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

NIH National Eye Institute

AREDS2
Age-Related Eye Disease Study 2
Funded by the National Institutes of Health

Age-Related Eye Disease Study 2

The Lutein/Zeaxanthin and Omega-3 Supplementation Trial

Age-Related Eye Disease Study 2

(AREDS2)

Research Group

LLUSM APC, March 8, 2014

Presenter:

Clement K. Chan, M.D. ,F.A.C.S.

Disclosure
Clement K. Chan

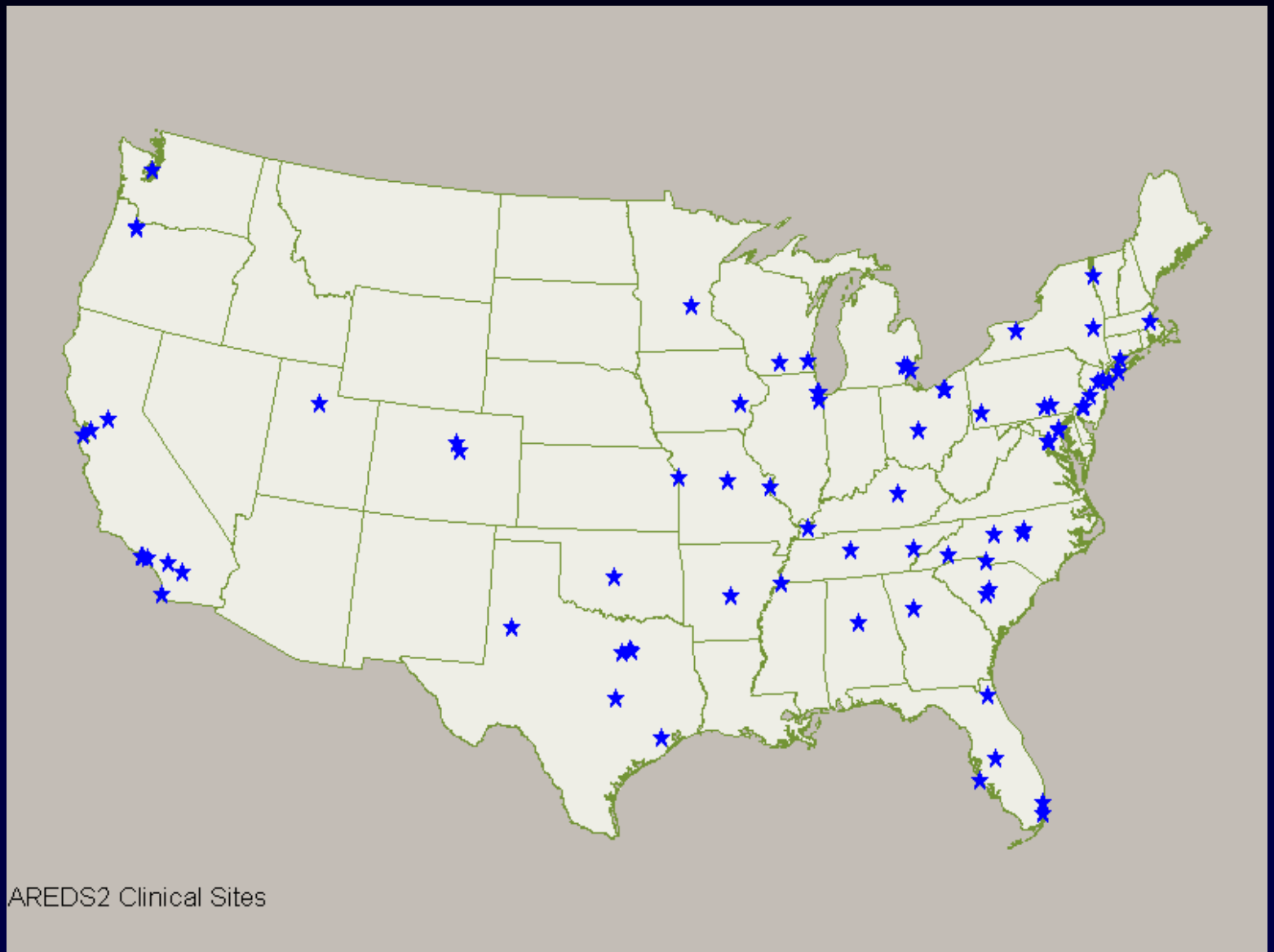
- **Genentech**
  - Grant, research support
  - Investigator
- **NEI**
  - Investigator
  - Grant
- **Acucela**
  - Investigator
- **Sequenom**
  - Research support
- **Regeneron**
  - Advisory board
  - Grant, research support
  - Investigator
- **ThromboGenics**
  - Advisory board
- **Allergan**
  - Advisory board
  - Honorarium

AREDS2 Study Design

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

AREDS 2
Age-Related Eye Disease Study 2

AREDS2 Clinical Centers



AREDS2 Clinical Sites

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COLORADO

Mary Lansing, MD
Eldorado Retina Associates, P.C.

Brian Joondeph, MD
Colorado Retina Associates, PC

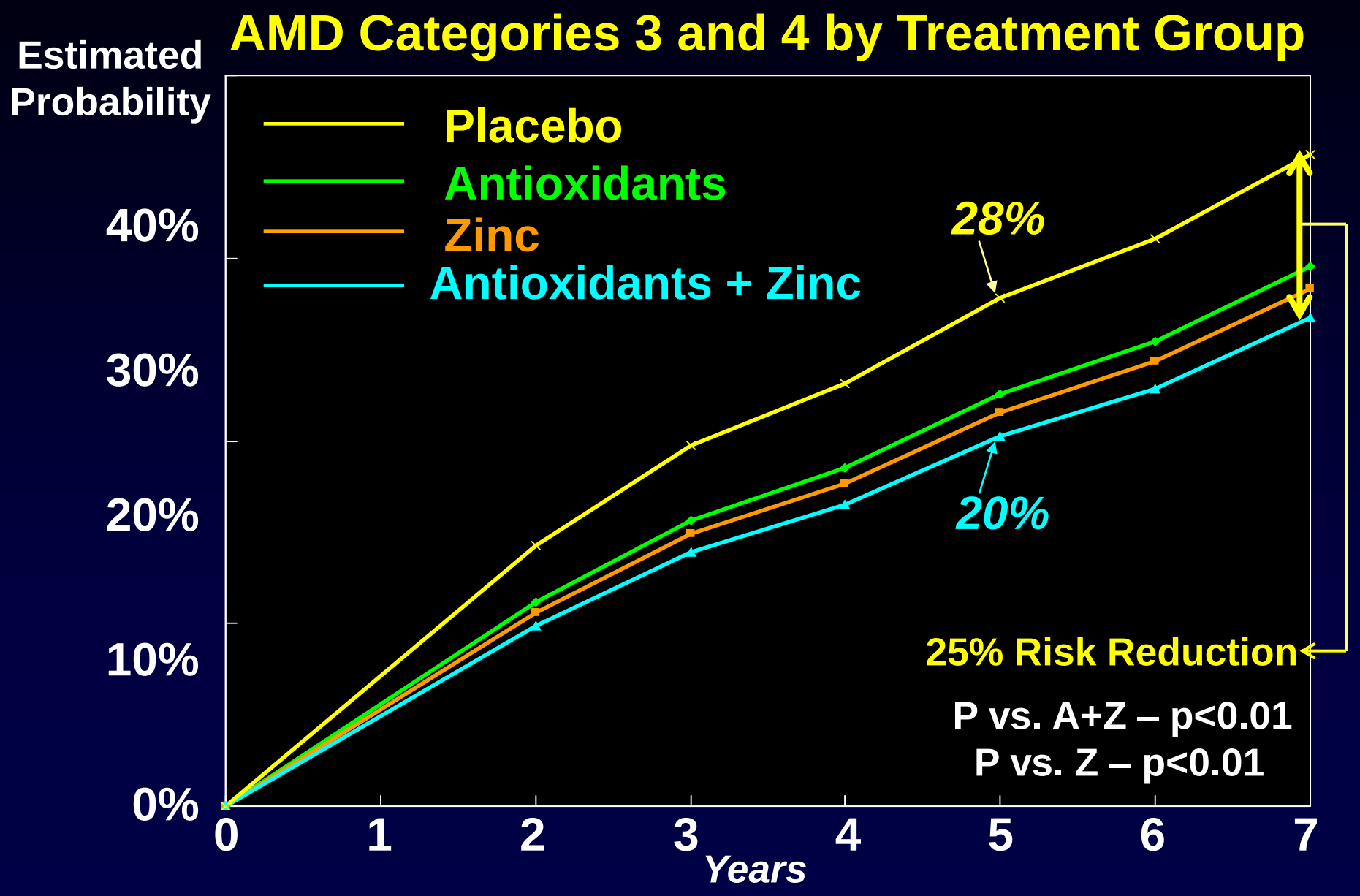
Age-Related Eye Disease Study 2 (AREDS2)

Background Information and Study Design

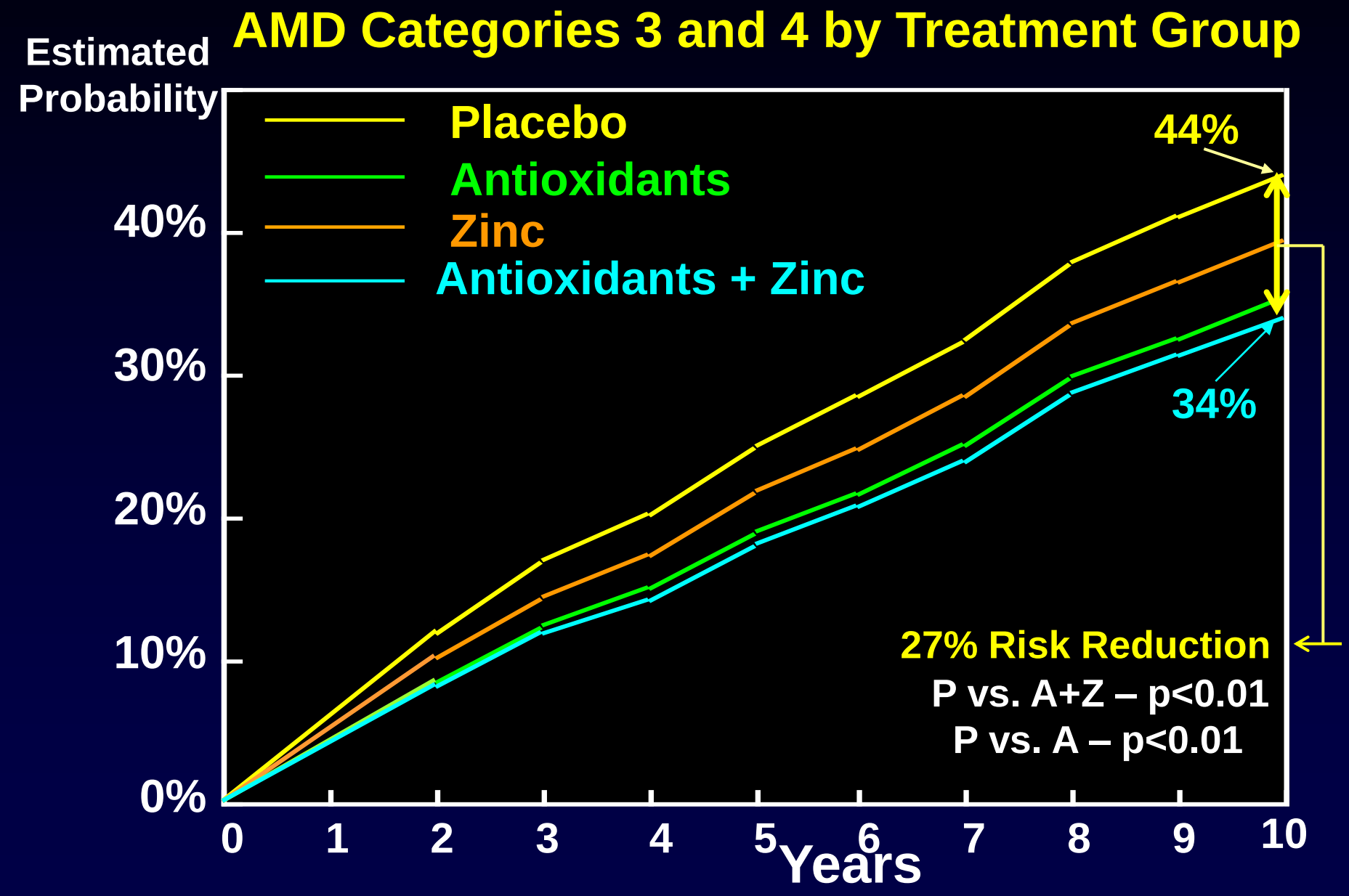
AREDS 1 Formulation

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

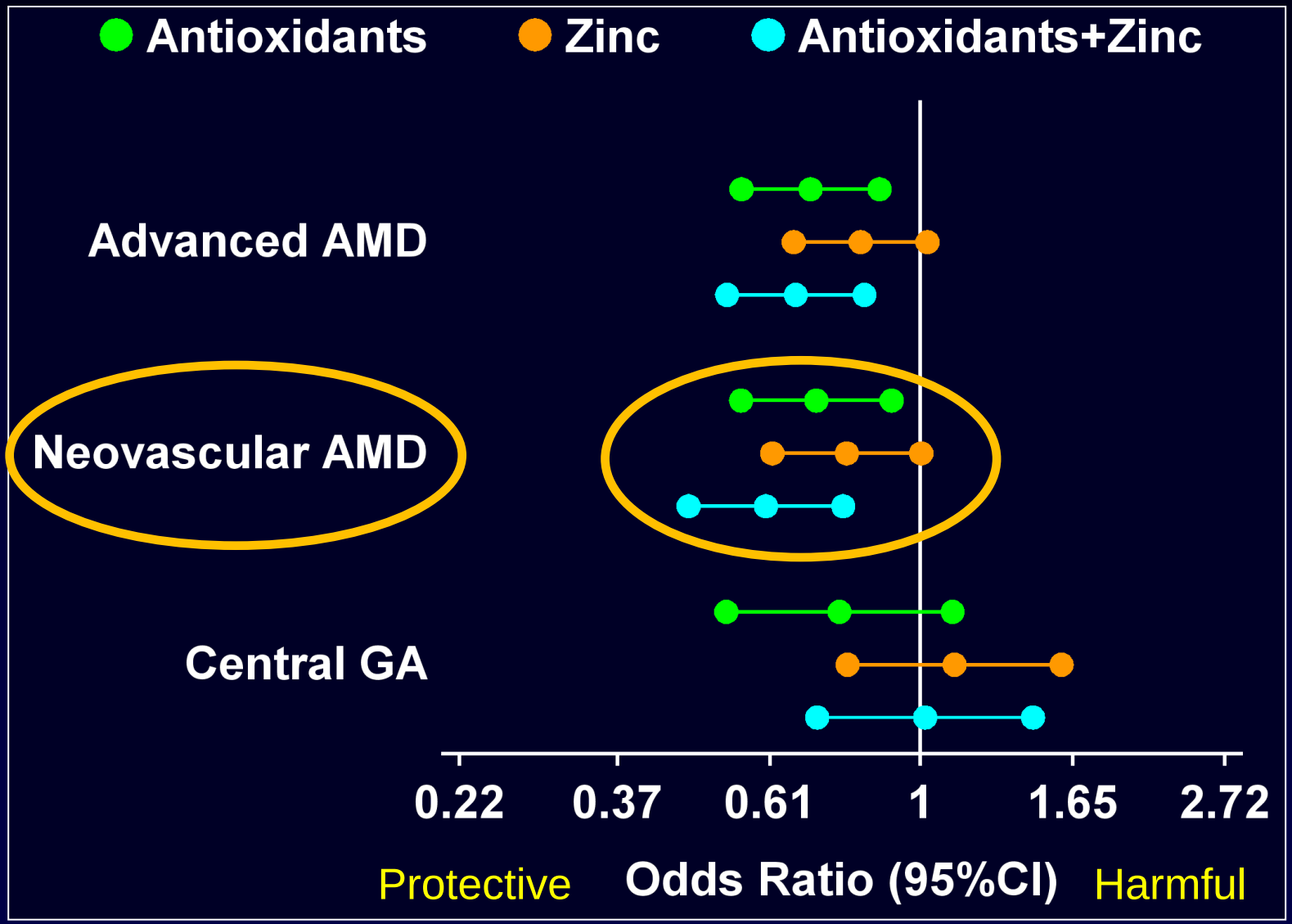
Rates to Advanced AMD



Long-Term Rates to Advanced AMD



Development of Advanced AMD AREDS Categories 3 & 4



The Age-Related Eye Disease Study 2

Lutein/Zeaxanthin

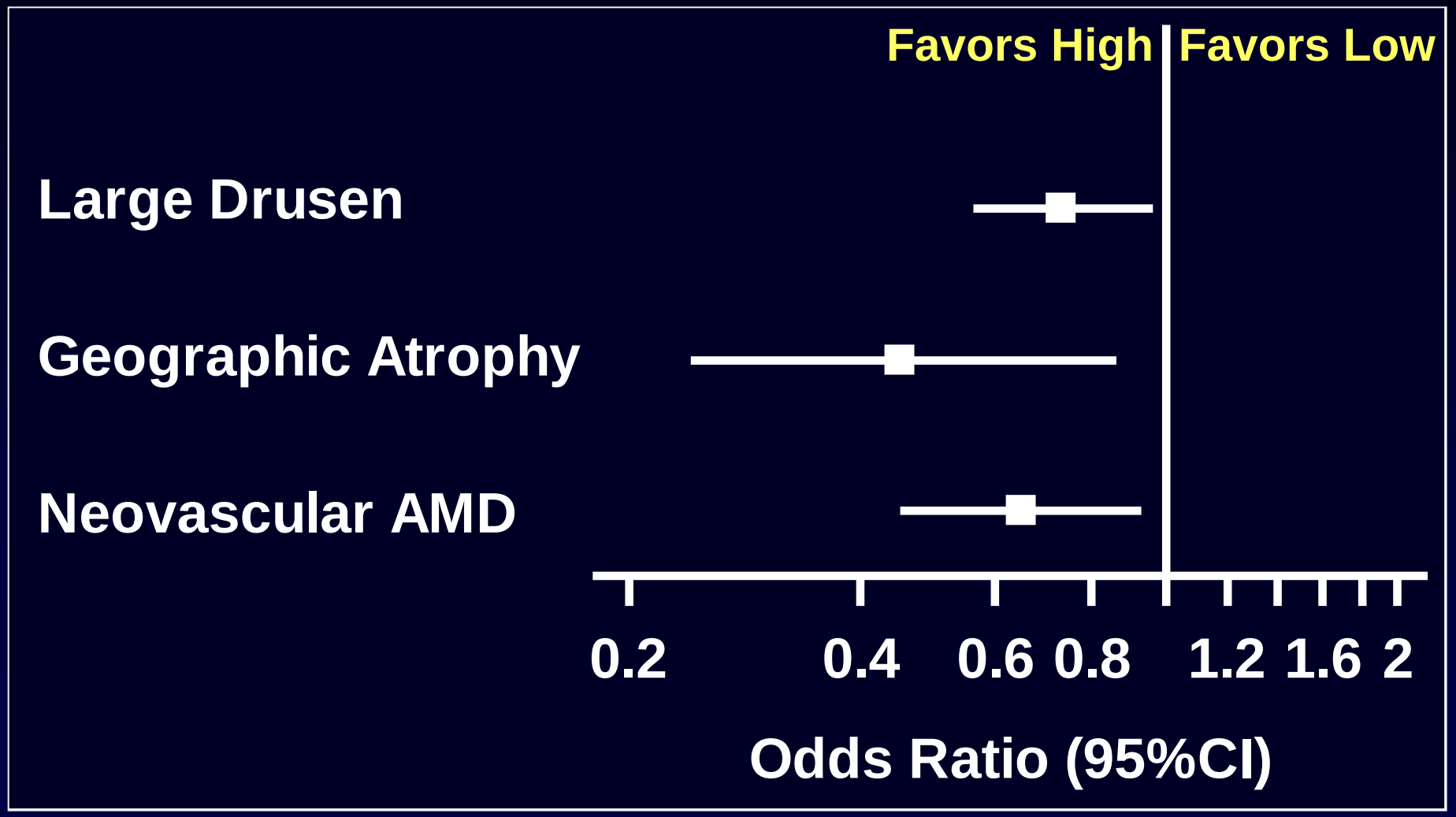


Spinach, Kale and Collard Greens

Omega-3 Long-chain Polyunsaturated Fatty Acids (LCPUFAs) (DHA/EPA)

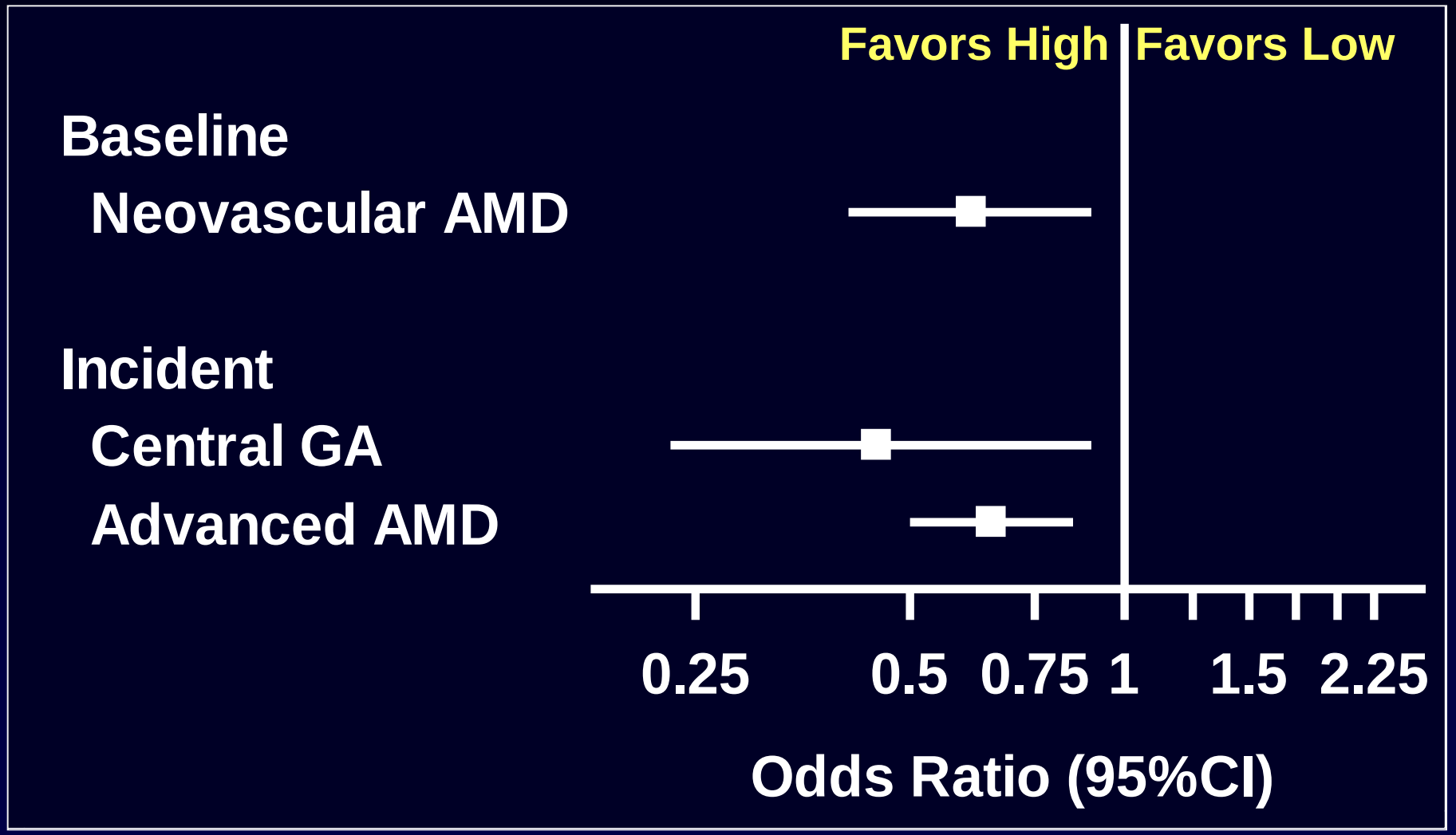
Self-reported Dietary Lutein/Zeaxanthin Association with Baseline AMD Status

Highest Intake vs. Lowest Intake (Quintile)



Self-reported Dietary Omega-3 Fatty Acids Association with Baseline AMD Status

Highest Intake vs. Lowest Intake (Quintile)



AREDS-2 : Primary Objective

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

AREDS2 Study Design

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

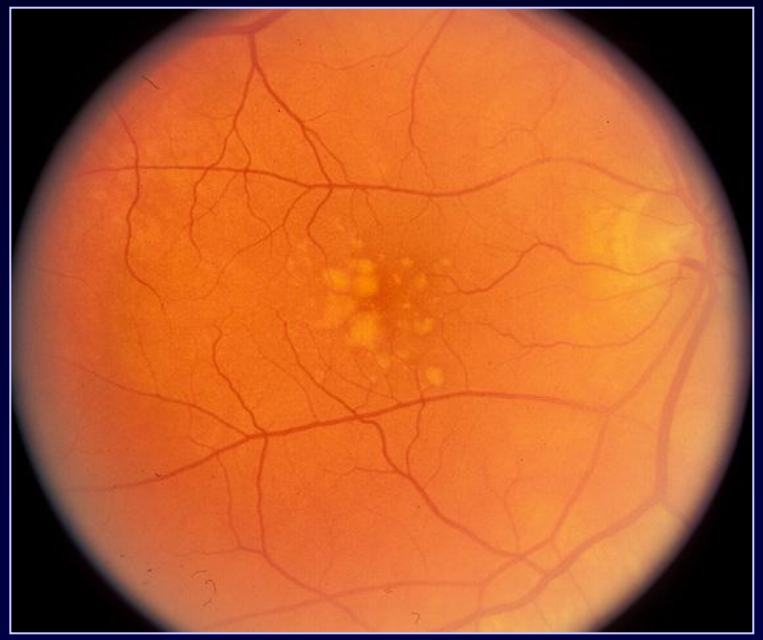
Ocular Characteristics

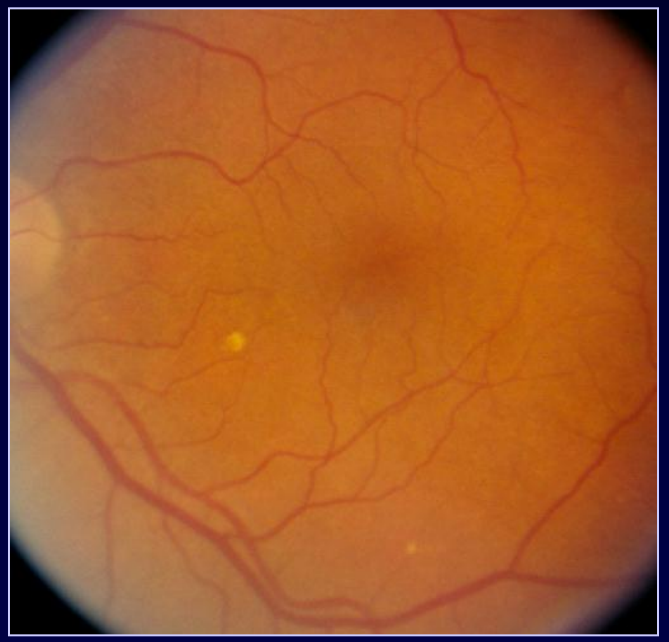
- Bilateral large drusen
- Advanced AMD in one eye and large drusen in the fellow eye

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 ≥ 125μ**)

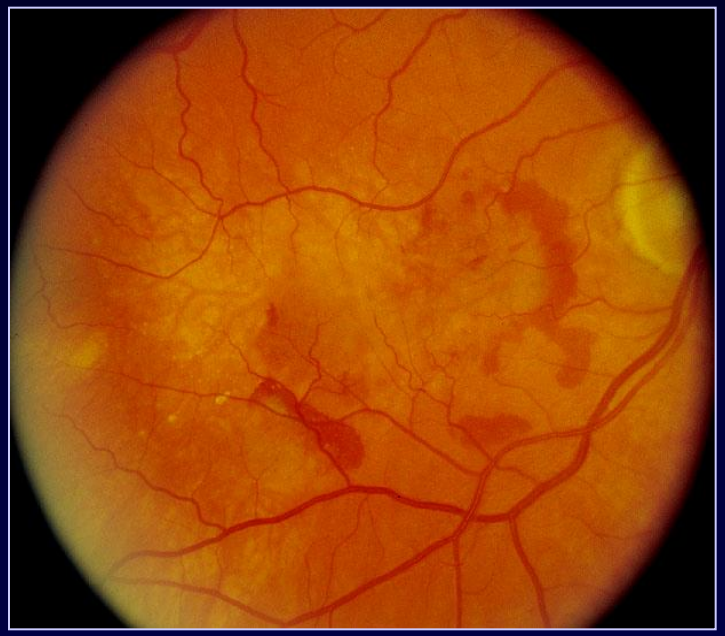




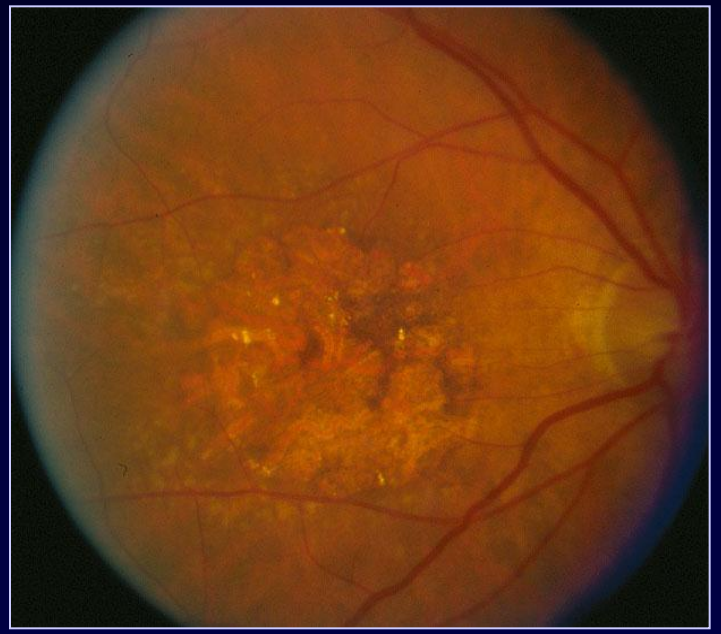
AREDS 2
Age-Related Eye Disease Study 2

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)

AREDS 2
Age-Related Eye Disease Study 2

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)

AREDS 2
Age-Related Eye Disease Study 2

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 ≥ 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

AREDS 2
Age-Related Eye Disease Study 2

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

AREDS 2
Age-Related Eye Disease Study 2

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

AREDS 2
Age-Related Eye Disease Study 2

Exclusion Criteria

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

AREDS 2
Age-Related Eye Disease Study 2

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:

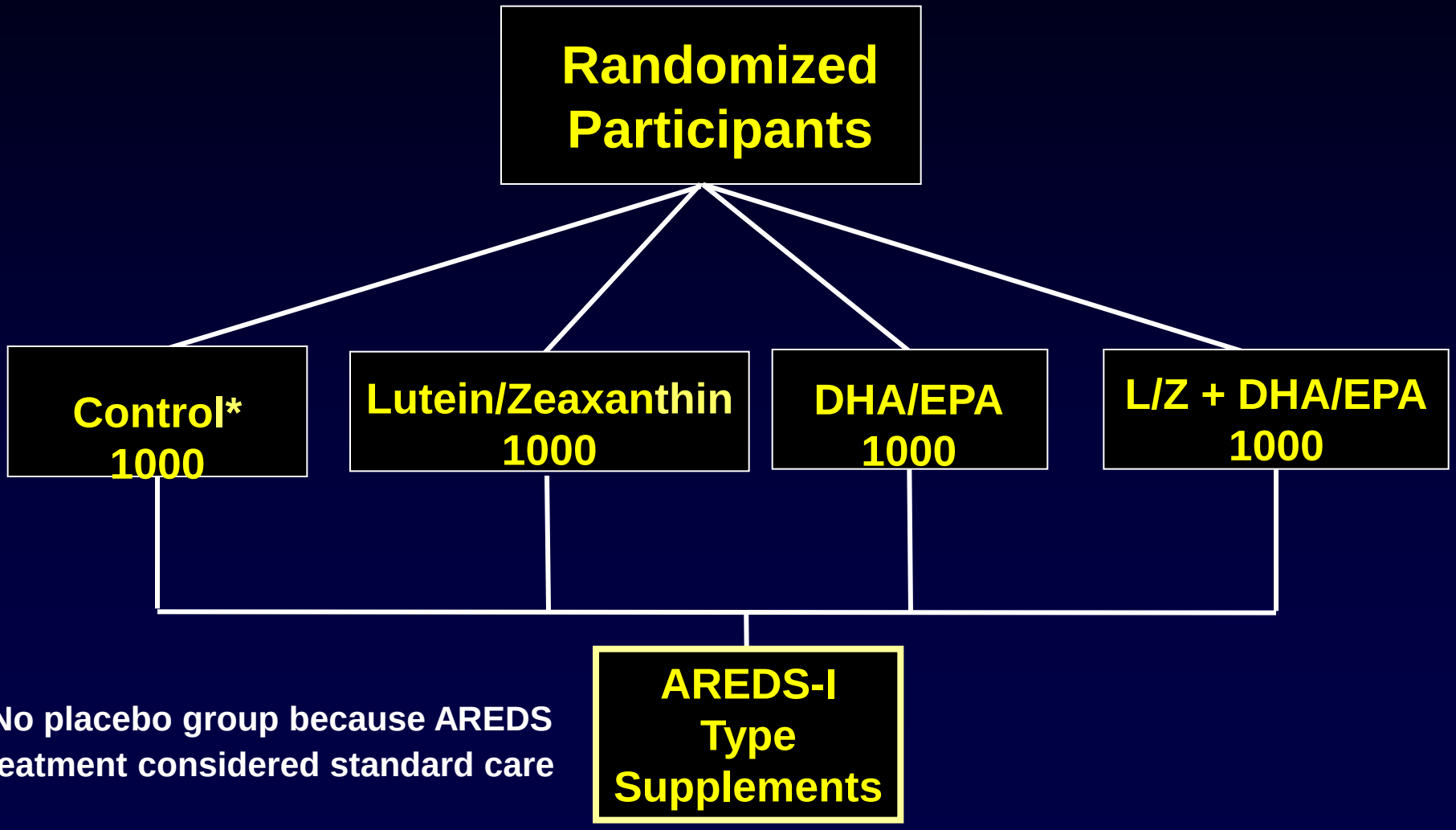
- *Progression to advanced AMD*
- *Progression to moderate vision loss*
- *Disease progression on the AMD scale*
- *Time to cataract surgery*
- *Progression of lens opacity*

Primary and Secondary Outcomes

Evaluate the effects of dietary supplements:

- *Cardiovascular Morbidity and Mortality*
- *Cognitive function status*

Primary Randomization



*No placebo group because AREDS treatment considered standard care

AREDS2 Secondary Randomization

AREDS 1-Type Supplement

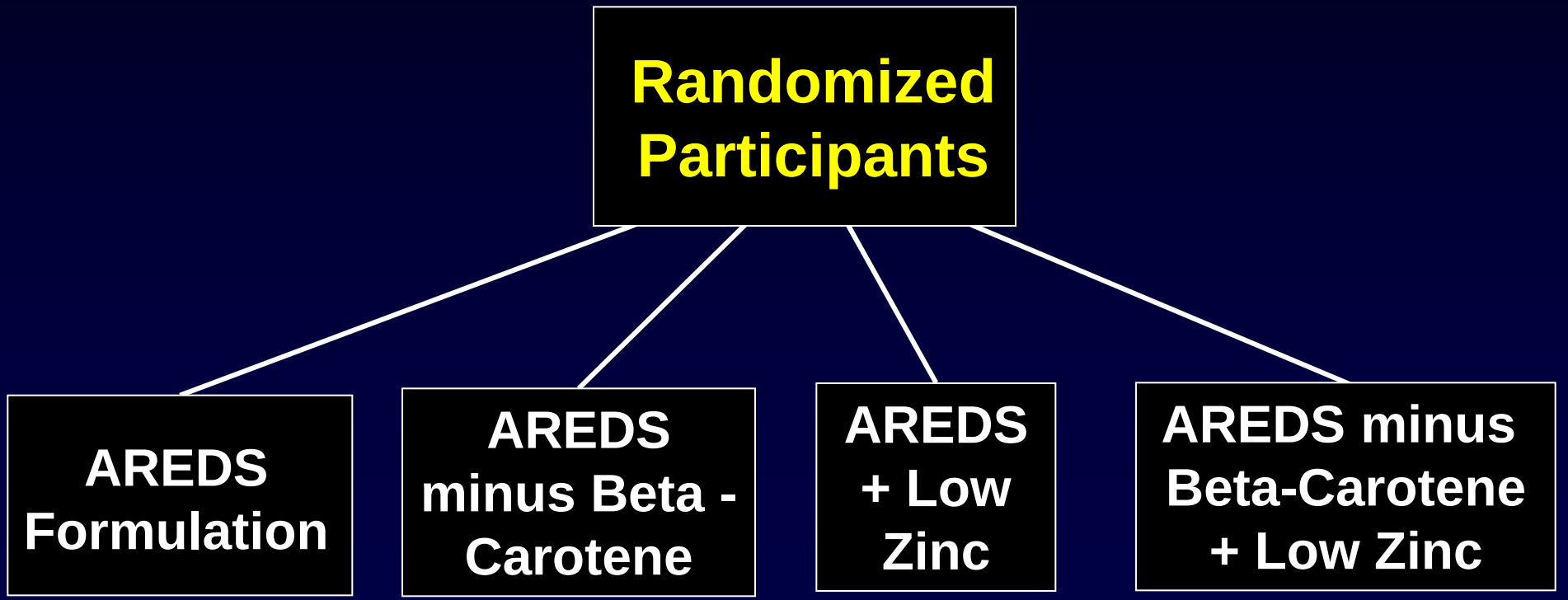
	Vitamin C	Vitamin E	β-carotene	Zinc Oxide	Cupric Oxide
1	500 mg	400 IU	15 mg	80 mg	2 mg
2*	500 mg	400 IU	0 mg	80 mg	2 mg
3	500 mg	400 IU	15 mg	25 mg	2 mg
4*	500 mg	400 IU	0 mg	25 mg	2 mg

***Smokers were randomized to one of two arms without beta-carotene.**

Smokers

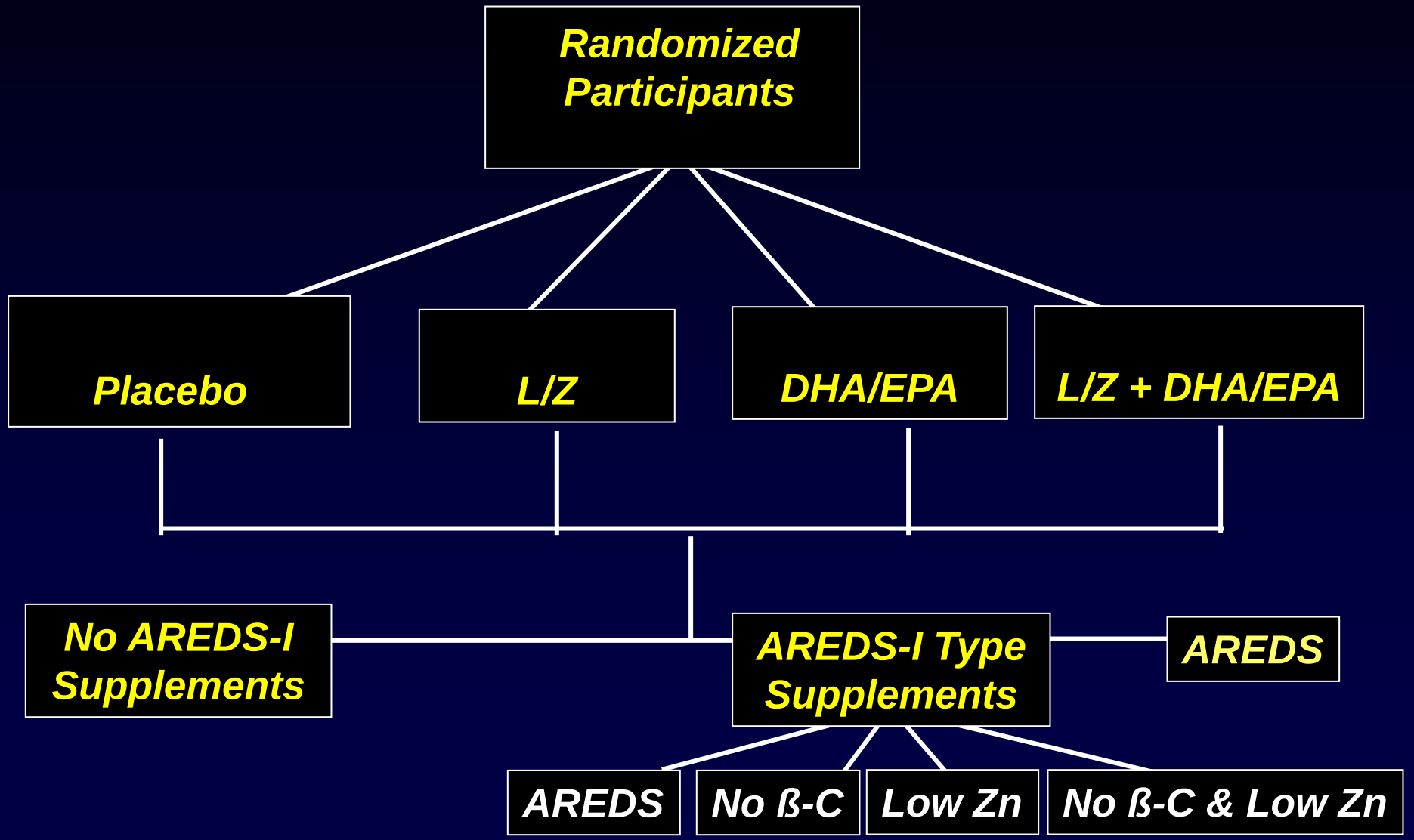
If a participant was a current smoker or a former smoker who has quit within the last year he or she was randomized to one of the two arms without beta-carotene. Smokers were not given the original AREDS-type supplement.

AREDS2-2nd Randomization
Modification of AREDS formulation

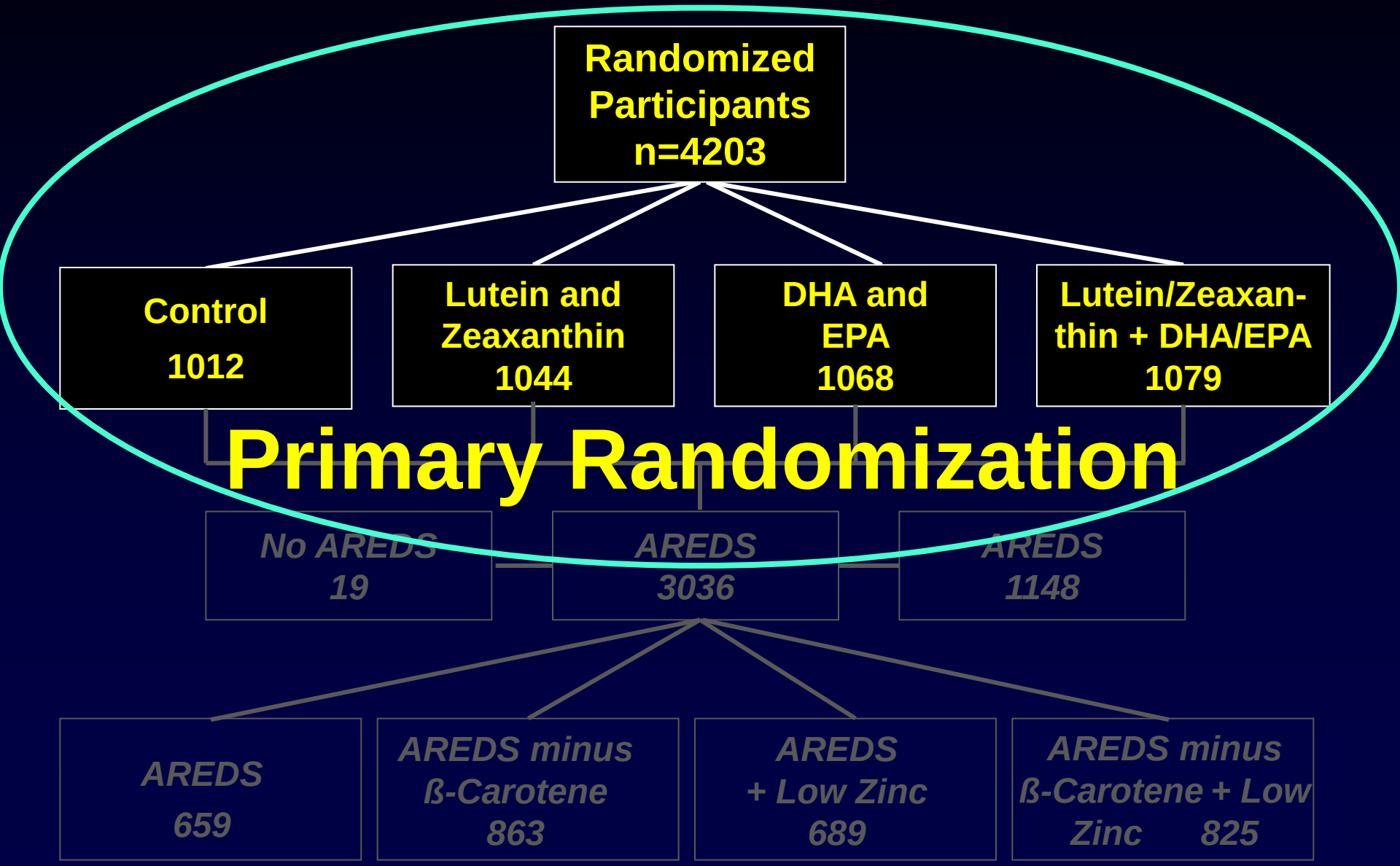


AREDS 2
Age-Related Eye Disease Study 2

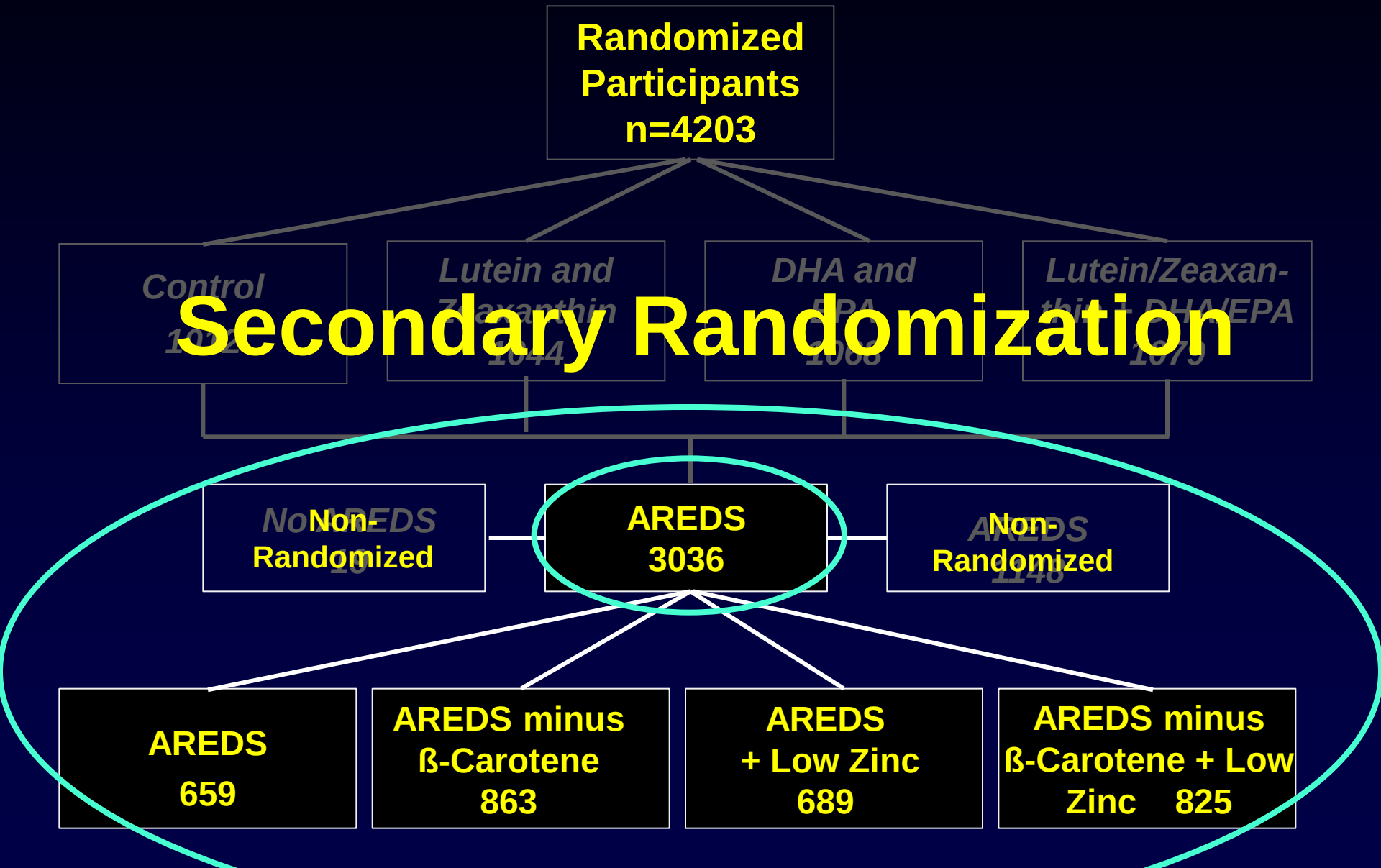
Secondary Randomization



Study Design

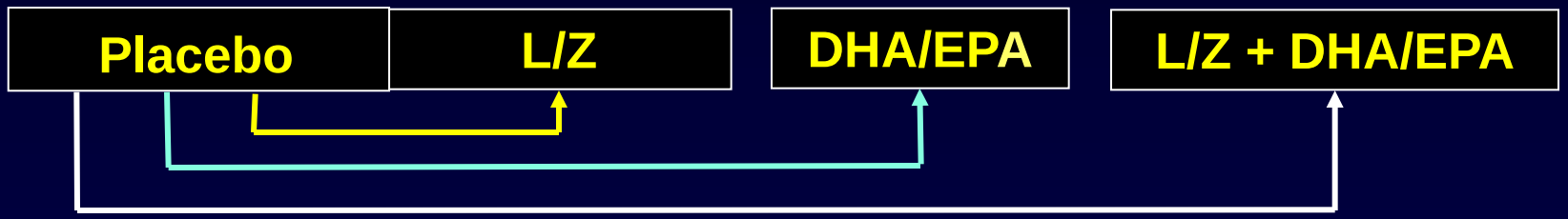


Study Design



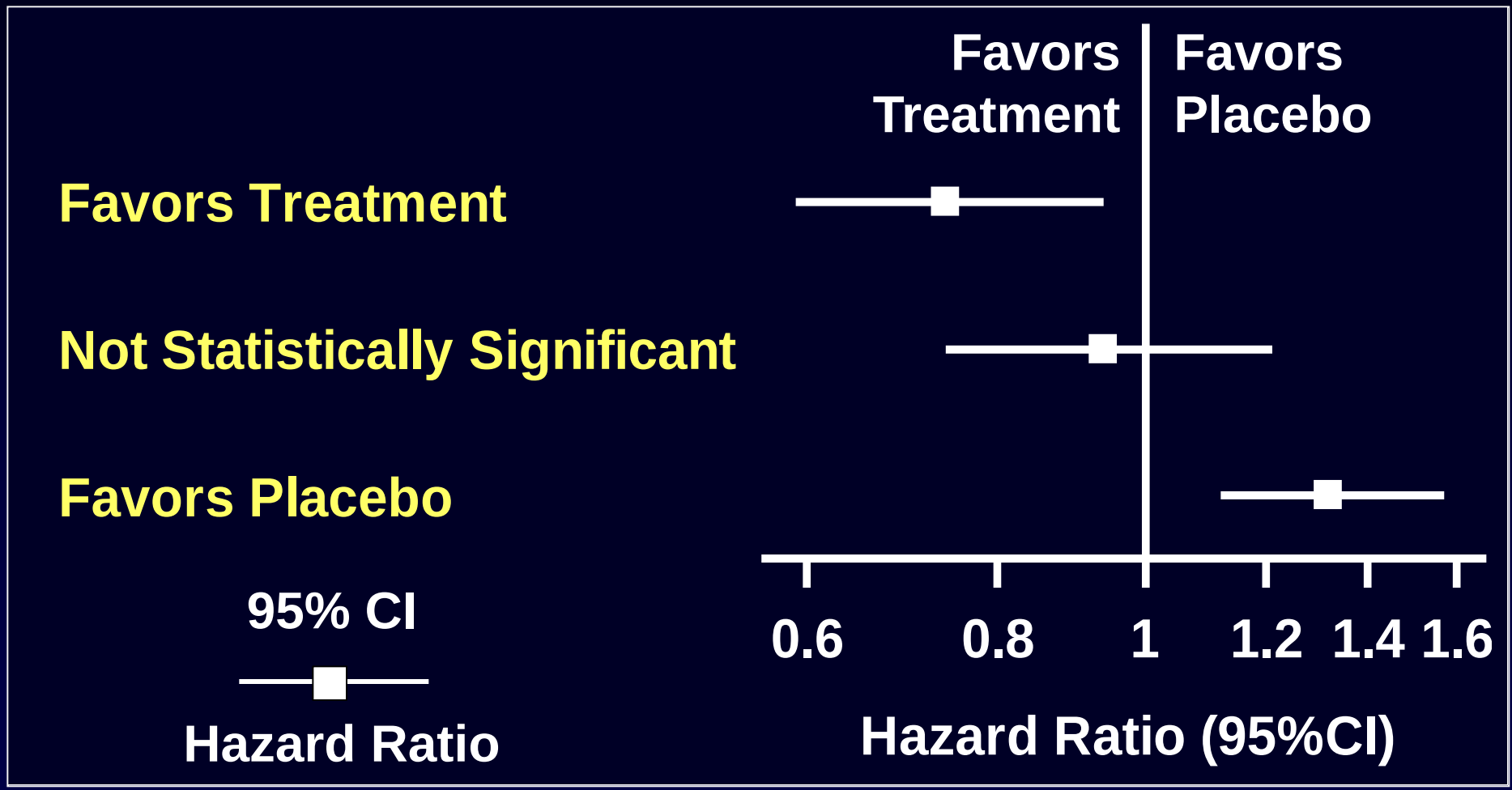
Statistical Analysis

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



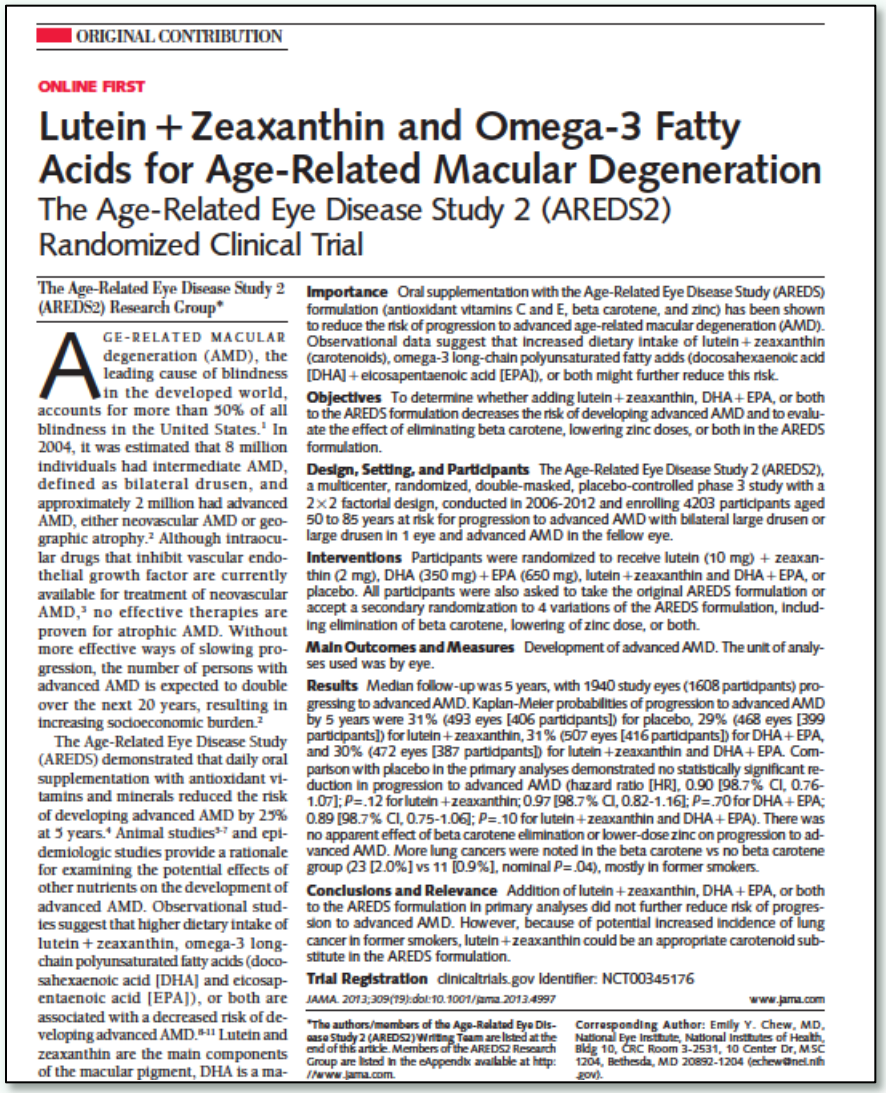
- Intention-to-Treat Analyses
- Unit of analysis was by eye
- Time-to-event analyses (Cox Proportional Hazards)

Hazard Ratio Tree



Age-Related Eye Disease Study 2 (AREDS2)

Study Results



ORIGINAL CONTRIBUTION

ONLINE FIRST

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*

Importance Oral supplementation with the Age-Related Eye Disease Study (AREDS) formulation (antioxidant vitamins C and E, beta carotene, and zinc) has been shown to reduce the risk of progression to advanced age-related macular degeneration (AMD). Observational data suggest that increased dietary intake of lutein + zeaxanthin (carotenoids), omega-3 long-chain polyunsaturated fatty acids (docosahexaenoic acid [DHA] + eicosapentaenoic acid [EPA]), or both might further reduce this risk.

Objectives 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.

Design, Setting, and Participants The Age-Related Eye Disease Study 2 (AREDS2), a multicenter, randomized, double-masked, placebo-controlled phase 3 study with a 2×2 factorial design, conducted in 2006-2012 and enrolling 4203 participants aged 50 to 85 years at risk for progression to advanced AMD with bilateral large drusen or large drusen in 1 eye and advanced AMD in the fellow eye.

Interventions Participants were randomized to receive lutein (10 mg) + zeaxanthin (2 mg), DHA (350 mg) + EPA (650 mg), lutein + zeaxanthin and DHA + EPA, or placebo. All participants were also asked to take the original AREDS formulation or accept a secondary randomization to 4 variations of the AREDS formulation, including elimination of beta carotene, lowering of zinc dose, or both.

Main Outcomes and Measures Development of advanced AMD. The unit of analyses used was by eye.

Results Median follow-up was 5 years, with 1940 study eyes (1608 participants) progressing to advanced AMD. Kaplan-Meier probabilities of progression to advanced AMD by 5 years were 31% (493 eyes [406 participants]) for placebo, 29% (468 eyes [399 participants]) for lutein + zeaxanthin, 31% (507 eyes [416 participants]) for DHA + EPA, and 30% (472 eyes [387 participants]) for lutein + zeaxanthin and DHA + EPA. Comparison with placebo in the primary analyses demonstrated no statistically significant reduction in progression to advanced AMD (hazard ratio [HR], 0.90 [98.7% CI, 0.76-1.07]; $P=.12$ for lutein + zeaxanthin; 0.97 [98.7% CI, 0.82-1.16]; $P=.70$ for DHA + EPA; 0.89 [98.7% CI, 0.75-1.06]; $P=.10$ for lutein + zeaxanthin and DHA + EPA). There was no apparent effect of beta carotene elimination or lower-dose zinc on progression to advanced AMD. More lung cancers were noted in the beta carotene vs no beta carotene group (23 [2.0%] vs 11 [0.9%], nominal $P=.04$), mostly in former smokers.

Conclusions and Relevance 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.

Trial Registration clinicaltrials.gov Identifier: NCT00345176

JAMA. 2013;309(19):doi:10.1001/jama.2013.4997

www.jama.com

AGE-RELATED MACULAR degeneration (AMD), the leading cause of blindness in the developed world, accounts for more than 50% of all blindness in the United States.[1] In 2004, it was estimated that 8 million individuals had intermediate AMD, defined as bilateral drusen, and approximately 2 million had advanced AMD, either neovascular AMD or geographic atrophy.[2] Although intraocular drugs that inhibit vascular endothelial growth factor are currently available for treatment of neovascular AMD,[3] no effective therapies are proven for atrophic AMD. Without more effective ways of slowing progression, the number of persons with advanced AMD is expected to double over the next 20 years, resulting in increasing socioeconomic burden.[2]

The Age-Related Eye Disease Study (AREDS) demonstrated that daily oral supplementation with antioxidant vitamins and minerals reduced the risk of developing advanced AMD by 25% at 5 years.[4] Animal studies[5-7] and epidemiologic studies provide a rationale for examining the potential effects of other nutrients on the development of advanced AMD. Observational studies suggest that higher dietary intake of lutein + zeaxanthin, omega-3 long-chain polyunsaturated fatty acids (docosahexaenoic acid [DHA] and eicosapentaenoic acid [EPA]), or both are associated with a decreased risk of developing advanced AMD.[8-11] Lutein and zeaxanthin are the main components of the macular pigment, DHA is a ma-

*The authors/members of the Age-Related Eye Disease Study 2 (AREDS2) Writing Team are listed at the end of this article. Members of the AREDS2 Research Group are listed in the eAppendix available at http://www.jama.com.

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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

Race	**97% White/ 1% Black**
Age	**74 yrs (median)**
Female	**57%**
Diabetes	**13%**
Smoking Status	50% Former / 7% Current

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

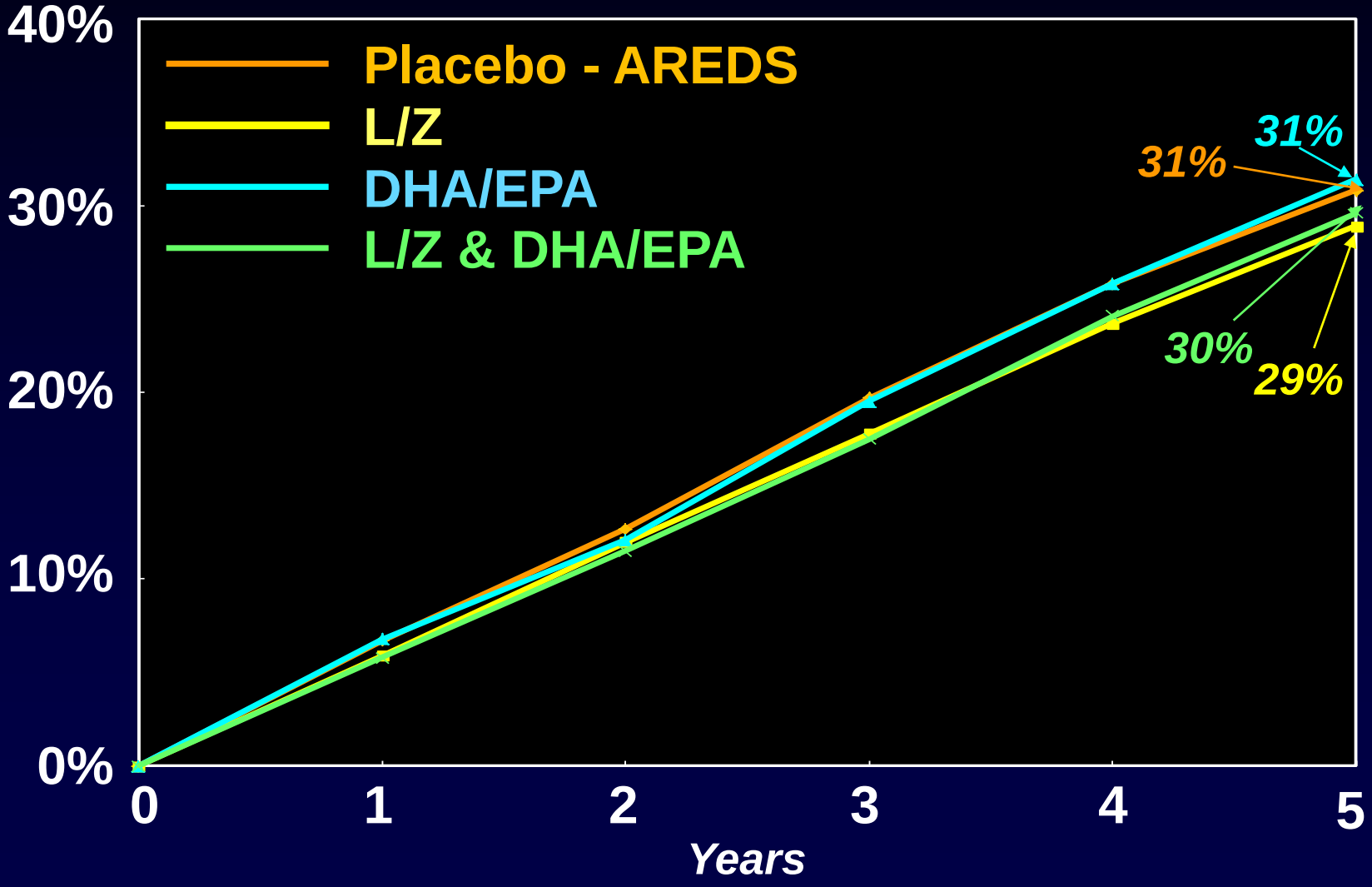
AREDS2 Dietary Intake and Serum Levels of Study Nutrients

- 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

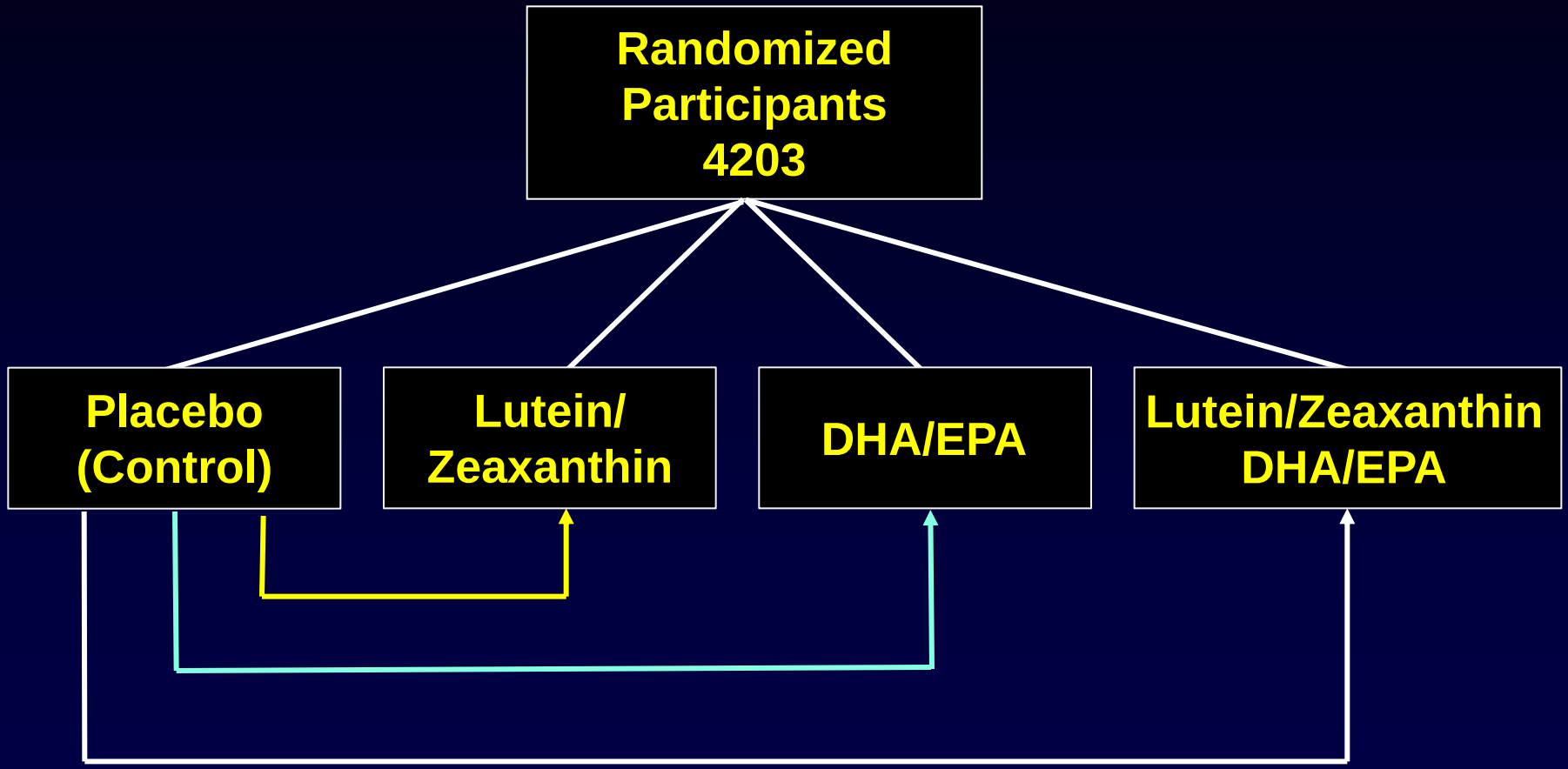
Competitive Absorption of Carotenoids

- 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)

Probability of Progression to AAMD

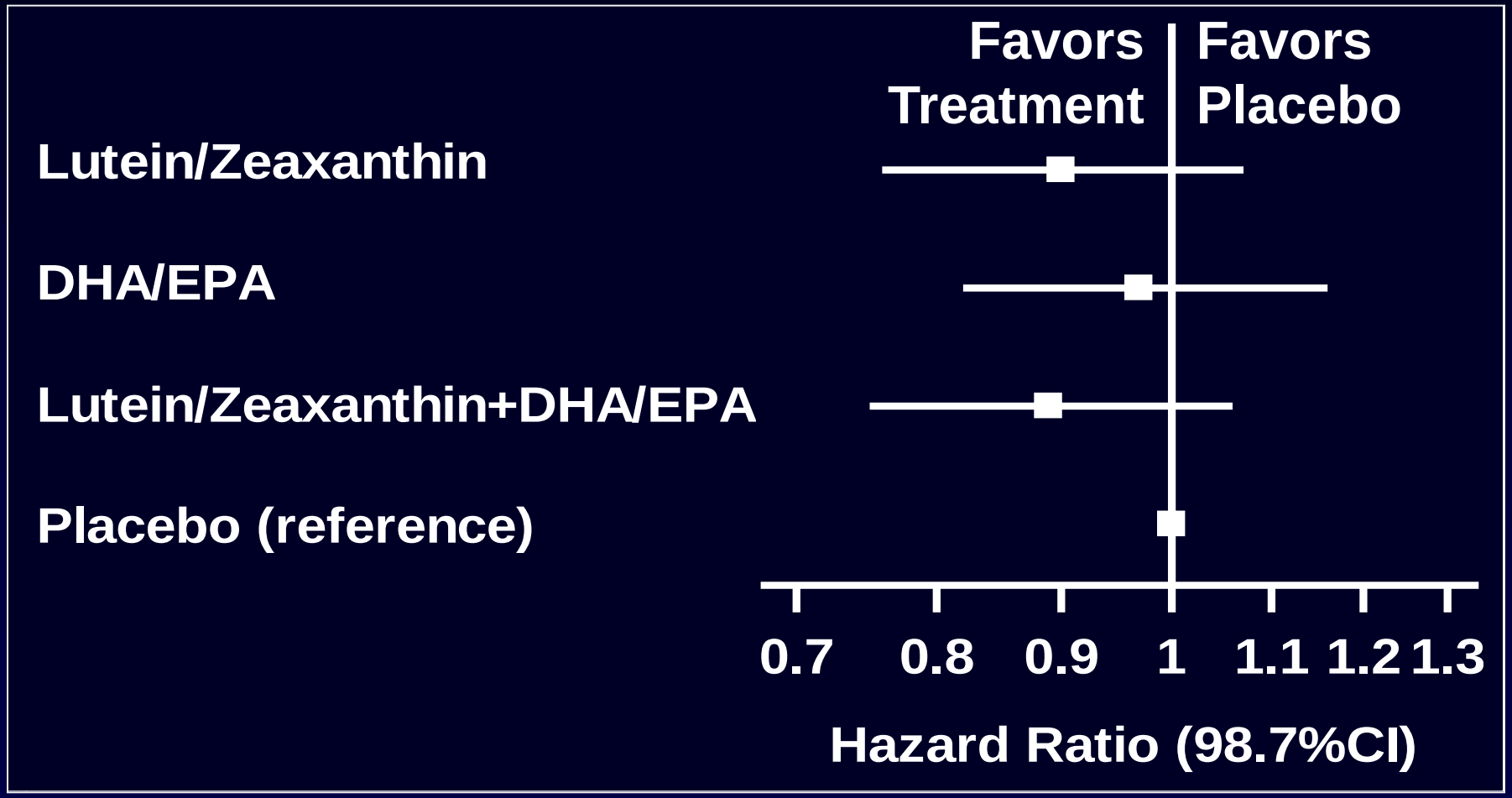


Primary Randomization

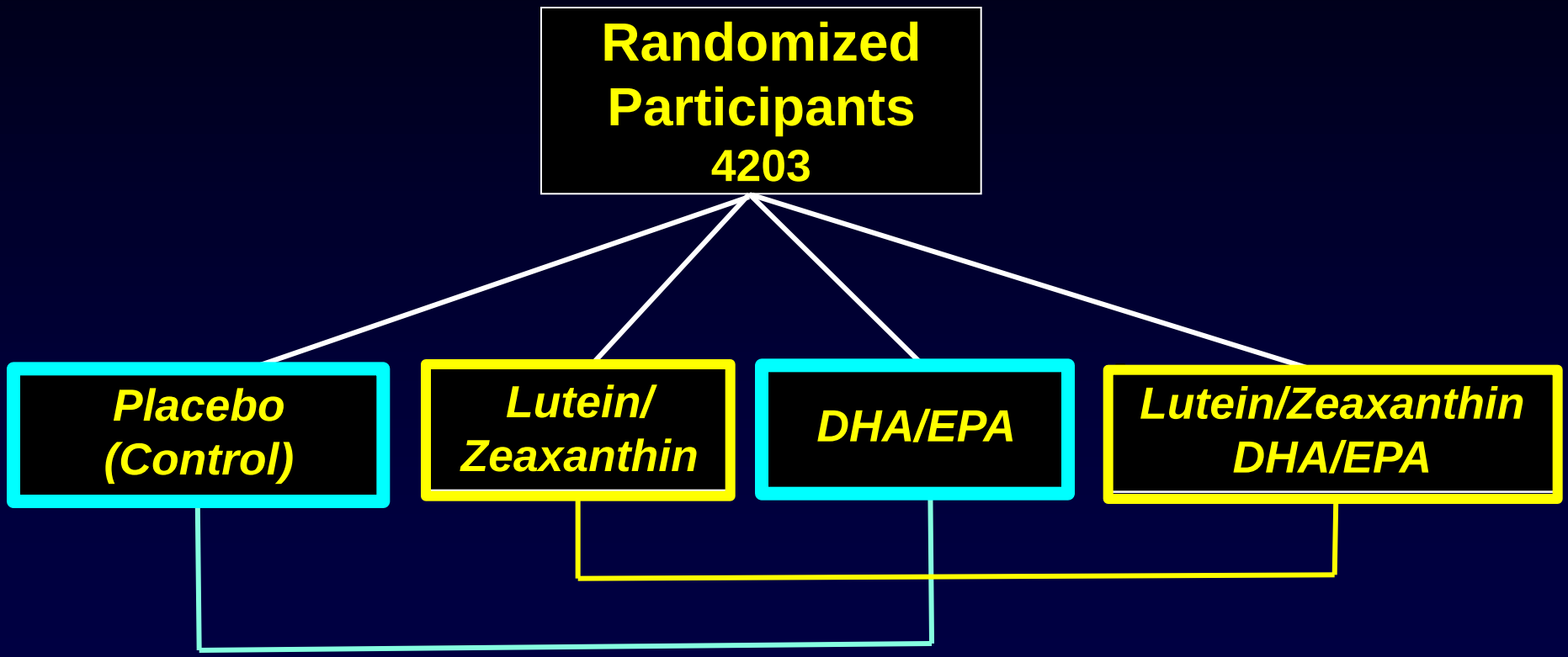


Three Primary Analyses

Primary Outcome Analyses
Progression to Advanced AMD



Primary Randomization



Analyses of Main Effects of Lutein/Zeaxanthin vs. No Lutein/Zeaxanthin

Post-Hoc exploratory analysis of effects of Lutein/Zeaxanthin

Research

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*

Editorial page 139

Supplemental content at jamaophthalmology.com

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.

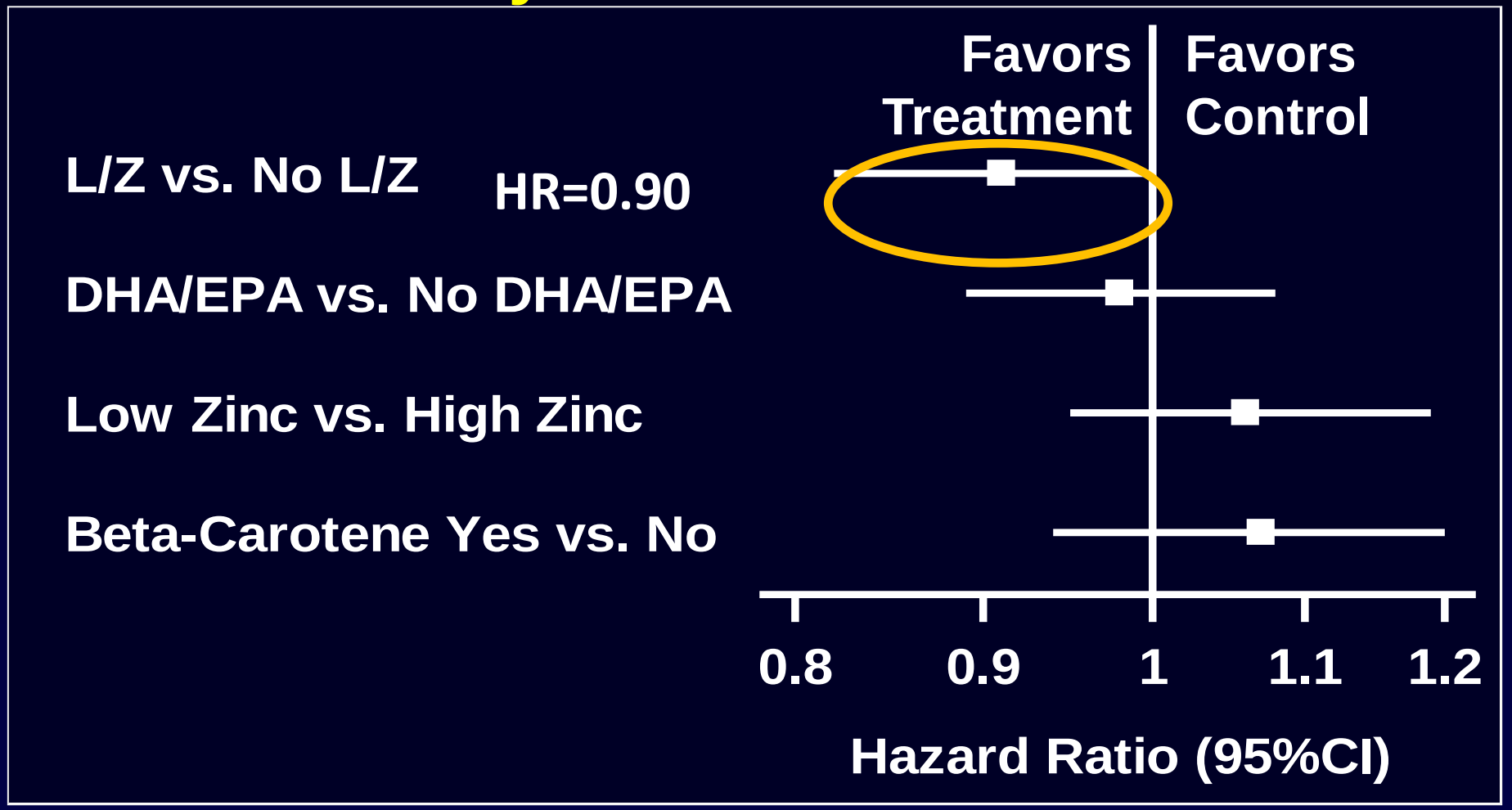
DESIGN, SETTING, PARTICIPANTS The Age-Related Eye Disease Study 2 is a multicenter, double-masked randomized trial of 4203 participants, aged 50 to 85 years, at risk for developing late AMD; 66% of patients had bilateral large drusen and 34% had large drusen and late AMD in 1 eye.

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 no lutein/zeaxanthin, the hazard ratio

Progression to Advanced AMD by Primary and Secondary Randomization Main Effects



Comparison of Lutein/Zeaxanthin vs. no Lutein/Zeaxanthin

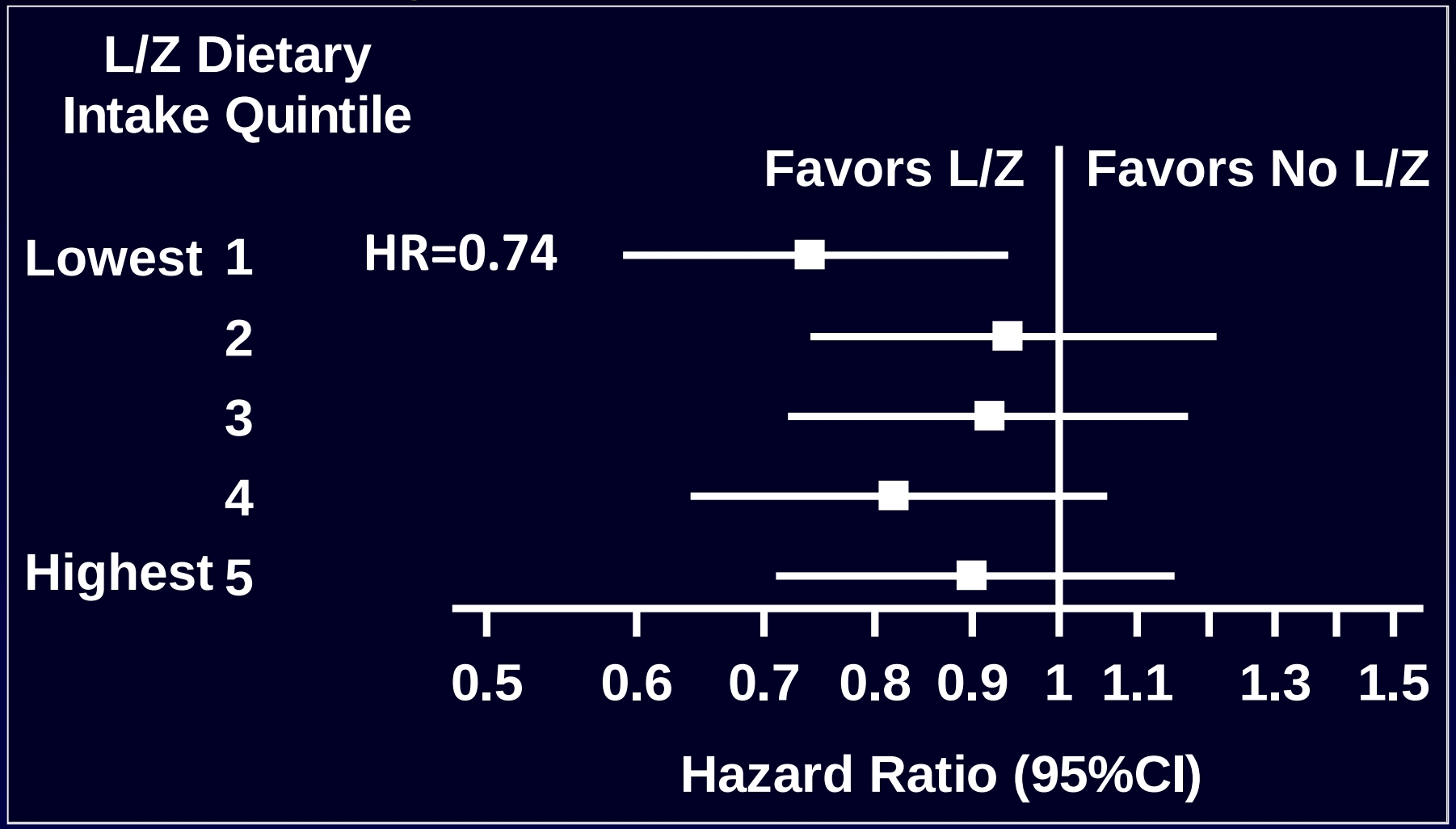
Advanced AMD: HR: 0.90 P=0.04

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

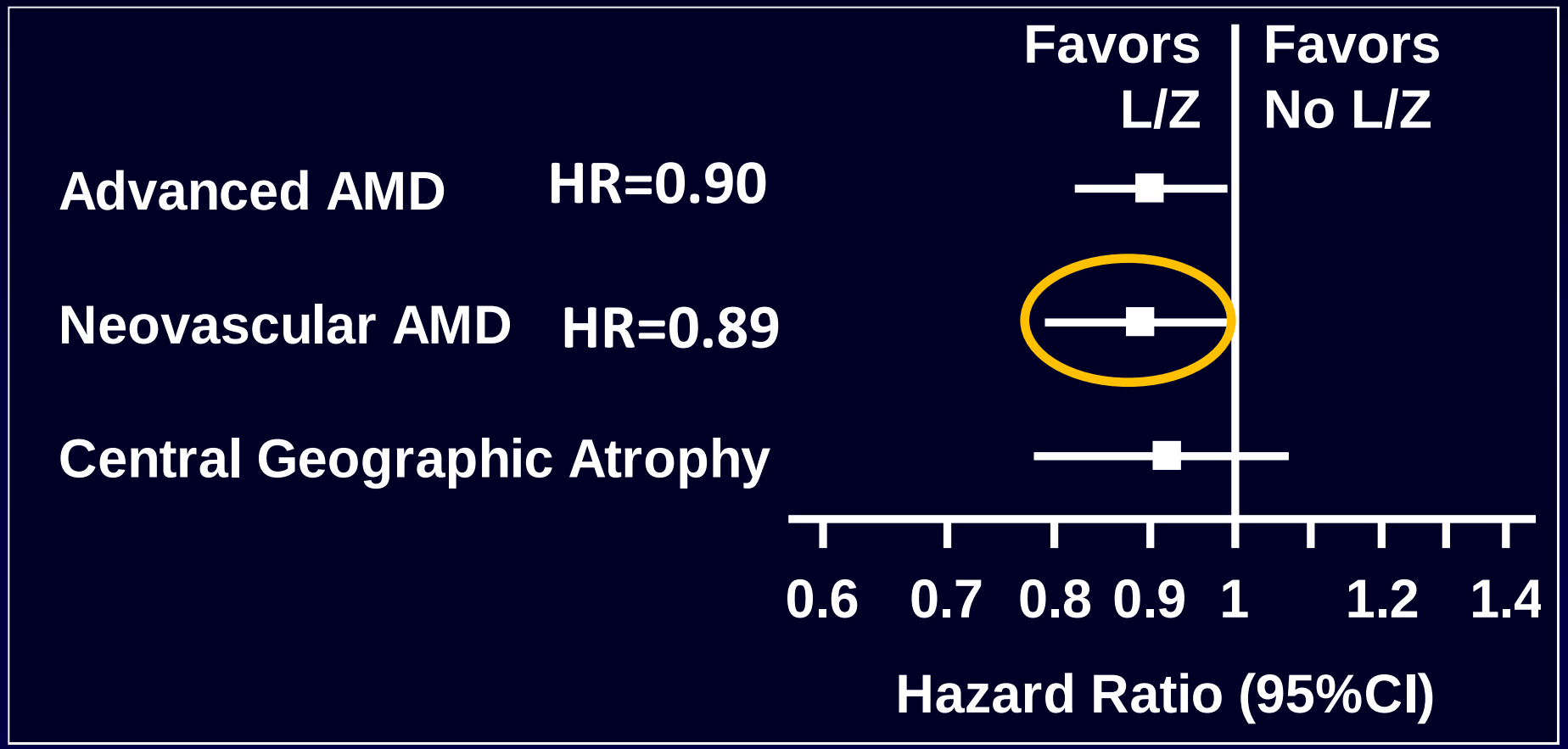


Lutein/Zeaxanthin vs. no Lutein/Zeaxanthin
Lowest Quintile of Dietary Lutein/Zeaxanthin

- 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



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 AREDS Formulation with Lutein/Zeaxanthin Substituted for Beta-carotene

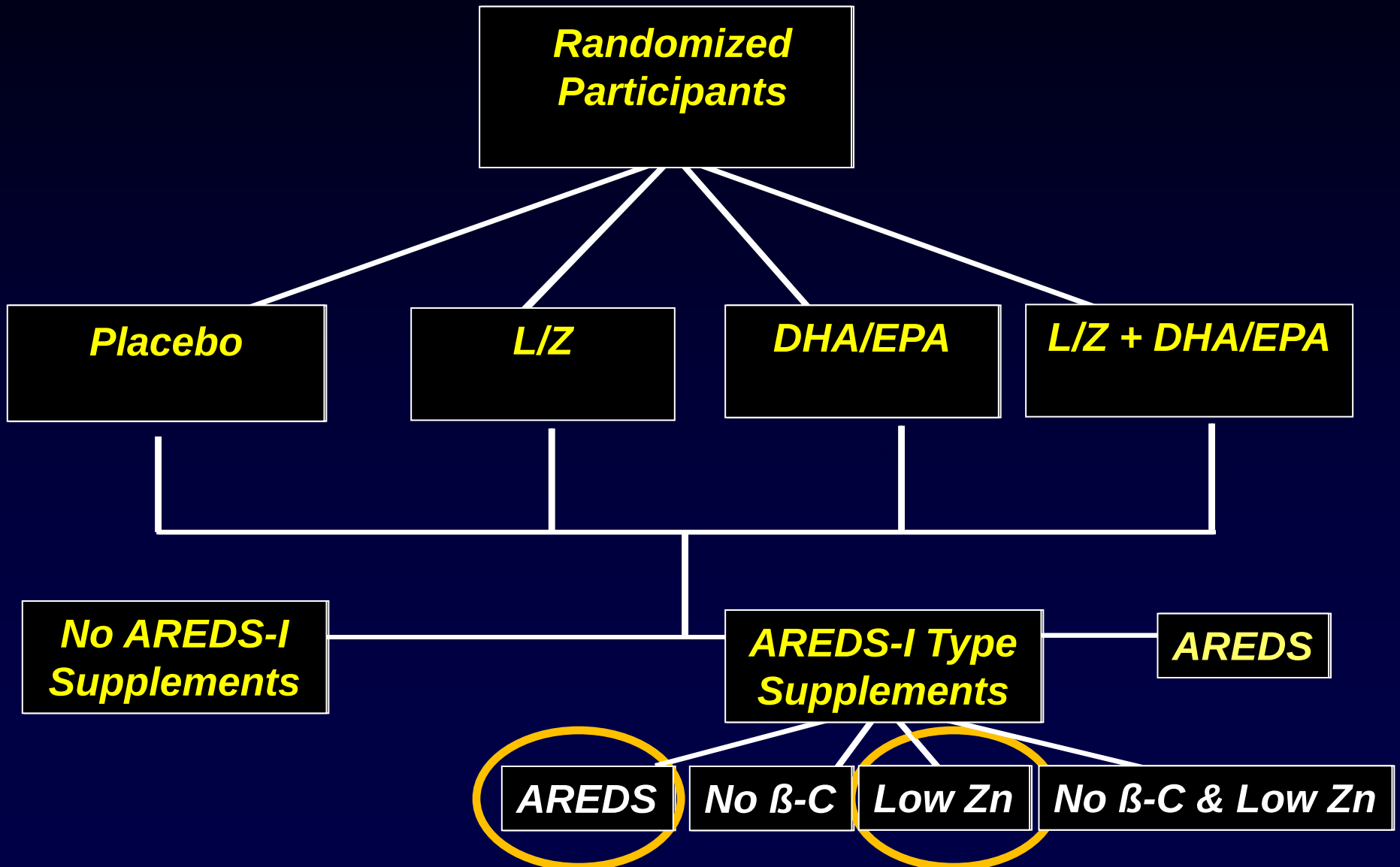
AREDS Formulation with Beta-Carotene
N = 683

vs.

Lutein/Zeaxanthin plus
AREDS Formulation minus Beta-Carotene
N = 674

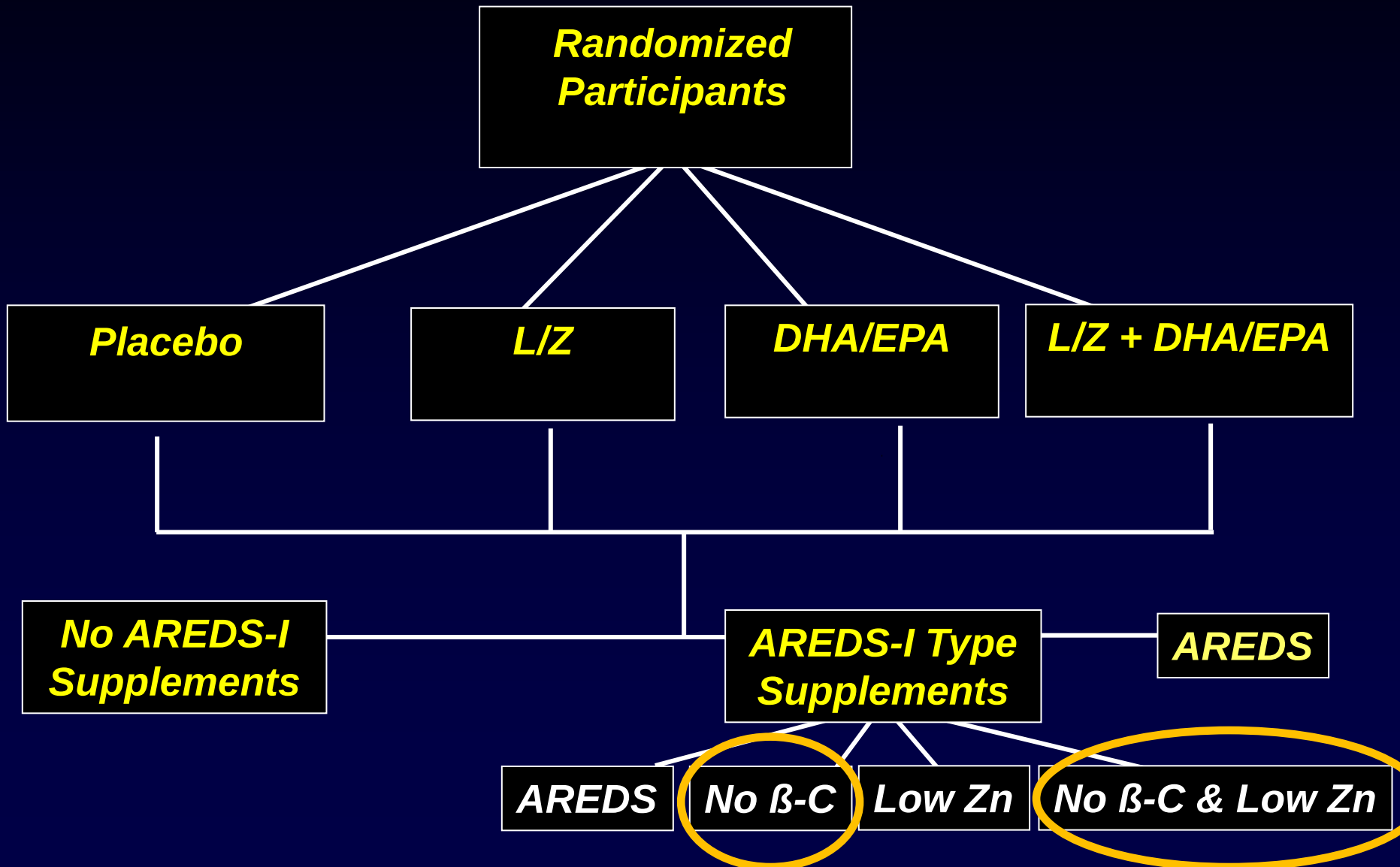
AREDS 2
Age-Related Eye Disease Study 2

Secondary Randomization

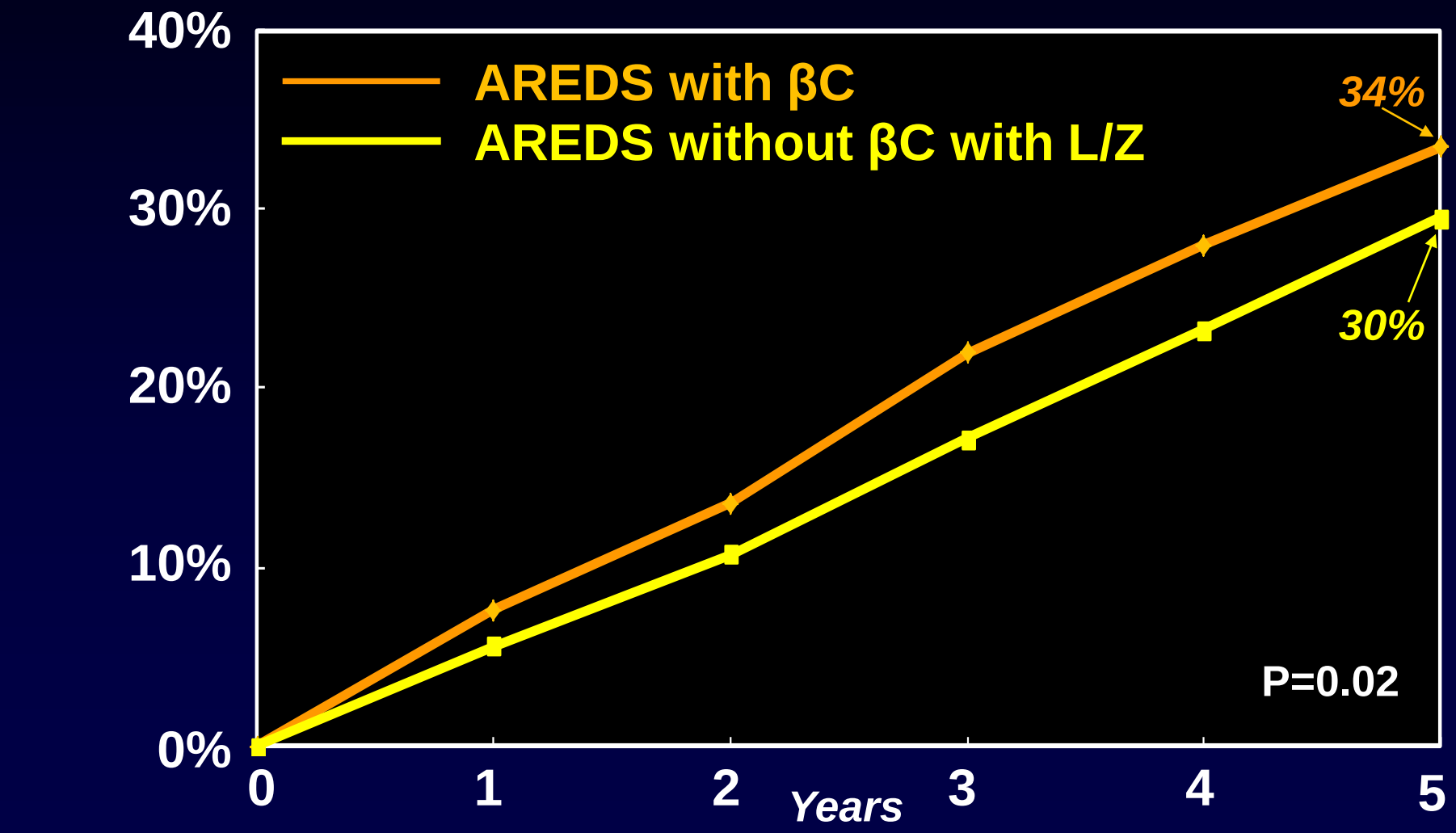


AREDS 2
Age-Related Eye Disease Study 2

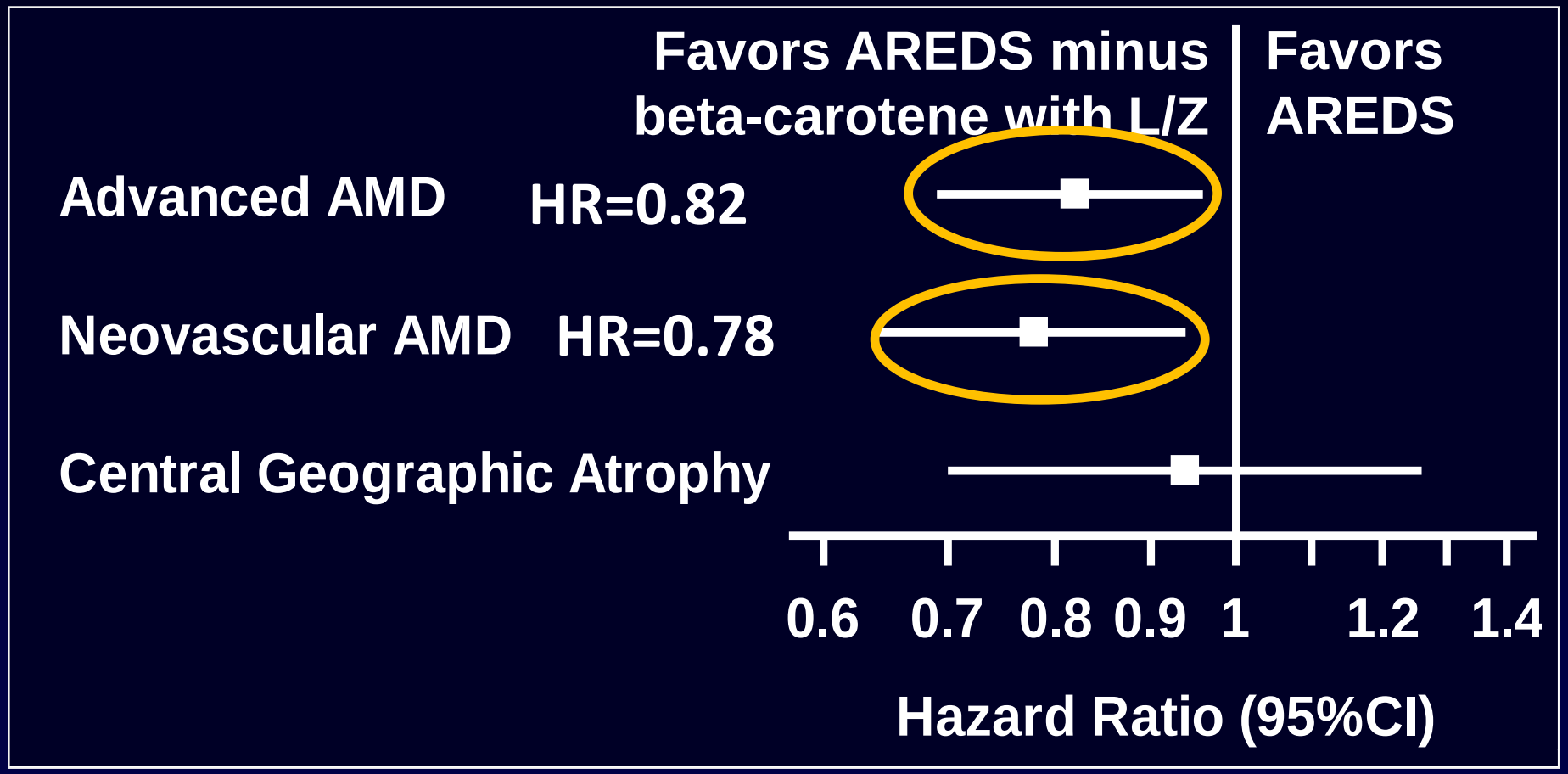
Secondary Randomization



Probability of Progression to AAMD



Progression to Advanced AMD
Exploratory Analyses of Lutein/Zeaxanthin



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

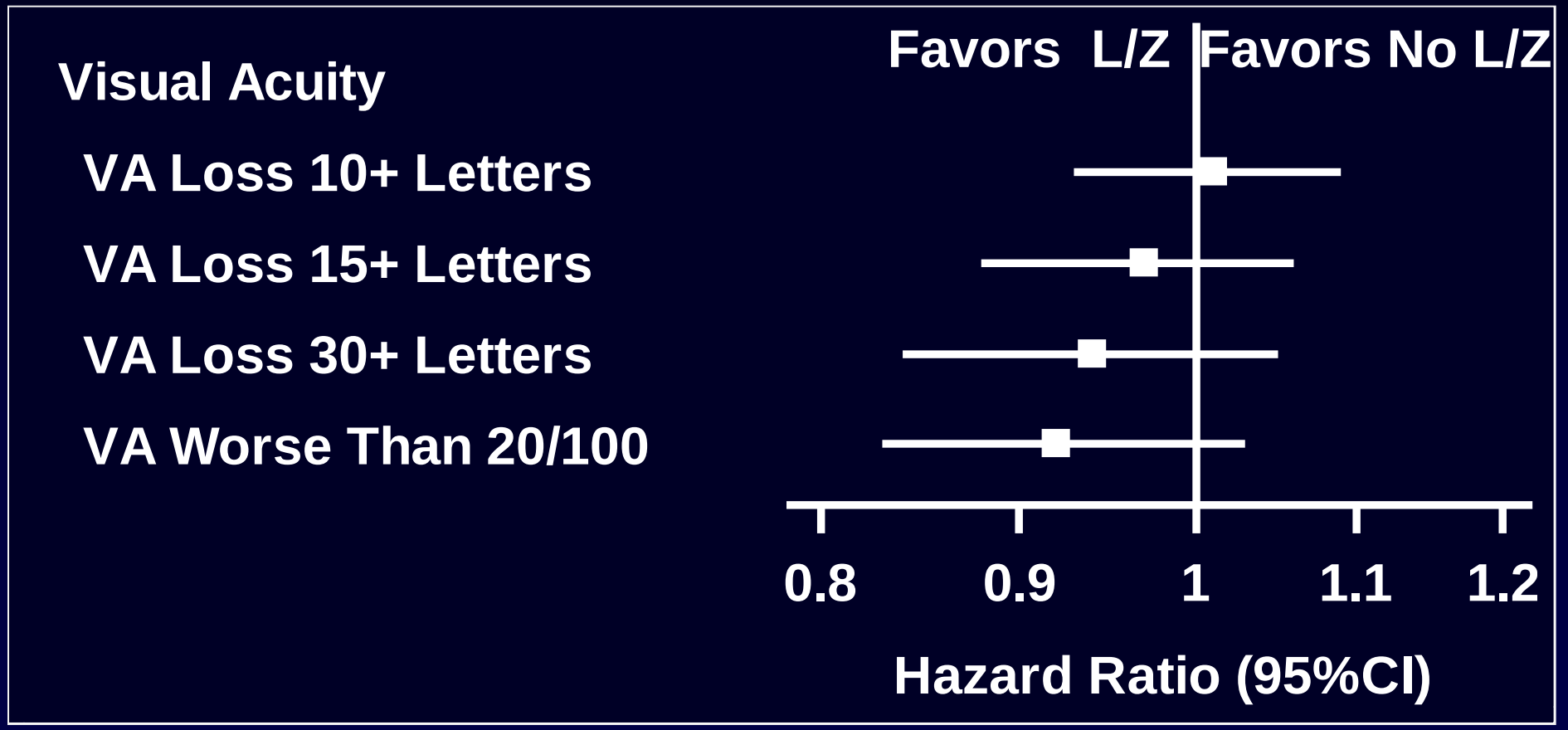
Neovascular AMD: HR: 0.78 P=0.01

22% reduction in the risk of progression to neovascular AMD with lutein/zeaxanthin

Not statistically significant for CGA

Visual Acuity Outcomes

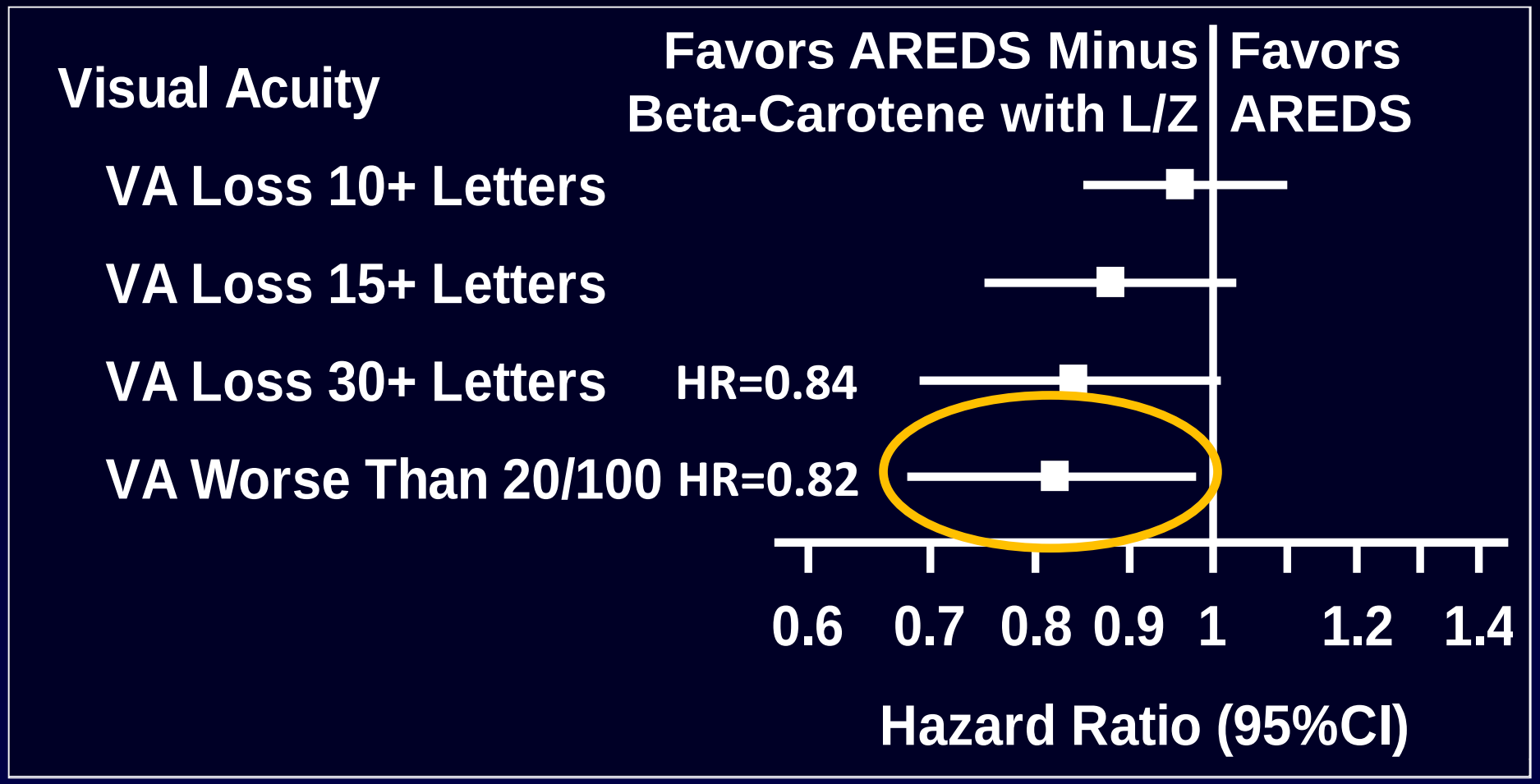
Exploratory Analyses of Lutein/Zeaxanthin



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

Visual Acuity Outcomes

Lutein/Zeaxanthin vs. Beta-Carotene



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

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

ONLINE FIRST | CLINICAL TRIAL

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**

Importance: 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.

Objective: 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 4203 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 3159 AREDS2 participants were phakic in at least 1 eye and 1389 of 6027 study eyes underwent cataract surgery during the study, with median follow-up of 4.7 years. The 5-year probability of progression to cataract surgery in the no lutein/zeaxanthin group was 24%. For lutein/zeaxanthin vs no lutein/zeaxanthin, the hazard ratios for progression to cataract surgery was 0.96 (95% CI, 0.84-1.10; $P=.54$). 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 0.68 (95% CI, 0.48-0.96; $P=.03$). 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.

Trial Registration: clinicaltrials.gov Identifier: NCT00345176.

JAMA Ophthalmol.
Published online May 5, 2013.
doi:10.1001/jamaophthalmol.2013.4412

AGE-RELATED CATARACT, the leading cause of blindness worldwide, is a leading cause of visual impairment in the United States.[1-3] The prevalence of age-related cataract is increasing, with an estimated 30.1 million Americans likely to be affected by 2020, escalating the already large public health and economic burden of the disease.[4] Numerous observational studies have reported inverse relationships between various dietary micronutrients and the development of age-related cataract or the occurrence of cataract surgery.[5-10] Of greatest interest have been micronutrients with antioxidant capabilities because of the importance of oxidative damage in cataract formation. In the absence of any consensus about the importance of specific micronutrients, several controlled clinical trials have tested whether selected micronutrients with antioxidant characteristics or multivitamins affect cataract development.[11-17] Because of variable results, no clear treatment recommendation has resulted from the trials conducted to date. This includes the Age-Related Eye Disease Study (AREDS), which tested a formulation containing vitamin C, 500 mg; vitamin E, 400 IU; and beta carotene, 15 mg;

*The AREDS2 Research Group is found online in the eAppendix at http://www.jamaophth.com. The members of the writing team and their affiliations are found at the end of this article.

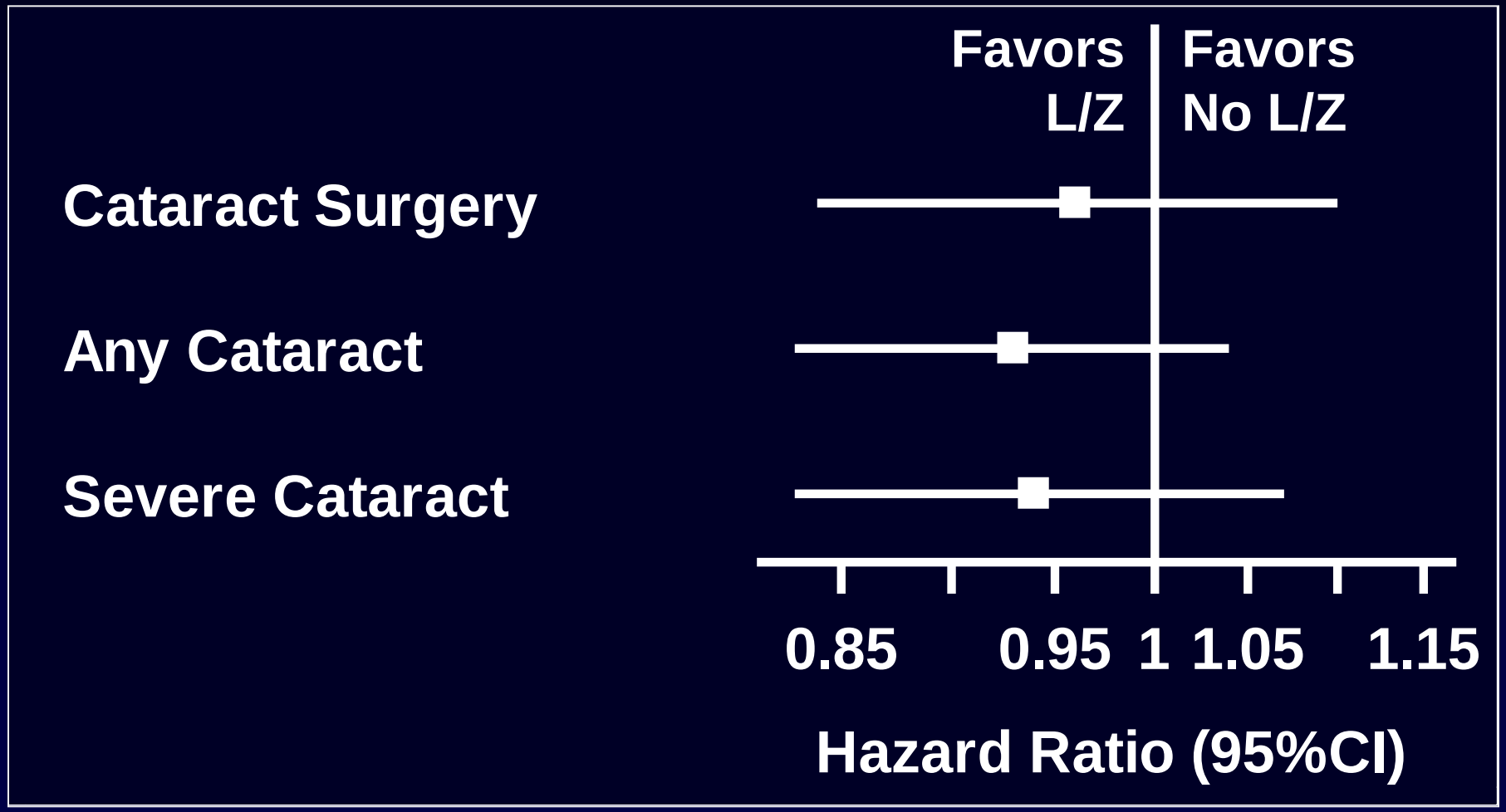
The Age-Related Eye Disease Study 2 Research Group

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

Published online May 5, 2013

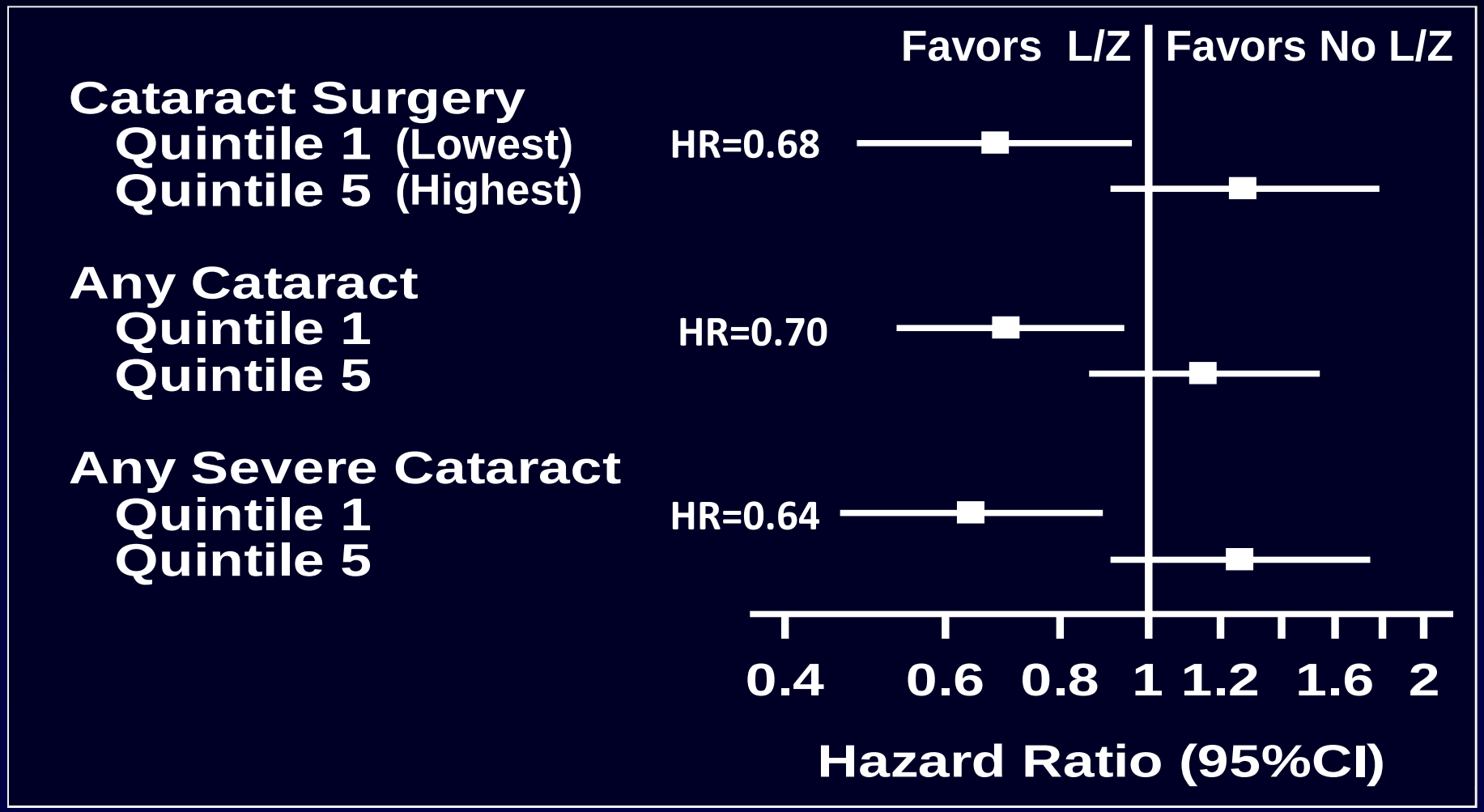
The JAMA Network

Cataract Surgery/Lens Opacity Progression

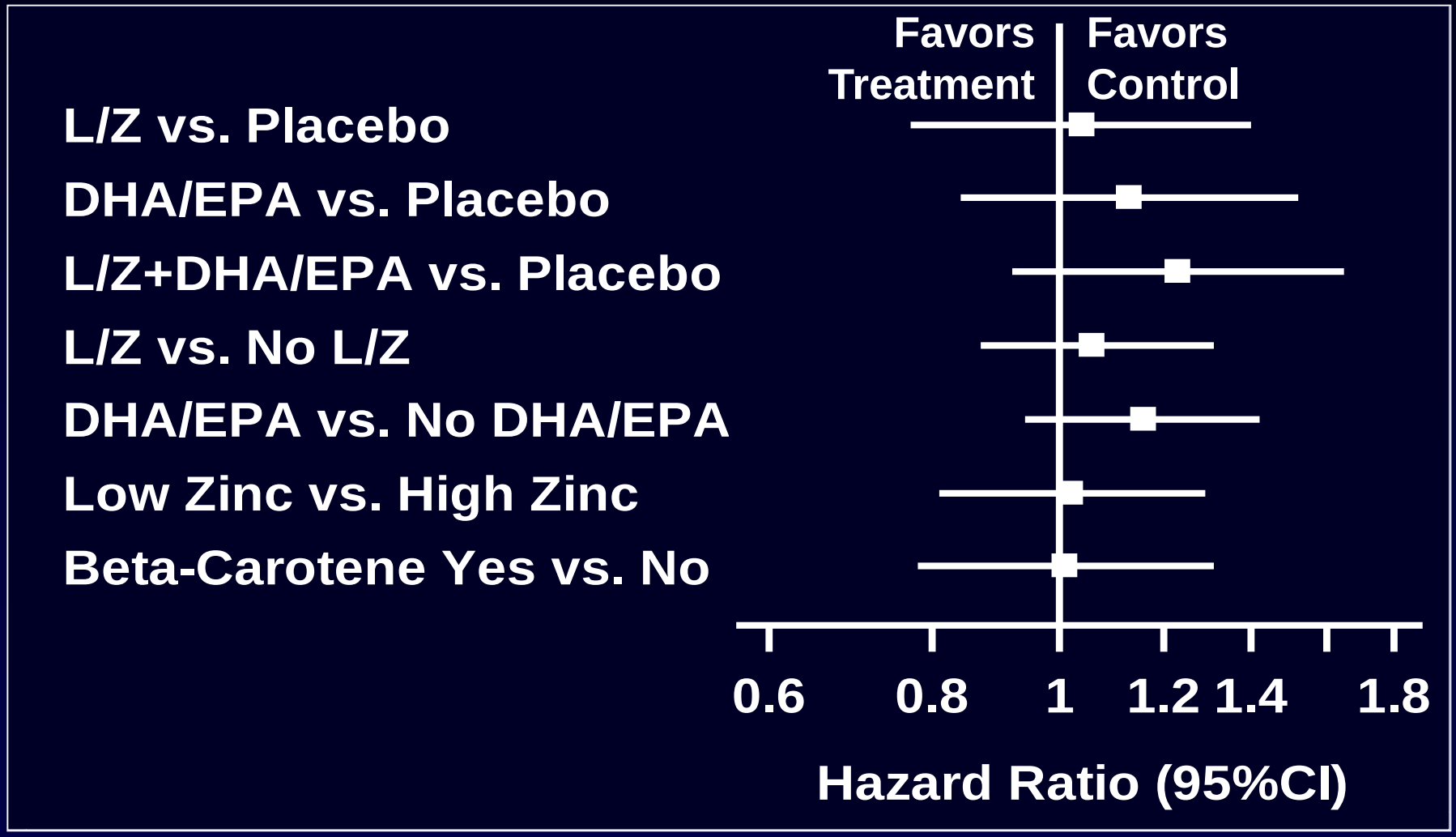


Cataract Surgery/Lens Opacity

Progression by Dietary Intake of Lutein/Zeaxanthin



Safety Outcome: Mortality



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

Beta-carotene Main Effect

β-Carotene (N = 1348)	No β-Carotene (N = 1341)	P-value
23 Cases (2.0%)	11 Cases (0.9%)	0.04

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

Analysis excludes smokers

Safety Outcome: Lung Cancer

Lutein/Zeaxanthin Main Effect		
Lutein/Zeaxanthin (N = 2123)	No Lutein/Zeaxanthin (N = 2080)	P-value
33 Cases (1.5%)	31 Cases (1.5%)	0.80
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

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Age-Related Eye Disease Study 2

The Lutein/Zeaxanthin and Omega-3 Supplementation Trial

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Age-Related Eye Disease Study 2

The Lutein/Zeaxanthin and Omega-3 Supplementation Trial

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The Lutein/Zeaxanthin and Omega-3 Supplementation Trial

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The Lutein/Zeaxanthin and Omega-3 Supplementation Trial

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Recognition

We want to thank :

- NEI Leadership for the support of AREDS2