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| **Author, Year Study Name** | **Study Design** | **Country Setting** | **Inclusion criteria** | **Randomized Analyzed Attrition** | **Intervention** |
| Chew, 201399  AREDS (Report #35) | RCT (long-term observational followup) | United States Multicenter | Age 55 to 80 years with AMD and BCVA ≥20/32 in at least one eye | n=2,459, focusing on AREDS categories 3 and 4 for vision-related outcomes; 3,476 for categories 2, 3, and 4; total sample 4,753 Attrition: NA | A. Antioxidant supplement (vitamin C 500 mg + vitamin E 400 IU + beta-carotene, 15 mg/day) B. Zinc 80 mg/day  C. Antioxidant supplement + zinc  D. Placebo |
| Chew, 2009112 AREDS (Report #25) | RCT (long-term observational followup) | United States Multicenter | Age 55 to 80 years with AMD and BCVA ≥20/32 in at least one eye | Randomized: 4,757 Analyzed (post-trial followup): 4,577 Attrition: NA | A. Any AREDS active treatment  B. Placebo |
| Ma, 2012106 | RCT | China Single center | Age 50-79 years with early AMD used AREDS classification | Randomized: 108 Analyzed: 107 Attrition: 0.9% (1/108) | A. Lutein 10 mg/day  B. Lutein 20 mg/day  C. Lutein 10 mg/day + zeaxanthin 10 mg/day  D. Placebo |
| Murray, 2013105 CLEAR | RCT | United Kingdom Multicenter | Age 50-80 years with AMD grade 0 to 4 (Rotterdam criteria); BCVA logMAR ≥0.5, with minimal cataract | Randomized: 84 Analyzed: 73 Attrition: 13% (11/84) | A. Lutein 10 mg/day  B. Placebo |
| Souied, 2013107 NAT2 | RCT | France Single hospital-based ophthalmology clinic | Age ≥55 to <85 years with visual acuity >0.4 logMAR in study eye with early age-related maculopathy (presence of drusen or reticular pseudodrusen) in study eye and AMD in the fellow eye | Randomized: 300 Analyzed: 263 for efficacy analysis, 300 for safety analysis Attrition: 21% (63/300) | A. Fish oil capsules (DHA 280 mg + EPA 90 mg + vitamin E 2 mg) 3x/day  B. Placebo (olive oil 602 mg) |

| **Author, Year Study Name** | **Study Participants** | **Duration of Followup** | **Results** |
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| Chew, 201399  AREDS (Report #35) | A vs. B vs. C vs. D\* Median age 69 vs. 70 vs. 69 vs. 69 years 55% vs. 57% vs. 56% vs. 56% female Race:  97% vs. 96% vs. 97% vs. 96% white 2% vs. 3% vs. 3% vs. 4% black 1% vs. 1% vs. <1% vs. <1% other AMD category: 2: 28% vs. 30% vs. 28% vs. 30% 3: 40% vs. 41% vs. 42% vs. 40% 4: 24% vs. 22% vs. 22% vs. 22% | 10 years | **A + C (antioxidant) vs. B+D (no antioxidant)** *(Participants with AMD category 2, 3 or 4 at baseline)* All-cause mortality: 24.0% (439/1831) vs. 23.6% (427/1806); aHR\* 1.06 (95% CI 0.93 to 1.21) CV mortality: aRR 1.20 (95% CI 0.97 to 1.49) Cancer mortality: aRR 1.07 (95% CI 0.83 to 1.38) Non-CV, non-cancer mortality: aRR 0.94 (95% CI 0.74 to 1.20) **B + C (zinc) vs. A + D (no zinc)** All-cause mortality: 22.4% (401/1790) vs. 25.2% (465/1847); aHR 0.83 (95% CI 0.73 to 0.95) CV mortality: aRR 0.80 (95% CI 0.64 to 0.99) Cancer mortality: aRR 0.84 (95% CI 0.65 to 1.08) Non-CV, non-cancer mortality: aRR 0.93 (95% CI 0.73 to 1.18) **A vs. D** Loss of visual acuity ≥15 letters ETDRS: OR 0.88 (95% CI 0.73 to 1.06) Visual acuity <20/100: OR 0.87 (95% CI 0.68 to 1.11) Progression to advanced AMD: OR 0.74 (95% CI 0.59 to 0.92) **B vs. D** Loss of visual acuity ≥15 letters ETDRS: OR 0.89 (95% CI 0.74 to 1.08) Visual acuity <20/100: OR 0.91 (95% CI 0.71 to 1.15) Progression to advanced AMD: OR 0.87 (95% CI 0.70 to 1.07) **C vs. D** Loss of visual acuity ≥15 letters ETDRS: OR 0.76 (95% CI 0.63 to 0.93) Visual acuity <20/100: OR 0.75 (95% CI 0.58 to 0.97) Progression to advanced AMD: C vs D: OR 0.69 (95% CI 0.56 to 0.86) *Participants with AMD category 3 or 4 at baseline* **A vs. D** Loss of visual acuity ≥15 letters ETDRS: OR 0.83 (95% CI 0.67 to 1.02) Visual acuity <20/100: OR 0.82 (95% CI 0.64 to 1.07) Progression to advanced AMD: OR 0.70 (95% CI 0.56 to 0.88) **B vs. D** Loss of visual acuity ≥15 letters ETDRS: OR 0.86 (95% CI 0.70 to 1.07) Visual acuity <20/100: OR 0.88(95% CI 0.69 to 1.14) Progression to advanced AMD: OR 0.82 (95% CI 0.66 to 1.02) **C vs. D** Loss of visual acuity ≥15 letters ETDRS: OR 0.71 (95% CI 0.57 to 0.88) Visual acuity <20/100: OR 0.72 (95% CI 0.56 to 0.94) Progression to advanced AMD: C vs D: OR 0.66 (95% CI 0.53 to 0.83) *Participants with AMD category 4 at baseline* **A vs. D** Loss of visual acuity ≥15 letters ETDRS: OR 0.75 (95% CI 0.53 to 1.06) Visual acuity <20/100: OR 0.76 (95% CI 0.52 to 1.12) Progression to advanced AMD: OR 0.64 (95% CI 0.46 to 0.91) **B vs. D** Loss of visual acuity ≥15 letters ETDRS: OR 0.68 (95% CI 0.48 to 0.96) Visual acuity <20/100: OR 0.66 (95% CI 0.45 to 0.98) Progression to advanced AMD: OR 0.68 (95% CI 0.49 to 0.96) **C vs. D** Loss of visual acuity ≥15 letters ETDRS: OR 0.54 (95% CI 0.38 to 0.78) Visual acuity <20/100: OR 0.58 (95% CI 0.38 to 0.86) Progression to advanced AMD: C vs D: OR 0.56 (95% CI 0.40 to 0.79) |
| Chew, 2009112 AREDS  (Report #25) | Not reported by treatment group for this analysis (see Chew 2013 for characteristics for the entire AREDS cohort) | Up to 11 years (mean followup not reported) | **A vs. B** Incident cataract surgery: 25.4% (798/3137) vs. 25.2% (369/1467); RR 1.01 (95% CI 0.01 to 1.13) |
| Ma, 2012106 | A vs. B vs. C vs. D Mean age 70 vs. 69 vs. 69 vs. 69 years 62% vs. 56% vs. 56% vs. 60% female Race not reported BCVA 0.30 vs. 0.28 vs. 0.28 vs. 0.31 logMAR 89% vs. 89% vs. 85% vs. 89% non-smoker | 48 weeks | **A vs. D** BCVA, mean change from baseline: -0.04 (95% CI -0.11 to 0.03) vs. -0.00 (95% CI -0.06 to 0.05); p=NS  **B vs. D** BCVA, mean change from baseline: -0.02 (95% CI -0.11 to 0.06) vs. -0.00 (95% CI -0.06 to 0.05); p=NS **C vs. D** BCVA, mean change from baseline: -0.04 (95% CI -0.10 to 0.01) vs. -0.00 (95% CI -0.06 to 0.05); p=NS |
| Murray, 2013105 CLEAR | A vs. B Mean age 71.9 vs. 69.1 years 56% vs. 65% female Race not reported Visual acuity 0.10 vs. 0.05 logMAR | 1 year | **A vs. B** Visual acuity, mean change from baseline: 0.01 v.s -0.04; p<0.05 |
| Souied, 2013107 NAT2 | A vs B Mean age 74 vs. 73 years 69% vs. 61% female Race not reported Mean visual acuity in study eye 0.14 vs. 0.12 logMAR Cataracts 61% vs. 62% Drusen: Absent: 0.7% vs. 0% <5: 0.7% vs. 2% 5-20: 17% vs. 22% >20: 81% vs. 76% Pigmentary changes: 23% vs. 22% Stage of maculopathy:  Stage 1: 78% vs. 78%  Stage 2: 22% vs. 22% Smoking history:  Current: 7% vs. 9%  Former: 14% vs. 17%  Nonsmoker: 79% vs. 74% CVD: 93% vs. 80% Metabolic and nutrition disorders: 53% vs. 59% Musculoskeletal and connective tissue disorders: 45% vs. 49% GI disorder: 30% vs. 33% Concomitant medications:  Lipid-lowering agents: 49% vs. 53% Renin-angiotensin system agents: 42% vs. 36% Anti-inflammatory and anti-rheumatic agents: 16% vs. 29% Diabetes: 12% vs. 10% | 3 years | **A vs. B** All-cause mortality: 2.2% (3/134) vs. 4.7% (6/129); RR 3.00 (95% 0.33 to 28) Best-corrected visual acuity, mean change from baseline (logMAR):  6 months: 0.040 (SD 0.122) vs. 0.007 (SD 0.118) 1 year: 0.0037 (SD 0.173) vs. 0.0008 (SD 0.122) 2 years: 0.086 (SD 0.231) vs. 0.057 (SD 0.201) 3 years: 0.155 (SD 0.297) vs. 0.116 (SD 0.258); p=0.311 Loss of visual acuity, proportion of subjects with decrease >15 letters on ETDRS chart:  6 months: 3.1% (4/131) vs. 1.6% (2/126); RR 1.92 (95% CI 0.36 to 10) 1 year: 5.3% (7/131) vs. 0.8% (1/123); RR 6.57 (95% CI 0.82 to 53) 2 years: 10.8% (13/120) vs. 9.5% (11/116); RR 1.14 (95% CI 0.53 to 2.45) 3 years: 17.8% (21/118) vs. 14.3% (16/112); RR 1.25 (95% CI 0.69 to 2.26) |

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| **Author, Year Study Name** | **Adverse Events** | **Sponsor** | **Quality** | **Comments** |
| Chew, 201399  AREDS (Report #35) | Not reported by treatment group; narrative report of no significant increase in incidence of hospitalization after adjustment for age, sex, smoking and treatment group | National Eye Institute/National Institutes of Health | Good | Hazard ratios for mortality outcomes adjusted for age, sex, race, education, smoking status, BMI, diabetes, angina, cancer, hypertension |
| Chew, 2009112 AREDS  (Report #25) | Not reported | National Eye Institute/National Institutes of Health | Good | None |
| Ma, 2012106 | Not reported by treatment group; narrative report of no adverse events related to interventions | Not reported | Good | None |
| Murray, 2013105 CLEAR | A vs. B Withdrawals due to adverse events: 7.1% (3/42) vs. 2.3% (1/42); RR 3.00 (95% 0.33 to 28) | BASF, UK Medical Research Council, Manchester Biomedical Research Center, Greater Manchester Comprehensive Local Research Network | Good | None |
| Souied, 2013107 NAT2 | A vs. B Any adverse event: 93.3% (125/134) vs. 89.1% (115/129); RR 1.05 (95% CI 0.97 to 1.13) Any serious AE: 31.3% (42/134) vs. 30.2% (39/129); RR 1.04 (95% CI 0.72 to 1.49) Treatment-related AE (investigator-determined): 3.7% (5/134) vs. 1.6% (2/129); RR 2.41 (95% CI 0.48 to 12) Serious ocular AE: 8.2% (11/134) vs 7.0% (9/129); RR 1.18 (95% CI 0.50 to 2.75) Ocular AE: 65.7% (88/134) vs 57.4% (74/129); RR 1.14 (95% CI 0.94 to 1.39) Cataract development, worsening or need for cataract surgery: 50% (67/134) vs. 62.5% (81/129); RR 0.80 (95 % CI 0.64 to 0.99) Serious non-ocular AE: 23.1% (31/134) v.s 23.2% (30/129); RR 0.99 (95% CI 0.64 to 1.54) | Bausch & Lomb | Good | None |

**Abbreviations:** AMD = age-related macular degeneration, aHR = adjusted hazard ratio, aRR = adjusted risk ratio, BCVA = best corrected visual acuity, CV = cardiovascular, DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid, ETDRS = Early Treatment Diabetic Retinopathy Study, IU = international units, mg = milligrams, NA = not applicable, OR = odds ratio, RCT = randomized controlled trial, RR = risk ratio, UK = United Kingdom.