are important components in the retina.

**Objective.** To further examine the effect of lutein/zeaxanthin supplementation on progression to late AMD.

**Design, Setting, Participants.** The Age-Related Eye Disease Study 2 is a multicenter, double-masked, randomized trial of 4,203 participants, aged 50 to 85 years, at risk for developing late AMD. 66% of patients had bilateral large drusen and 34% had large drusen and late AMD in 1 eye.

**Interventions.** In addition to taking the original or a variation of the AREDS supplement, participants were randomly assigned in a factorial design to 1 of the following 4 groups: placebo, lutein/zeaxanthin, 10 mg/2 mg omega-3 long-chain polyunsaturated fatty 3 acids, 1.0 g, or the combination.

**Main Outcomes and Measures.** Documented development of late AMD by central, masked grading of annual retinal photographs or by treatment history.

**Results.** In exploratory analysis of lutein/zeaxanthin vs. lutein/zeaxanthin, the hazard ratio

Editorial page 139
Supplemental content at journalsphthiologey.com
# Progression to Advanced AMD by Primary and Secondary Randomization Main Effects

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L/Z vs. No L/Z</td>
<td>Favors Treatment</td>
</tr>
<tr>
<td>DHA/EPA vs. No DHA/EPA</td>
<td>Favors Control</td>
</tr>
<tr>
<td>Low Zinc vs. High Zinc</td>
<td></td>
</tr>
<tr>
<td>Beta-Carotene Yes vs. No</td>
<td></td>
</tr>
</tbody>
</table>

- **L/Z vs. No L/Z**: HR = 0.90
- **Beta-Carotene Yes vs. No**: Favors Treatment
- **DHA/EPA vs. No DHA/EPA**: Favors Control
- **Low Zinc vs. High Zinc**: Favors Control

*Note: The graph shows a hazard ratio of 0.90 for L/Z vs. No L/Z, indicating a protective effect.*
Comparison of Lutein/Zeaxanthin vs. no Lutein/Zeaxanthin

Advanced AMD: HR: 0.90   P=0.04

10% additional reduction in the risk of progression to AAMD with lutein/zeaxanthin

Other HRs were not statistically significant
### Progression to Advanced AMD by Quintiles

**Dietary Intake of Lutein/Zeaxanthin**

<table>
<thead>
<tr>
<th>L/Z Dietary Intake Quintile</th>
<th>Favors L/Z</th>
<th>Favors No L/Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowest 1</td>
<td>HR=0.74</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highest 5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Hazard Ratio (95%CI)**

- 0.5 to 0.6
- 0.7 to 0.8
- 0.9
- 1 to 1.1
- 1.3 to 1.5
Lutein/Zeaxanthin vs. no Lutein/Zeaxanthin
Lowest Quintile of Dietary Lutein/Zeaxanthin

• Lowest Quintile – 26% Reduction in Risk (p<0.01)

• Higher Quintiles – Not Statistically Significant
Progression to Neovascular AMD or Central Geographic Atrophy (CGA)
Exploratory Analyses of Lutein/Zeaxanthin

Advanced AMD  HR=0.90
Neovascular AMD  HR=0.89
Central Geographic Atrophy

Hazard Ratio (95%CI)
Comparison of Lutein/zeaxanthin vs. no Lutein/Zeaxanthin

Advanced AMD: HR: 0.90    P=0.04
10% reduction in the risk of progression to AAMD with lutein/zeaxanthin

Neovascular AMD: HR: 0.89    P=0.05
11% reduction in the risk of progression to neovascular AMD with lutein/zeaxanthin

Not statistically significant reduction for CGA
Compare AREDS Formulation with Beta-carotene
N = 683
vs.
Lutein/Zeaxanthin plus AREDS Formulation minus Beta-carotene
N = 674
Secondary Randomization

Randomized Participants

Placebo
L/Z
DHA/EPA
L/Z + DHA/EPA

No AREDS-I Supplements
AREDS-I Type Supplements
AREDS

AREDSS
No β-C
Low Zn
No β-C & Low Zn
Secondary Randomization

Randomized Participants

- Placebo
- L/Z
- DHA/EPA
- L/Z + DHA/EPA

No AREDS-I Supplements

AREDS-I Type Supplements

- AREDS
- No β-C
- Low Zn
- No β-C & Low Zn

AREDS

- No AREDS
- I
Estimated Probability

Probability of Progression to AAMD

- AREDS with βC
- AREDS without βC with L/Z

P=0.02
Progression to Advanced AMD
Exploratory Analyses of Lutein/Zeaxanthin

Favors AREDS minus beta-carotene with L/Z

Advanced AMD  HR=0.82
Neovascular AMD  HR=0.78
Central Geographic Atrophy

Hazard Ratio (95%CI)
L/Z plus AREDS Minus Beta-Carotene vs. AREDS (with Beta-Carotene)

Advanced AMD: HR: 0.82    P=0.02
18% reduction in the risk of progression to AAMD with lutein/zeaxanthin

Neovascular AMD: HR: 0.78    P=0.01
22% reduction in the risk of progression to neovascular AMD with lutein/zeaxanthin

Not statistically significant for CGA
Visual Acuity Outcomes
Exploratory Analyses of Lutein/Zeaxanthin

<table>
<thead>
<tr>
<th>Visual Acuity</th>
<th>Favors L/Z</th>
<th>Favors No L/Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA Loss 10+ Letters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VA Loss 15+ Letters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VA Loss 30+ Letters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VA Worse Than 20/100</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Eyes with NV-AMD included in all VA loss groups
# Visual Acuity Outcomes

## Lutein/Zeaxanthin vs. Beta-Carotene

<table>
<thead>
<tr>
<th>Visual Acuity</th>
<th>Favors AREDS Minus Beta-Carotene with L/Z</th>
<th>Favors AREDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA Loss 10+ Letters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VA Loss 15+ Letters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VA Loss 30+ Letters</td>
<td>HR=0.84</td>
<td></td>
</tr>
<tr>
<td>VA Worse Than 20/100</td>
<td>HR=0.82</td>
<td></td>
</tr>
</tbody>
</table>

* Eyes with NV-AMD included in all VA loss groups

Hazard Ratio (95%CI)
L/Z plus AREDS Minus Beta-Carotene vs. AREDS with Beta-Carotene for Vision

Vision loss of 30+ letters compared with baseline: HR: 0.84 P=0.06

16% reduction in this degree of vision loss with lutein/zeaxanthin

Visual Acuity <20/100: HR: 0.82 P=0.03

18% reduction in the risk of legal blindness with lutein/zeaxanthin
Clinical Trials

Lutein/Zeaxanthin for the Treatment of Age-Related Cataract
AREDS2 Randomized Trial Report No. 4
The Age-Related Eye Disease Study 2 (AREDS2) Research Group

Purpose: Age-related cataract is a leading cause of visual impairment in the United States. The prevalence of age-related cataract is increasing, with an estimated 30.1 million Americans likely to be affected by 2020.

Objectives: To determine whether daily oral supplementation with lutein/zeaxanthin affects the risk for cataract surgery.

Design, Setting, and Patients: The Age-Related Eye Disease Study 2 (AREDS2), a multicenter, double-masked clinical trial, enrolled 2,835 participants, aged 50 to 85 years, at risk for progression to advanced age-related macular degeneration.

Interventions: Participants were randomly assigned to daily placebo; lutein/zeaxanthin, 10mg/2mg; omega-3 long-chain polyunsaturated fatty acids, 1 g; or a combination to evaluate the effects on the primary outcome of progression to advanced age-related macular degeneration.

Main Outcomes and Measures: Cataract surgery was documented at annual study examination with the presence of pseudophakia or aphakia, or reported during telephone calls at 6-month intervals between study visits. Annual best-corrected visual acuity testing was performed. A secondary outcome of AREDS2 was to evaluate the effects of lutein/zeaxanthin on the subsequent need for cataract surgery.

Results: A total of 3,059 AREDS participants were placebo, 3,059 AREDS participants were lutein/zeaxanthin, and 3,059 AREDS participants were omega-3 long-chain polyunsaturated fatty acids. The hazard ratio for progression to cataract surgery was 0.94 (95% CI, 0.84-1.06; P = .34). For participants in the lowest quintile of dietary intake of lutein/zeaxanthin, the hazard ratio comparing lutein/zeaxanthin vs no lutein/zeaxanthin for progression to cataract surgery was 0.88 (95% CI, 0.77-0.99; P = .03). The hazard ratio for 3 or more lines of vision loss was 1.03 (95% CI, 0.93-1.13; P = .61) for lutein/zeaxanthin vs no lutein/zeaxanthin.

Conclusions and Relevance: Daily supplementation with lutein/zeaxanthin had no statistically significant overall effect on rates of cataract surgery or vision loss.

Published online May 5, 2013

The Age-Related Eye Disease Study 2 Research Group

Lutein/Zeaxanthin for the Treatment of Age-Related Cataract: AREDS2 Randomized Trial Report No. 4
Cataract Surgery/Lens Opacity Progression

<table>
<thead>
<tr>
<th></th>
<th>Favors L/Z</th>
<th>Favors No L/Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cataract Surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any Cataract</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe Cataract</td>
<td></td>
<td></td>
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</tbody>
</table>

Hazard Ratio (95% CI)

0.85 0.95 1 1.05 1.15
Cataract Surgery/Lens Opacity
Progression by Dietary Intake of Lutein/Zeaxanthin

<table>
<thead>
<tr>
<th>Condition</th>
<th>Quintile 1 (Lowest)</th>
<th>Quintile 5 (Highest)</th>
<th>Favors L/Z</th>
<th>Favors No L/Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cataract Surgery</td>
<td></td>
<td></td>
<td>HR=0.68</td>
<td></td>
</tr>
<tr>
<td>Any Cataract</td>
<td></td>
<td></td>
<td>HR=0.70</td>
<td></td>
</tr>
<tr>
<td>Any Severe Cataract</td>
<td></td>
<td></td>
<td>HR=0.64</td>
<td></td>
</tr>
</tbody>
</table>

Hazard Ratio (95%CI)

- Favors L/Z
- Favors No L/Z
Safety Outcome: Mortality

- L/Z vs. Placebo
- DHA/EPA vs. Placebo
- L/Z+DHA/EPA vs. Placebo
- L/Z vs. No L/Z
- DHA/EPA vs. No DHA/EPA
- Low Zinc vs. High Zinc
- Beta-Carotene Yes vs. No

Hazard Ratio (95%CI)
Safety Outcome: Adverse Events

• No statistically significant differences in serious adverse events between treatment groups

• Analyses were conducted in non-smokers or former-smokers for lung cancer for beta-carotene.
Safety Outcome: Lung Cancer

<table>
<thead>
<tr>
<th>Beta-carotene Main Effect</th>
<th>No β-Carotene (N = 1341)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-Carotene (N = 1348)</td>
<td></td>
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<tr>
<td>23 Cases (2.0%)</td>
<td>11 Cases (0.9%)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Increased risk of lung cancer with β-Carotene
91% former smokers (quit > 1 year prior to randomization)

Analysis excludes smokers
Safety Outcome: Lung Cancer

<table>
<thead>
<tr>
<th>Lutein/Zeaxanthin Main Effect</th>
<th>No Lutein/Zeaxanthin</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lutein/Zeaxanthin (N = 2123)</td>
<td>No Lutein/Zeaxanthin (N = 2080)</td>
<td>0.80</td>
</tr>
<tr>
<td>33 Cases (1.5%)</td>
<td>31 Cases (1.5%)</td>
<td></td>
</tr>
</tbody>
</table>

No increased risk of lung cancer
62% were former smokers, equal in both arms

Analysis excludes smokers
Discussion

• Limitations
  • Complex study design involving a secondary randomization and secondary analyses
  • Highly educated and well-nourished cohort
  • Competitive absorption of carotenoids

• Strengths
  • Low attrition rate
  • Consistently good adherence to treatment regimen
Conclusions

• The addition of lutein/zeaxanthin to the AREDS formulation did NOT have an effect on cataract progression or cataract surgery.

• Whether lutein/zeaxanthin may reduce the risk of developing lens opacities in persons with the low dietary intake of lutein/zeaxanthin needs further evaluation.
Conclusions

• Comparisons of the three active arms to control (primary analyses) did not significantly reduce risk of progression to AAMD.

• The addition of lutein/zeaxanthin to the AREDS formulation as analyzed by the main effect showed 10% decrease in risk of progression to AAMD.

• No main effect efficacy with DHA/EPA.
Conclusions

• Secondary randomization suggests no differences in the progression to AAMD for elimination of beta-carotene or lowering zinc dose

• No differences in adverse side-effects (gastrointestinal disorders or others) between “low” and high zinc groups

• Insufficient data to make recommendation for zinc
Conclusions

- The main effect of lutein/zeaxanthin demonstrated 10% reduction of AAMD.

- ~20% reduction in the risk of progression to AAMD of L/Z beyond the effects of AREDS supplement in persons with the lowest dietary intake of L/Z.

- ~20% reduction in the risk of progression to AAMD, particularly neovascular AMD, of L/Z in head-to-head comparison with beta-carotene.
Conclusions

• Improve the safety of the AREDS supplements by removing beta-carotene to decrease the risk of lung cancer in smokers and former smokers who compose >50% of persons with AMD.
Conclusions

• Considering the totality of evidence, lutein/zeaxanthin may be an appropriate carotenoid substitution for beta-carotene in the AREDS formulation
AREDS2 Formulation

- Vitamin C (500 mg)
- Vitamin E (400 IU)
- Beta Carotene (15 mg)
- Lutein (10 mg)/Zeaxanthin (2 mg)
- Zinc (80 mg zinc oxide)
- Copper (2 mg cupric oxide)
- Omega-3 fatty acids (DHA/EPA)
Study Team

- Funded by the National Eye Institute
- Coordinating Center – The EMMES Corporation
- Fundus Photograph Reading Center – The University of Wisconsin - Madison
- Central Lab – Centers for Disease Control and Prevention (CDC)
- Drug Distribution – The United States Public Health Service (PHS) Supply Service Center (Perry Point, MD)
TAKE HOME POINTS:

? Omega-3 does not work!

? Beta Carotene is dead!

? Lutein reigns supreme!
IMPORTANT TAKE HOME POINT:

Good diet trumps supplements
THANK YOU
AREDS2 Clinical Sites

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<table>
<thead>
<tr>
<th>CONNECTICUT</th>
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<tr>
<td>Ron Adelman, MD</td>
<td>James Folk, MD</td>
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<td>Yale University Eye Center</td>
<td>University of Iowa</td>
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<td>Philip Rosenfeld, MD</td>
<td>David Orth, MD</td>
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<td>Bascom Palmer Eye Institute</td>
<td>Ingalls Memorial Hospital</td>
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<tr>
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<td>Alice Lyon, MD</td>
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<tr>
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<td>Lawrence Halperin, MD</td>
<td>Lawrence Ulanski II, MD</td>
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<tr>
<td>Retina Group of Florida</td>
<td>The University of Illinois</td>
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<tr>
<td>Marc Levy, MD</td>
<td>Aaron Weinberg, MD</td>
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<td>Sarasota Retina Institute</td>
<td>NorthShore University HealthSystems</td>
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<td>G. Baker Hubbard, MD</td>
<td>Carl Baker, MD</td>
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<td>Emory University Eye Center</td>
<td>Paducah Retinal Center</td>
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<tr>
<td>Sandeep Grover, MD</td>
<td>Ricky Isernhagen, MD</td>
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<td>University of Florida Health Science Center</td>
<td>Retina Associates of Kentucky</td>
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<th><strong>NORTH CAROLINA</strong></th>
<th><strong>NEW YORK</strong></th>
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<tr>
<td>Andrew Antoszyk, MD</td>
<td>Richard Rosen, MD</td>
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<td>Craig Greven, MD</td>
<td>Glenn Stoller, MD</td>
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<td>Ophthalmic Consultants of Long Island</td>
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<td>W. Copley McLean, Jr., MD</td>
<td>Fadi El Baba, MD</td>
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<td>Western Carolina Retinal Assoc.</td>
<td>The Research Foundation of SUNY/SB</td>
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<td>Odette Houghton, MD</td>
<td>Paul Beer, MD</td>
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<td>UNC Department of Ophthalmology</td>
<td>Retina Consultants, PLLC</td>
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<td>Cynthia Toth, MD</td>
<td>Michael Cooney, MD, MBA</td>
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<td>Duke University</td>
<td>Manhattan Eye, Ear, and Throat Hospital</td>
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<tr>
<td>Darma Ie, MD</td>
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<td>Delaware Valley Retina Associates</td>
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<td>Neelakshi Bhagat, MD, MPH</td>
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<td>UMDNJ</td>
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<td>David DiLoreto, MD</td>
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<td>Univ. of Rochester Eye Institute</td>
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Judy Kim, MD
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Recognition

We want to thank:

• NEI Leadership for the support of AREDS2