AREDS 2 Results

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Decisions, Decisions…
Original AREDS Study

Age-Related Eye Disease Study
• NEI (National Eye Institute) Sponsored Study
• Results published 2001

Objective
• Evaluate the effect of high-dose antioxidants (vitamins C and E, beta carotene) and/or zinc on:
  • AMD progression
  • Reduction in moderate visual acuity loss (≥ 15 letters)
AREDS Definitions

Early AMD
• several small drusen
OR
• few medium drusen

Intermediate AMD
• many medium drusen
OR
• ≥ 1 large drusen
OR
• non-central geographic atrophy

Advanced AMD
• central geographic atrophy
OR
• neovascular wet disease
AREDS Definitions

High Risk Group
• intermediate AMD in one or both eyes
OR
• advanced AMD in one eye
AREDS Formula

Vitamin C (500mg)
Vitamin E (400 IU)
Beta-carotene (15 mg)
Zinc oxide (80mg)
Copper (2mg) – to prevent copper deficiency associated with high zinc levels
AREDS Design

4,757 participants
Randomized to four groups

<table>
<thead>
<tr>
<th></th>
<th>Antioxidants</th>
<th>No Antioxidants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zinc</td>
<td>1: Antioxidants + zinc</td>
<td>2: Zinc</td>
</tr>
<tr>
<td>No Zinc</td>
<td>3: Antioxidants</td>
<td>4: Placebo</td>
</tr>
</tbody>
</table>
AREDS Results

In those with high risk AMD

<table>
<thead>
<tr>
<th></th>
<th>Antioxidants Plus Zinc</th>
<th>Zinc Alone</th>
<th>Antioxidants Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction of the relative risk of developing</td>
<td>25%</td>
<td>21%</td>
<td>17%</td>
</tr>
<tr>
<td>advanced AMD</td>
<td></td>
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<tr>
<td>Reduction of the relative risk of vision loss</td>
<td>19%</td>
<td>11%</td>
<td>10%</td>
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<td>(three or more lines)</td>
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</table>
AREDS 2

Results published 2013

Objective

- To determine whether adding lutein/zeaxanthin (10mg/2mg), omega-3 fatty acids (DHA/EPA [350mg/650mg]), or both to the AREDS formula decreased risk of developing advanced AMD
- Evaluate the effect of eliminating beta carotene
- Evaluate the effect of lower zinc dosage
Background

Higher intake of carotenoids (lutein and zeaxanthin), omega-3 long-chain polyunsaturated fatty acids (docosahexaenoic acid [DHA] and eicosapentaenoic acid [EPA]), or both may decrease risk of AMD progression

- Lutein and zeaxanthin
  - Types of carotenoids (like beta carotene)
  - main components of macular pigment (absorb harmful blue and UV light)
- DHA
  - major structural component of the retina
- EPA
  - precursor to signaling molecules with potential to influence retinal function
  - anti-inflammatory effects
Background

Beta carotene
- Vitamin A pre-cursor and converted to retinal
- Used in initial AREDS because lutein/zeaxanthin not commercially available at that time
- Associated with a higher risk of lung cancer, especially in previous or current smokers
- Unknown time period after smoking cessation when no longer significant risk

Zinc
- High doses actually not absorbed. Maximal level absorbed = 25mg
- High doses may cause GI or GU side effects
AREDS 2 Design

Enrolled those at high risk for progression to advanced AMD
- Bilateral large drusen
- Large drusen in 1 eye and advanced AMD in fellow eye

5 year follow-up

Serum lutein/zeaxanthin levels and dietary habits also measured

2x2 factorial design
- Primary and Secondary Randomization groups
- Able to study effect of each factor on AMD progression as well as effect of interactions between factors on AMD progression
AREDS 2 Design

Primary Randomization (AREDS With Lutein and Zeaxanthin, DHA and EPA, or Both)

5,178 Patients assessed for eligibility

975 Excluded
- 494 Did not meet inclusion criteria
- 481 Other
  - 247 Refused randomization
  - 211 Found ineligible by fundus center
  - 77 Poor adherence to run-in phase
  - 1 Declined to participate

4,203 Randomized (6,916 eyes)

Randomized to receive placebo
1,012 Received intervention (1,695 eyes)

Randomized to receive lutein + zeaxanthin
1,044 Received intervention (1,714 eyes)

Randomized to receive DHA + EPA
1,068 Received intervention (1,753 eyes)

Randomized to receive zeaxanthin and DHA + EPA
1,079 Received intervention (1,754 eyes)
Secondary Randomization (AREDS With No Beta Carotene, With Low-Dose Zinc, or Both)

4203 Eligible for secondary randomization

1167 Excluded (refused randomization) (1929 eyes)
1148 Taking original AREDS supplement (1897 eyes)
19 Not taking AREDS supplement (32 eyes)

3036 Randomized (4987 eyes)

- Randomized to receive AREDS supplement
  - Received intervention (101 eyes)

- Randomized to receive AREDS supplement with no beta carotene
  - Received intervention (1410 eyes)

- Randomized to receive AREDS supplement with low-dose zinc
  - Received intervention (1127 eyes)

- Randomized to receive supplement with no beta carotene and with low-dose zinc
  - Received intervention (1349 eyes)
AREDS 2 Design

Primary Randomization

- Placebo
- Lutein/zeaxanthin
- DHA/EPA
- Lutein/zeaxanthin + DHA/EPA

Secondary Randomization

- AREDS
- AREDS - beta carotene
- AREDS with low dose zinc (25mg)
- AREDS - beta carotene with low dose zinc (25mg)

Note: no true placebo as subjects received AREDS if refused secondary randomization OR received AREDS or modified AREDS as part of secondary randomization.
AREDS 2 Results

Primary Randomization

No statistically significant reduction in progression to advanced AMD among the 3 treatment groups versus placebo.
AREDS 2 Results

Lutein/Zeaxanthin Sub-analyses

- Lutein/zeaxanthin group had 10% reduction in risk of progression to advanced AMD compared with no lutein/zeaxanthin
AREDS 2 Results

Lutein/Zeaxanthin Sub-analyses

- In those with lowest dietary intake of lutein/zeaxanthin, 26% reduction in risk or progression to advanced AMD
AREDS 2 Results

Head-to-head lutein/zeaxanthin vs beta carotene

- 18% reduction in risk of progression to advanced AMD and 25% reduction in progression to neovascular AMD

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Treatment Eyes</th>
<th>Advanced AMD Events</th>
<th>Control Eyes</th>
<th>Advanced AMD Events</th>
<th>Hazard Ratio (95% CI)</th>
<th>Favors</th>
<th>Favors</th>
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<tbody>
<tr>
<td>Advanced AMD</td>
<td></td>
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<tr>
<td>Lutein + zeaxanthin</td>
<td>3451</td>
<td>940</td>
<td>3440</td>
<td>1000</td>
<td>0.90 (0.82-0.99)</td>
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<tr>
<td>AREDS supplement with lutein + zeaxanthin</td>
<td>1114</td>
<td>310</td>
<td>1117</td>
<td>347</td>
<td>0.82 (0.69-0.96)</td>
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<tr>
<td>Neovascular AMD</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Lutein + zeaxanthin</td>
<td>3451</td>
<td>607</td>
<td>3440</td>
<td>655</td>
<td>0.89 (0.79-1.00)</td>
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<tr>
<td>AREDS supplement with lutein + zeaxanthin</td>
<td>1114</td>
<td>209</td>
<td>1117</td>
<td>248</td>
<td>0.78 (0.64-0.94)</td>
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<td>Central geographic atrophy</td>
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</tr>
<tr>
<td>Lutein + zeaxanthin</td>
<td>3451</td>
<td>367</td>
<td>3440</td>
<td>398</td>
<td>0.92 (0.78-1.07)</td>
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<tr>
<td>AREDS supplement with lutein + zeaxanthin</td>
<td>1114</td>
<td>112</td>
<td>1117</td>
<td>117</td>
<td>0.94 (0.70-1.26)</td>
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</table>
AREDS 2 Results

DHA/EPA Sub-analyses

- No statistically significant effect on progression to advanced AMD comparing DHA/EPA vs. no DHA/EPA
### AREDS 2 Results

#### Secondary Randomization

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Eyes</th>
<th>Advanced AMD Events</th>
<th>Control</th>
<th>Advanced AMD Events</th>
<th>Hazard Ratio (95% CI)</th>
<th>Favors Treatment</th>
<th>Favors Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>AREDS: lutein + zeaxanthin + EPA</td>
<td>3451</td>
<td>940</td>
<td>AREDS: lutein + zeaxanthin</td>
<td>3440</td>
<td>0.91 (0.82-1.00)</td>
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<tr>
<td>Low-dose zinc</td>
<td>3491</td>
<td>979</td>
<td>Low-dose zinc</td>
<td>3400</td>
<td>0.98 (0.89-1.08)</td>
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<tr>
<td>Beta-carotene</td>
<td>2468</td>
<td>726</td>
<td>Beta-carotene</td>
<td>2501</td>
<td>1.06 (0.95-1.19)</td>
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<td>Low-dose zinc</td>
<td>2221</td>
<td>647</td>
<td>Low-dose zinc</td>
<td>2212</td>
<td>1.07 (0.94-1.20)</td>
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</tbody>
</table>

No statistically significant difference on progression to advanced AMD with original AREDS versus the other modifications.
AREDS 2 Results

In beta carotene group, statistically significant increase in the incidence of lung cancer in former smokers
  • current smokers did not receive AREDS
No increased risk of lung cancer in lutein/zeaxanthin group
Simultaneous use of beta-carotene with lutein and zeaxanthin decreases the absorption of the nutrients
  • secondary to competitive absorption of carotenoids
AREDs 2 Conclusions

1) adding lutein/zeaxanthin, DHA/EPA, or both to the AREDS showed no statistically significant overall effect on progression to advanced AMD

2) lutein/zeaxanthin had beneficial effects for reducing risk of advanced AMD, particularly neovascular AMD, especially in persons with the lowest intake of lutein/zeaxanthin AND in the head-to-head comparisons with beta carotene
AREDS 2 Conclusions

3) beta carotene leads to decreased absorption of lutein/zeaxanthin into the body if taken together

4) beta carotene had an increased risk of lung cancer in former smokers

5) DHA/EPA showed no added benefit or harmful effects
   • observational data suggests diet rich in omega-3 fatty acids

6) no statistically significant differences between the 2 doses of zinc, and no differences in adverse side-effects.
All for one and one for all…

AREDS
- Vitamin C (500mg)
- Vitamin E (400 IU)
- Beta-carotene (15 mg)
- Zinc oxide (80mg)
- Copper (2mg)

AREDS 2
- Vitamin C (500mg)
- Vitamin E (400 IU)
- Lutein/Zeaxanthin (10mg/2mg)
- Zinc oxide (80 mg)
- Copper (2mg)
References


SanGiovanni JP, Agrón E, Meleth AD, et al; Age-Related Eye Disease Study Research Group. ω-3 Long-chain polyunsaturated fatty acid intake and 12-y incidence of neovascular age-related macular degeneration and central geographic atrophy: AREDS report 30, a prospective cohort study from the Age-Related Eye Disease Study. Am J Clin Nutr. 2009;90:1601-