



Safety and Efficacy of Lutein and Zeaxanthin in the AREDS2 Formulation for Age-Related Macular Degeneration

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ABSTRACT

Age-related macular degeneration (AMD) is a progressive degenerative disease of the central retina and is a leading cause of vision loss among older adults worldwide. The original Age-Related Eye Disease Study (AREDS) supplement formula reduced the risk of progression to advanced AMD. However, the beta-carotene in this formula was associated with a higher risk of lung cancer in current and former smokers. AREDS2 evaluated lutein and zeaxanthin as safer substitutes for beta-carotene. These macular carotenoids have antioxidant effects and a better safety profile. Studies show that lutein and zeaxanthin help slow AMD progression through antioxidant effects and retinoprotective mechanisms. Researchers have also studied genetic factors, including complement factor H (CFH) and age-related maculopathy susceptibility 2 (ARMS2). However, current evidence is not strong enough to support individualized treatment based on these factors. Overall, lutein and zeaxanthin appear to provide a favorable balance of efficacy and safety as replacements for beta-carotene in the AREDS2 formulation.

Keywords: Age-related macular degeneration, AMD, AREDS2, lutein, zeaxanthin.



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INTRODUCTION

Age-related macular degeneration (AMD) is a degenerative disease affecting the macula. The disease involves the accumulation of focal yellow extracellular deposits called drusen. Drusen have two main types. Hard drusen are small and have clear borders. Soft drusen have less clear borders, and they often merge into larger lesions. Soft drusen also carry a higher risk of disease progression.¹ Drusen in the macula often indicate early dry AMD, which is usually asymptomatic. AMD has four stages: early AMD, intermediate AMD, advanced non-neovascular AMD (dry AMD), and advanced neovascular AMD (wet AMD) (**Table 1**). Neovascularization is the main difference between dry and wet AMD. Dry AMD does not contain abnormal new blood vessels, while wet AMD contains new blood vessels under the retina.²

AMD is a multifactorial disease with a complex pathogenesis. The disease affects the macula, the central part of the retina, and

fovea which plays an important role in central vision, lies at the center of the macula.³ In AMD, damage mainly affects the outer retinal layers, including the retinal pigment epithelium (RPE), Bruch's membrane, choriocapillaris, and choroid.

The retina has high metabolic activity and is vulnerable to environmental damage. High-intensity light, including ultraviolet A and blue light, can produce large amounts of reactive oxygen species (ROS).^{2,4} As people age, higher ROS levels can cause oxidative stress, mitochondrial dysfunction, impaired proteostasis, and drusen accumulation. Drusen are abnormal deposits of lipids and proteins, and act as an early sign of AMD.⁵ Cytotoxic lipofuscin can also cause inflammation and stimulate new blood vessel growth in neovascular AMD. An imbalance between matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) can disturb the extracellular matrix (ECM) in Bruch's membrane. This disturbance

can support drusen formation and progression. Genetic factors, such as high-temperature requirement factor A1 (HTRA1) and age-related maculopathy susceptibility 2 (ARMS2), may also affect AMD development by altering ECM function.^{6,7}

Several studies show that AMD is an important health problem among older adults. These studies also describe risk factors for the disease. The 2015 Rapid Assessment of Avoidable Blindness (RAAB) survey in Jakarta found neovascular AMD in 3.45% of 87 participants.⁸ The survey also identified smoking as an important risk factor for AMD in adults aged 50 years or older in Jakarta. A study in East Jakarta from 2008 to 2009 reported a prevalence of 4.1% for non-neovascular AMD and 0.2% for neovascular AMD.⁹ Demographic data also show that AMD prevalence increases with age. The prevalence increased from 3.4% among adults aged 40–49 years to 4.8% among adults aged 50–59 years. It reached

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Table 1. Classification of age-related macular degeneration based on the Age-Related Eye Disease Study.¹

Early AMD	Intermediate AMD	Advanced Non-Neovascular AMD	Advanced Neovascular AMD
- Small drusen or a few medium-sized drusen in one or both eyes. - Pigmentary changes.	Many medium-sized drusen, one large druse, and/or geographic atrophy that does not involve the central macula (fovea).	Geographic atrophy that involves the central macula or fovea.	Choroidal neovascularization in one eye.

7.4% among adults older than 70 years.¹⁰ Researchers estimate that almost 300 million people worldwide will have AMD by 2040.¹¹

AMD has a major emotional and functional effect on patients. A survey from nine countries used a cross-sectional questionnaire among patients with wet AMD. The survey found that 44.9% of patients feared permanent vision loss. It also found that sadness is felt in 39.9%, frustration in 37.3%, and depression in 34.0% of patients.¹² The survey showed that 61.1% of patients had difficulty reading. It also showed that 38.5% could not drive and 27.8% felt limited in social activities. Central blurred vision affected 69.7% of patients, and difficulty seeing fine detail affected 64.1%. These symptoms became worse over time.¹²

In 1986, the National Eye Institute (NEI) initiated efforts that ultimately led to the Age-Related Eye Disease Study (AREDS) in response to the high prevalence of AMD and the lack of effective preventive treatments. The study evaluated the safety and efficacy of nutrients for slowing the progression of AMD and age-related cataracts. Researchers had limited evidence on using vitamins and minerals at pharmacological doses.¹² The AREDS results led to the development of AREDS2. AREDS2 replaced beta-carotene with lutein and zeaxanthin to avoid the risk of lung cancer in smokers.^{12,13} AREDS2 was important because it identified a specific nutritional intervention that could slow AMD progression.¹⁴

This literature review evaluates the safety and efficacy of lutein and zeaxanthin as substitutes for beta-carotene in the AREDS2 formulation for age-related macular degeneration. This supplementation strategy aims to slow the progression from intermediate to advanced AMD. It is especially relevant for smokers, who should not take beta-carotene. This

review compares the AREDS and AREDS2 formulas. It also examines the efficacy of lutein and zeaxanthin, the safety and toxicity of supplement components, and how genetic factors interact with the response to supplementation.

Lutein and Zeaxanthin in the AREDS2 Formula Lutein and zeaxanthin are carotenoids that help protect the retina from light damage and oxidation.¹⁵ This combination may protect patients with established AMD, especially those with a high genetic risk of AMD.¹⁶ Large amounts of lutein and zeaxanthin accumulate in the fovea. These carotenoids reduce light damage by filtering blue light. The formula also contains vitamin C and vitamin E. Vitamin C is a water-soluble antioxidant that reduces oxidative stress in ocular tissues, especially the photoreceptors and RPE. Vitamin E is a fat-soluble antioxidant that protects lipid membranes in retinal cells.¹⁷

Lutein is a 40-carbon xanthophyll carotenoid. Two 20-carbon geranylgeranyl pyrophosphate (GGPP) precursors form this structure. The human macula contains a high concentration of lutein. Lutein plays an important role in reducing the risk of progression from intermediate to advanced AMD.¹⁸ Lutein is a strong antioxidant that removes reactive oxygen species (ROS), which can damage cells. Lutein also filters blue light and protects photoreceptors from photo-oxidative damage. In addition, lutein has anti-inflammatory and anti-angiogenic effects. It can reduce cytokine-induced oxidation, regulate inflammation-related genes, and reduce vascular endothelial growth factor (VEGF) expression. VEGF contributes to abnormal angiogenesis in wet AMD.^{18,19}

In the AREDS2 supplement, lutein is combined with zeaxanthin. Zeaxanthin is an antioxidant that accumulates in the macula and forms

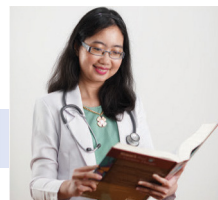
part of the macular pigment.¹⁹ It protects the eye from free radicals and absorbs harmful blue light that can damage cells.²⁰ Some studies also link zeaxanthin to better visual memory and learning in adults aged 40–75 years. Zeaxanthin may support white matter health, reduce oxidative damage, prevent retinal injury, and inhibit the formation of harmful compounds.^{19,20}

Macular pigment optical density (MPOD) describes the blue-light-filtering capacity of lutein and zeaxanthin in the central retina. MPOD is considered clinically important because it may influence an individual's risk of developing AMD. The amount of lutein and zeaxanthin in the macula is directly related to MPOD.²¹ Higher amounts of these carotenoids in the retina lead to higher MPOD values. However, researchers do not fully understand how lutein and zeaxanthin prevent AMD. MPOD usually decreases with age. Supplements that contain lutein, zeaxanthin, and meso-zeaxanthin can increase MPOD in patients with AMD and in healthy people. Higher doses may produce a larger increase. Higher MPOD is also associated with higher blood levels of lutein and zeaxanthin.^{20,21}

MAIN REVIEW

Efficacy of Lutein and Zeaxanthin in the AREDS2 Formula

Many studies have validated the efficacy of the AREDS2 formula in slowing AMD progression. The original AREDS study showed that supplementation with vitamin C, vitamin E, beta-carotene, and zinc reduced the risk of progression to advanced AMD by 25% over five years.^{22,23} This finding supported the protective role of nutrients in eye health. However, a 10-year follow-up showed that beta-carotene almost doubled the risk of lung cancer in smokers.²⁴ The AREDS2 study therefore replaced beta-carotene with 10 mg lutein and 2 mg zeaxanthin. AREDS2 showed



a 10% reduction in the risk of progression to advanced AMD compared with the control group.²⁵ The original AREDS study also found that 80 mg zinc combined with antioxidants significantly reduced the risk of progression from intermediate to advanced AMD. Antioxidant effects may reduce oxidative stress and inflammation.¹² AREDS2 also tested a lower zinc dose of 25 mg instead of 80 mg. Because the two zinc doses showed no significant difference, the standard AREDS2 formulation still contains 80 mg zinc.¹⁴ Lutein and zeaxanthin did not increase the risk of lung cancer in current or former smokers.²³ They were also associated with a lower risk of advanced AMD. A 2-by-2 factorial analysis of AREDS2 evaluated several nutrients over 10 years. Lutein and zeaxanthin significantly reduced the risk of advanced AMD compared with the control intervention (HR = 0.91; 95% CI: 0.84–0.99; $p = 0.02$).²⁰ **Figure 1** shows these results. A direct comparison with beta-carotene showed a 15% lower risk (HR = 0.85; 95% CI: 0.73–0.98; $p = 0.02$).²⁴ DHA/EPA, low-dose zinc, and beta-carotene did not provide significant protection against advanced AMD.²³

The Nurses' Health Study (NHS) included 63,443 women,²⁵ and the Health Professionals Follow-up Study (HPFS) included 38,603 men.²⁶ Analyses from these studies showed that adding lutein and zeaxanthin to the AREDS formula did not provide overall protection against AMD. In most participants, the addition did not significantly reduce the risk of AMD progression.^{25,26} However, participants in the lowest quintile of dietary lutein and zeaxanthin intake exhibited a 26% higher risk of progression from intermediate to advanced AMD.²⁴ Overall, AREDS and AREDS2 supplements can slow AMD progression, but they cannot prevent it.¹⁸

Researchers have also tested vitamin C, vitamin E, and zinc as part of supplement formulas aimed at slowing AMD progression. Some studies did not find a significant benefit from these nutrients compared with the original formula. Geographic differences may explain these results.^{12,27} For example, many participants in the US AREDS study already had high vitamin C levels because they used multivitamins. Therefore, extra vitamin C produced a smaller response in the US group than in European populations, which had lower vitamin C levels at baseline.^{12,28}

Before AREDS2, researchers found that the combined use of vitamin E and beta-carotene was associated with an approximately 18% increase in adverse pulmonary outcomes among smokers. This finding showed that antioxidants do not always provide benefits.¹² Vitamin E still has several important roles in AMD prevention and management. First, vitamin E deficiency can damage the outer parts of photoreceptors, increase lipofuscin accumulation, and impair RPE metabolic function.²⁹ Second, vitamin E can have anti-angiogenic effects. The retina is highly

vulnerable to oxidative stress because it has high metabolic activity and blood flow. Tocotrienol, a form of vitamin E, can reduce endothelial cell growth and inhibit the formation of new capillary networks. This angiogenesis is a key feature of wet AMD.³⁰ Third, vitamin E can act as an immunomodulator. AMD involves immune processes, such as inflammasome activation, cytokine release, and complement pathway activation.³¹ Vitamin E may inhibit complement activation. For example, it may reduce iC3b levels in RPE cells that accumulate A2E, which is a major component of lipofuscin.^{28,32}

Table 2 shows the differences between the AREDS and AREDS2 formulas. The AREDS2 formula does not contain beta-carotene because beta-carotene is associated with a higher risk of lung cancer in smokers.²³ The formula contains copper as cupric oxide to prevent copper deficiency during zinc supplementation.^{11,19}

Safety of Lutein and Zeaxanthin in the AREDS2 Formula

Lutein and zeaxanthin do not increase the risk of lung cancer. Therefore, they are safer

Table 2. Composition of the AREDS and AREDS2 supplement formulas.²⁰

Nutrient	AREDS	AREDS2
Vitamin C	500 mg	500 mg
Vitamin E	400 IU	400 IU
Beta-carotene	15 mg	-
Copper (cupric oxide)	2 mg	2 mg
Lutein	-	10 mg
Zeaxanthin	-	2 mg
Zinc	80 mg	80 mg

Treatment	No. of eyes (No. of events)		Hazard ratio (95% CI)
	Treatment	Control	
Lutein/zeaxanthin	3180 (1475)	3171 (1565)	0.91 (0.84-0.99)
DHA/EPA	3203 (1523)	3148 (1517)	1.01 (0.93-1.09)
Low zinc	2263 (1123)	2288 (1090)	1.04 (0.94-1.14)
Beta carotene	2034 (989)	2036 (997)	1.04 (0.94-1.15)

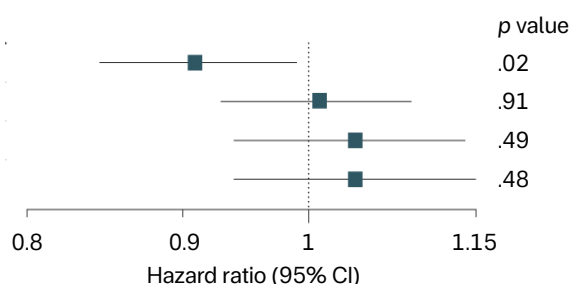


Figure 1. Hazard ratios for progression to advanced AMD in the AREDS2 intervention groups.²⁰



than beta-carotene for current and former smokers.^{18,25} A long-term prospective cohort study linked a higher intake of lutein and zeaxanthin to a reduction of up to 40% in the risk of advanced AMD.²³ Edwards' toxicology study showed a very good safety profile, and zeaxanthin had very low toxicity.¹³ An acute toxicity study gave Wistar rats up to 1,000 mg/kg body weight of zeaxanthin. This dose did not cause death or clinical signs of toxicity.¹⁶ High doses did not cause maternal toxicity, fetal toxicity, or congenital abnormalities.^{20,33} The only visible change in the animals was yellow coloration of fat tissue. This finding showed that the body absorbed and distributed zeaxanthin like other carotenoids. Overall, the study found no toxicity in any organ after high-dose exposure.¹⁶

Vitamin E has antioxidant benefits, but high doses can also cause harm. A dose of 400 IU/day or more may cause heart failure, bleeding through inhibition of vitamin K, drug interactions with warfarin or statins, thyroid hormone disorders, and higher triglyceride levels. Excessive intake may also impair liver and kidney function.³² The body needs zinc, but excessive zinc intake can cause toxic effects. These effects include lower renal blood flow and lower inulin clearance, which indicates reduced renal filtration.³⁴ Excessive zinc intake can also impair the activity of the copper/zinc superoxide dismutase enzyme because it causes copper deficiency. This process can increase free radicals and oxidative stress. Oxidative stress can damage DNA and raise renal 8-OHdG levels. Clinicians should use caution in older adults who have risk factors for kidney disease.^{34,35}

Three independent academic centers reviewed the available data and assessed whether other teams could reproduce the findings. All three groups concluded that the evidence did not support genotype-based treatment for AMD.³⁵ AMD pathogenesis has clear links with specific genetic factors. These factors include the rs1061170 risk allele in complement factor H (CFH) and the rs10490924 risk allele in age-related maculopathy susceptibility 2 (ARMS2). Researchers therefore studied these genes as candidates for supplement interactions.^{35,36} Some studies have reported possible interactions between nutrients and genotypes.

Lutein, zeaxanthin, omega-3 fatty acids, and zinc may interact with CFH polymorphisms. The ARMS2 risk allele may also change the effects of omega-3 fatty acids and zinc on early AMD.^{35,37} However, a post hoc analysis of the AREDS2 randomized controlled trial included 1,684 White participants with complete genetic data. The analysis found no significant interaction between CFH or ARMS2 variants and AREDS2 supplement efficacy. This finding supports clinical guidelines recommending the AREDS2 formula for patients with intermediate AMD or advanced AMD in one eye, regardless of genetic risk profile. The protective effect of AREDS2 therefore appears to be independent of genetic susceptibility. **Figure 2** summarizes the benefits of the AREDS2 formula.

CONCLUSION

Evidence shows that the AREDS2 formula, which replaces beta-carotene with lutein and zeaxanthin, significantly slows progression from intermediate to advanced age-related macular degeneration (AMD). Lutein (10

mg) and zeaxanthin (2 mg) protect the retina through antioxidant and anti-inflammatory effects, blue-light filtration, and reduced VEGF expression. Reduced VEGF expression can limit pathological. The AREDS2 formulation is an evidence-based nutritional intervention to reduce the risk of progression to advanced AMD in appropriately selected patients with intermediate AMD or advanced AMD in one eye. Current evidence does not support tailoring AREDS2 supplementation based on individual genetic profiles. In Indonesia, the AREDS2 formulation is now included as a standard clinical approach to AMD management, in accordance with the 2023 national guideline issued by the Indonesian Vitreo Retinal Society (INAVRS). Patients taking zinc long-term need regular kidney function monitoring. Clinicians should limit vitamin E doses to prevent adverse effects. Education about early detection and a healthy lifestyle remains important for prevention. Further studies should evaluate long-term efficacy and possible interactions between genetic factors and nutrients.

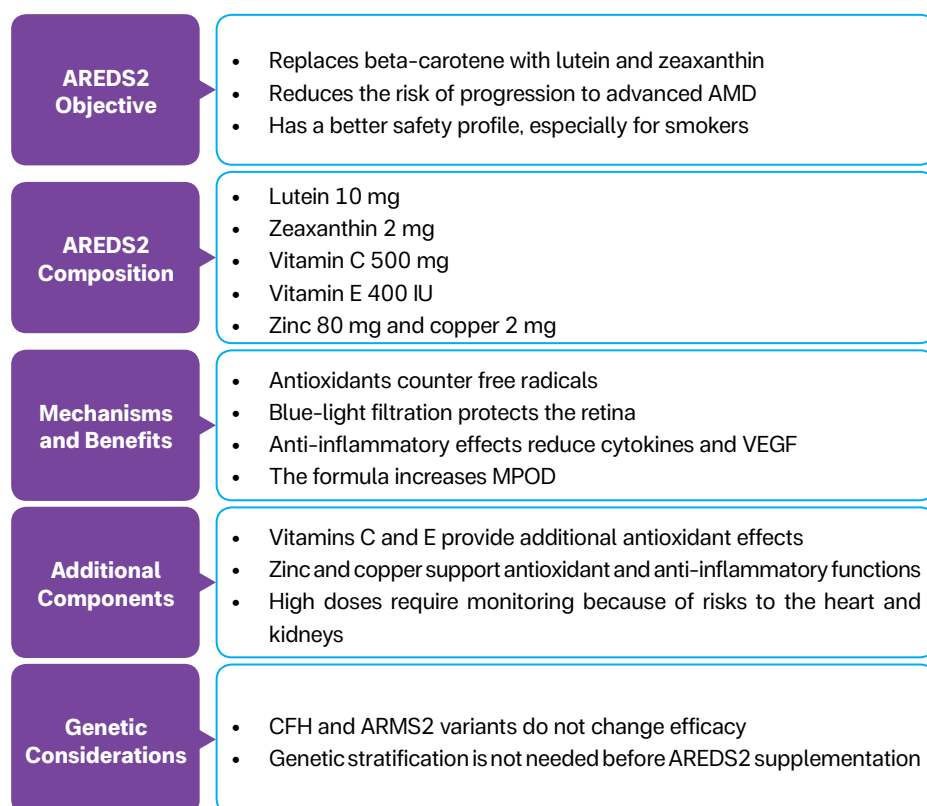


Figure 2. Summary of the AREDS2 formula.

Source: Danuartha, 2025.

Abbreviations: AMD: Age-related macular degeneration; VEGF: Vascular endothelial growth factor; MPOD: Macular pigment optical density; CFH: Complement factor H; ARMS2: Age-related maculopathy susceptibility 2; AREDS2: Age-Related Eye Disease Study 2.



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Author Contributions

H.D.K. initiated and conceptualized the study. Y.R.H.W., H.A.T., and M.A.D. drafted the initial manuscript. A.G.S. conducted the literature search and review, and revised the manuscript. H.D.K. performed the English translation.

All authors reviewed and approved the final manuscript.

Conflict of Interest

The authors declare that they have no financial or non-financial conflicts of interest.

Declaration on the Use of Artificial Intelligence (AI)

The authors declare that no artificial

intelligence tools were used in the conduct of this study or the preparation of this manuscript.

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