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Association of Mortality with Ocular Diseases and Visual Impairment in the Age-Related Eye Disease Study 2 (AREDS2):

AREDS2 Report Number 13

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Abstract

Objectives—To evaluate the association of mortality with visual acuity (VA) impairment, age-related macular degeneration (AMD), and cataract surgery.

Design—Cohort study

Subjects—Participants with at least intermediate AMD enrolled in a randomized controlled clinical trial of lutein/zeaxanthin and/or omega-3 fatty acids, the Age-Related Eye Disease Study 2 (AREDS2) for treatment of AMD and cataract.

Methods—Baseline and annual eye examinations included best-corrected visual acuity (BCVA) assessments, slit lamp examinations, and stereoscopic fundus photographs that were centrally graded for development of late AMD (central geographic atrophy or neovascular AMD) or pseudophakia. Cause-specific mortality was determined based on ICD-9 or ICD-10 codes. Risk of all-cause and cause-specific mortality was assessed with Cox proportional hazards models adjusted for age, sex, AMD severity, VA, history of cataract surgery, and assigned AREDS2 study treatment. Analyses included baseline covariates: race, education, smoking status, diabetes, and cardiovascular disease.

Results—During follow-up (median 5 years), 368 (9%) of the 4203 AREDS2 participants died. Participants with neovascular AMD in 1 eye at baseline had a statistically significant increased risk for mortality compared to participants with no or few drusen (hazard ratio [HR] 1.56, 95% confidence interval [CI], 1.21–2.01; p-value [p]<0.001). Poorer survival was associated with bilateral cataract surgery prior to enrollment compared with baseline bilateral phakia (HR, 1.63; 95% CI, 1.29–2.07; p<0.001); and with BCVA of less than 20/40 compared with participants with 20/40 or better (HR, 1.56; 95% CI, 1.06–2.30; p=0.024), adjusted for age, sex and statistically

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significant covariates. Participants who received anti-vascular endothelial growth factor therapies for neovascular AMD had decreased mortality compared with those who did not (HR: 0.71, 95% CI 0.57–0.88; p=0.002). The association between all-cause mortality and AREDS2 treatment whether assessing the main or individual treatment effect was not significantly different [omega-3 fatty acids main effect HR 1.18, 95% CI 0.96–1.45, p=0.12; lutein/zeaxanthin main effect HR 1.04, 95% CI 0.85–1.28, p=0.71].

Conclusions—In AREDS2, the presence of late AMD, bilateral cataract surgery and visual acuity less than 20/40 were associated with decreased survival. However, oral supplementation with omega-3 fatty acids, lutein plus zeaxanthin, zinc, or beta-carotene had no statistically significant impact on mortality.

Introduction

Age-related eyes diseases including age-related macular degeneration (AMD) and cataract are the leading causes of visual impairment in the older population in the United States.[1] Visual impairment has been reported to be associated with mortality in several studies[2–7, 11,12,19,23,29]. Although the relationship between AMD or cataract with survival has been less clear, AMD was associated with decreased survival in some studies[7–8,11–12], but others reported no statistical significance after adjustment for appropriate confounders[3,13,18–19,28]. The pathogenesis of AMD is unknown; however, it is commonly noted that AMD shares several risk factors for cardiovascular and other systemic comorbidities that could attribute to shorter survival[12,14–17]. However, few studies have evaluated the impact of late AMD (non-foveal or center-involved geographic atrophy or neovascularization) on mortality in a large cohort. Cataract has been linked to decreased survival, particularly for the nuclear opacity type vs cortical or subcapsular, in some[2–3, 8–10, 19–21] but not all studies[13, 18,28]. The association of mortality and a clinical history of cataract surgery has not been well established[26–27,29–32]. While reasons for shorter survival in persons with cataracts or cataract surgery are not known, the presence of cataract may be possible markers for biological aging. The role of oxidative stress and inflammatory processes may also be suggested by previous studies of decreased survival with cataract[3,8,26–27].

The Age-Related Eye Disease Study 2 (AREDS2) is a randomized, clinical trial of nutritional supplements in persons with at least intermediate AMD. The mean age of the population was 74 years of age and they were followed for a median follow-up of 5 years.[24] The AREDS2 study offers an opportunity to study the relationship of ocular diseases and mortality. This current study is undertaken to assess the impact of visual impairment, AMD, and history of cataract surgery on survival.

Methods

Study Population

The AREDS2 study, a randomized, double-masked, controlled trial of oral supplements sponsored by the National Eye Institute, enrolled between 2006 and 2008, 4,203 men and women aged 50 to 80 with bilateral intermediate AMD or late AMD in one eye. The study

concluded in October 2012 with a median follow-up of 5 years. This 2x2 factorial trial evaluated the addition of high dose antioxidants lutein (10mg) and zeaxanthin (2 mg) and/or omega-3 long-chain polyunsaturated fatty acids: docosahexaenoic acid (DHA [350mg]) and eicosapentaenoic acid (EPA [650mg]) to the original AREDS formulation in reducing the primary outcome of AMD and cataract progression. The original AREDS formulation consisted of vitamin C (500mg), E (400 IU), beta-carotene (15mg), zinc (80mg as zinc oxide), and copper (2mg as cupric oxide). The AREDS2 participants underwent primary randomization to four arms: controls (n=1012), lutein/zeaxanthin (n=1044), DHA plus EPA (n=1069), and a combination of lutein/zeaxanthin and DHA plus EPA (n=1078). Approximately three-quarters of the population agreed to a secondary randomization that tested the original AREDS supplements with and without beta-carotene (15mg) and high (80mg) or low-dose (25mg) zinc formulations.[34]

Participants eligible for the study included those who were willing and able to undergo yearly examination for at least five years and demonstrated adherence to the run-in regimen (consumption of 75% of run-in medication determined by pill weight or pill count). Participants had to be free of any health conditions that would make follow-up or compliance with study interventions difficult. Participants with any systemic disease with a poor 5-year survival prognosis or had previous retinal or ocular surgeries (other than cataract extraction) that may confound evaluation were excluded. This study protocol was reviewed and approved by each of the institutional review boards, and written informed consent was obtained from all participants. The research was conducted according to the tenets of the Declaration of Helsinki and complied with the Health Portability and Accountability Act.

Baseline and annual study visits included best-corrected visual acuity (BCVA) assessment, slit lamp examination, dilated fundus examinations and ocular imaging (red reflex lens photos, stereoscopic color fundus photographs, and fundus autofluorescence). At baseline visits, participant demographics including education level, smoking status, comorbidity such as diabetes or cardiovascular health, and medication use were collected. At telephone interviews at the 6-month interval between annual study visits, we gathered data on the occurrence of cataract surgery, AMD treatment, and other medical conditions as well as adverse effects. The ocular images were evaluated at baseline and annually by certified and trained masked readers at a central reading center at the University of Wisconsin.

Participants enrolled in the study were at high risk for progression to late AMD ranging from bilateral large drusen to large drusen in one eye and late AMD in the fellow eye. This translates to the AREDS AMD Simple Scale of 2, 3, and 4.[35] The simple scale was a person-scale that included both eyes and the scale was based upon the presence of large drusen or retinal pigment epithelial hypo/hyperpigmentary changes or the presence of late AMD.[35, 25] The reading center also evaluated the progression to late AMD (either central geographic atrophy or neovascular AMD) based upon stereoscopic fundus photographs obtained at annual visits. The presence of pseudophakia was also noted on the red reflex lens photos as well as at the slit lamp examination at the study visit.

Primary Outcome Measure

The primary outcome measure for this study was all-cause mortality. The underlying cause of death (defined by the World Health Organization [WHO] as the injury or the disease that initiated events that led to death } was usually selected as the primary cause of death. In the case that the death certificate was not provided then the immediate cause of death was used. The immediate cause of death is defined by WHO as the disease or injury that led directly to the cause of death. In cases of discrepancy, a mortality review team consisting of diagnostic coders and physicians determined the cause of death.

Statistical Analysis

Risk of all-cause and cause-specific mortality was assessed using age and sex-adjusted Cox proportional hazards regression models with AMD severity (Simple Scale score 1 to 4) and type of late AMD, neovascular or geographic atrophy associated with AMD, visual acuity (VA), history of cataract surgery prior to enrollment, and assigned AREDS2 treatment as independent variables to estimate risk ratios. Baseline covariates included race (non-Hispanic white vs other), education (high school or less vs. more than high school), smoking status (never, former, or current), diabetes, medication-use (Centrum multivitamins and/or non-steroidal anti-inflammatory drugs (NSAID)/other anti-inflammatory agents), cancer, and cardiovascular health status (history of congestive heart disease, coronary heart disease, angina, myocardial infarction, stroke, and hypercholesterolemia). Analyses also included self-reported hypertension as a covariate. Significant covariates ($P<0.05$) were added to models predicting the effects of ocular characteristics on mortality. Age was stratified to 4 different age groups: <65 years, 65–74 years, 75–79 years and ≥80 years, since this covariate has been strongly associated with risk of developing AMD and mortality[7,11]. All analyses were conducted using SAS version 9.2 (SAS Institute Inc, Cary, NC).

Results

Between 2006 and 2008, AREDS2 enrolled 4,203 participants aged 50 to 80 years with bilateral intermediate AMD or late AMD in one eye. The median age at baseline was 74 years and 57% were women. From September 2006 to December 2012, 368 (9%) of the AREDS2 study population died. The effects of baseline characteristics on all-cause mortality are shown in Table 1. After adjustment for age and sex, mortality rates were higher for increasing age. The hazard ratios (HRs) for age-stratified analysis almost doubled for each decade of age (65–74 years, HR of 2.25; 75–79 years, HR of 4.64; 80+ years, HR of 7.79). Adjusted mortality rates were lower for females, “other” races (black, Asian and others), and participants with education level more than high school. Mortality rates were higher for current smokers, persons with diabetes, and participants with high blood pressure and history for CVD (congestive heart failure, myocardial infarction, coronary heart disease, and stroke).

All-Cause Mortality

All-cause mortality rates are shown in Table 2. Mortality rates increased with increasing AMD severity in age and sex adjusted Cox-regression models, adjusting for all the covariates. Persons with the most severe AMD simple scale of 4 had a hazard ratio (HR) of

1.72, 95% confidence interval (CI) 1.19–2.50, p-value (p)=0.004, when compared with simple scale of 1 and 2, which consist of milder disease with either large drusen in only one eye or large drusen in both eyes or retinal pigment epithelial changes. Those participants with AREDS Simple Scale level 3 were also at an increased risk of mortality with HR of 1.60, 95% CI: 1.07–2.40, p=0.022. When the severity of AMD was classified as intermediate, geographic atrophy at the center, or neovascular AMD, the risk of mortality was associated with neovascular AMD (HR: 1.56, 95% CI: 1.21–2.01; $p < 0.001$). Note in this comparison, the reference group consisted of those with intermediate AMD in both eyes.

Mortality rates were higher for those participants who had bilateral cataract surgery prior to enrollment into AREDS2 (HR of 1.63, 95% CI: 1.29–2.07; $p<0.001$) compared with no surgery. BCVA less than 20/40 in one or both eyes were associated with statistically significant increased risk of all-cause mortality. For unilaterally affected participants, the HR was 1.32 and 95% CI 1.05–1.66; p=0.017 while for bilaterally affected, the HR was 1.56; 95% CI, 1.06 – 2.30; p=0.024 when compared with participants with vision better than 20/40 in both eyes. The association between all-cause mortality and the AREDS2 treatment effect whether assessing the main effect of each nutrient or individual treatment arms was not significant after adjustments for age, sex, demographics, lifestyle and comorbid conditions. As previously published[38], the main treatment effects of combination DHA and EPA and the antioxidants lutein and zeaxanthin did not show significant benefit or harm on mortality (HR: 1.18, 95% CI: 0.96–1.45; p=0.12 and HR: 1.04, 95% CI: 0.85–1.28; p=0.71, respectively). No statistical association was found with primary randomization of individual treatment groups DHA/EPA and lutein/zeaxanthin (Table 2). AREDS2 treatment secondary randomization to high (80 mg) vs low zinc (25 mg) and beta-carotene vs no beta-carotene did not have a significant effect on mortality (Table 2). Kaplan-Meier curves for mortality by AREDS AMD simple scale score, cataract surgery, visual impairment, and AREDS2 nutritional treatments are demonstrated in Figure 1(A, B, C, and D).

Cause-Specific Mortality

Cause-specific mortality rates are shown in Table 3. Neovascular AMD was associated with a statistically significant increase in circulatory system and neoplastic causes of death, HR of 1.68 (95% CI 1.04–2.71; p=0.034) and HR of 1.87 (95% CI 1.08–3.24; p=0.027), respectively (Table 3). Geographic atrophy was associated with neoplastic causes of death, HR of 3.37 (95% CI 1.56– 7.29, p=0.002). For other causes of mortality which include infections, pneumonia, chronic pulmonary disease, trauma and others, more severe AMD as classified by the AREDS simple scale, specifically simple scale scores of 3 and 4 were associated with increased risk of mortality: HR: 1.89 (95% CI: 1.01–3.55; p=0.048) and HR: 2.29 (95% CI: 1.28–4.10; p=0.005), respectively (Table 3). Bilateral cataract surgery and bilateral visual impairment were also associated with increased risk of other-cause mortality: HR: 2.12 (95% CI: 1.51–2.97; $p<0.001$) and HR: 2.17 (95% CI: 1.35–3.50; p=0.001), respectively (Table 3).

Anti-VEGF Therapies and Mortality

Since 1,606 AREDS2 participants received anti-vascular endothelial growth factor (VEGF) therapy for neovascular AMD, we evaluated the impact of this therapy on all-cause mortality. There was reduced mortality risk for those receiving anti-VEGF therapies with the HR of 0.71 and 95% CI of 0.57–0.88, p=0.002 (Table 2).

Causes of Death

Specific causes of death and broad-based groupings are shown in Table 4. ICD-9 and ICD-10 codes were available for cause of death for 325 (88.3%) out of 368 participants who died. Some of the known causes of deaths were cardiovascular (88/269 or 23.9%) and neoplastic (90/269 (24.4%) in origin (Table 4). Cause of death was unknown for 43(11.7%) participants without sufficient mortality follow-up data while the remainder were due to a number of other causes (147/368 or 39.9%) (Table 4).

Discussion

As expected, the mortality rates were increased in those AREDS2 participants who were older, current smokers, had diabetes, less formal education and/or comorbid cardiovascular conditions. We also found an association of increased mortality in those with more severe AMD, either simple score 3 and 4 or those with late forms of AMD, neovascular AMD or geographic atrophy. Previous studies assessing the relationship between AMD and mortality have been inconclusive.[3,7–8,10–13,18–19,28] During a median follow-up of 6.5 years, the original AREDS study found decreased survival in those with late AMD compared to those with mild AMD in fully-adjusted models (HR 1.41, 95% CI 1.08–1.86).[8] The Reykjavik Study which examined mortality in association with AMD in community-dwelling elders found that participants 83 years and older had significantly increased all-cause mortality risk (HR 1.76, 95% CI 1.20–2.57) and CVD (HR 2.37, 95% CI 1.41–3.98) in the presence of late AMD. No association was seen in individuals with early AMD at any age and late AMD in those <83 years.[11] A study assessing AMD and mortality over a 15-year follow-up period in a population of older women in the United States also showed increased all-cause mortality (HR 1.42, 95% CI 1.13–1.78) and cardiovascular mortality (HR 1.45, 95% CI 1.01–2.09) for those 80 years and older with any AMD. In this same study, late AMD was associated with cardiovascular disease mortality in women younger than 80 years.[7] In contrast, five large population-based cohort studies, including the Rotterdam Study[13], Beijing Eye Study[19], Beaver Dam Eye Study[3], Blue Mountains Eye Study[10], and Singapore Malay Eye Study[18] showed no statistically significant association between late AMD and decreased survival. The mean age of participants in these studies were younger (range 60–70 years) and had fewer participants with late AMD than those in the AREDS2 cohort (mean age 74 years). In the Atherosclerosis in the Community Study, persons with late AMD were more likely in 10 years to die (23.5%) compared with those without late AMD (8.9%, p=0.088). Those with late AMD were also more likely to develop incident cardiovascular event (30.9%) vs. those without late AMD (10.0%, P=0.049).[39] After the 10 years of follow-up in participants aged less than 75 years at baseline, the Blue Mountains Eye Study reported both two-fold and five-fold increased risk of cardiovascular mortality in those persons with early AMD or late AMD, respectively.[40] Late AMD also predicted a ten-fold higher risk of stroke mortality.

In the analyses for the cause-specific mortality in AREDS2, it appeared that two specific causes, cardiovascular (or circulatory), neoplastic and other causes were associated with more severe AMD. The cause-specific mortality for neovascular AMD was associated with both circulatory system and neoplasms while central geographic atrophy was associated with neoplasms. When the AMD was classified by the AREDS simple scale, both levels 3 and 4 were found to be associated with other causes of death. Participants with late AMD are likely to be older with comorbidities impacting survival. We cannot fully adjust for the effects of age and other unknown confounders.

For both visual impairment (BCVA <20/40 in both eyes) and bilateral cataract surgery in AREDS2 participants, we found a doubling of the risk of mortality compared to those without visual impairment or bilateral cataract surgery. Similarly, in AREDS, visual impairment (BCVA <20/40 in at least one eye) and cataract surgery were also associated with decreased survival.[8] Late AMD was strongly associated with visual impairment, and the visual impairment findings in AREDS were not independent from AMD severity. Other studies that evaluated the impact of visual impairment on mortality independent of other comorbidities or risk factors reported conflicting results. The Blue Mountains Eye Study found no association of visual impairment with mortality.[10] The Beaver Dam Eye Study[3] reported a significant association with visual impairment and all-cause mortality after adjustment for systemic and lifestyle characteristics. The Melbourne Visual Impairment Project[5,22] noted more than a two-fold increase in mortality risk in fully-adjusted models for participants with BCVA <6/18, suggesting that visual impairment may be associated with increased falls and accidents contributing to increased mortality rates. However, it is uncertain to what extent AMD status plays a role in visual impairment, since AMD data were not collected on these participants.

The relationship between age-related cataract and poor survival has been observed in several epidemiology studies[2,3,8,10,19–21]. In previous analysis of the AREDS cohort, all-cause mortality was significantly increased for those participants with nuclear cataract or history of cataract surgery[8]. These participants also had increased deaths from neoplasms. History of bilateral cataract surgery at baseline was statistically significantly associated with all-cause mortality but not related to neoplastic causes in the AREDS2 cohort. Cataract surgery was associated with other causes of death. History of cataract surgery has not been consistently shown to be associated with poor survival in prior studies[26–27,31–32]. Several large population-based studies that reported no association between cataract surgery at baseline and mortality include the Rotterdam Study[13], Singapore Malay Eye Study[18], and the Blue Mountains Eye Study[3]. However, a retrospective cohort study investigating a random 5% sample of the United States Medicare population (2002–2012) with cataract (1.5 million participants) found that those who underwent cataract surgery and followed up for an average of close to 3 years had a lower adjusted hazard of mortality compared to those surgery-free (HR 0.73, 95% CI 0.72–0.74)[9]. This study and others[29,30] reported a protective association after cataract surgery after adjusting for ocular and systemic comorbidities. The conflicting findings from studies may arise from the inherent differences in the cataract surgery group vs the non-surgery group. In addition, the factors involved in selecting eligible participants for cataract surgery may further complicate data interpretation.

The mechanism of action surrounding the association between visual impairment caused by cataract and AMD and mortality is not clear. One hypothesis supported by some studies suggests that visual impairment may have a direct impact on survival, affecting functional status of participants and even psychological health[4,6,28]. Poor vision can result in limited mobility, falls, and accidents resulting in a variety of injuries[7,9]. In the AREDS2 cohort, very few deaths were attributed to automobile accidents, falls or trauma-related deaths (0.04%). Visual impairment could be associated with depression, which has been linked with poor quality of life and decreased life span[23,36]. Cause-specific analyses did not show excess mortality among AREDS2 participants with mental health disorders (0.03%). Ocular-related depression may have played a factor as participants included in the study were at high risk to progression to late AMD. However, our analyses of the test of depression, the Center for Epidemiologic Studies' Depression Scale (CES-D) (Table 1) which was administered at baseline, showed no association of depression with mortality (HR: 1.25, 95% CI: 0.98 – 1.58, p=0.072).

The mechanisms for the association AMD and cataract with increased risk of mortality remain to be elucidated. Analyses in the AREDS cohort suggested AMD shares risk factors for comorbid conditions, especially cardiovascular disease[12,14–17]. Non-cardiovascular/non-cancer cause-specific mortality was significant in AREDS2 follow-up with a majority of deaths categorized under respiratory diseases (16%) or unknown (12%). Mortality was more prevalent in elderly participants (75+ years) with severe AMD. This AMD-mortality relationship was further supported by other studies, including the Beaver Dam Eye Study that reported more severe AMD classification with increasing age[3]. Systemic processes accelerating the aging process and contributing to poor survival could partially explain these findings. Similarly, cataract may reflect systemic aging and possibly contribute to inflammatory pathways leading to shorter survival[8,26–27].

A somewhat surprising finding is the increased survival of those AREDS2 participants who had received anti-VEGF therapies compared with those who have not received anti-VEGF therapies. However, in about 40% of this group, we were not able to ascertain the number of injections administered as these were participants who had exposure to the anti-VEGF therapies at baseline. We collected the data on the number of anti-VEGF therapies given only during the course of the study. The HR for mortality for the group who had exposure to anti-VEGF at baseline but the number of injections was unknown, was not statistically significantly different from those who had not received anti-VEGF therapy. In the participants whose numbers of injections were known, there was a dose-response in that participants with greater injections of anti-VEGF therapies were associated with lower mortality. A limitation to these data was the small number of participants who received the larger number of injections. We also found an interaction of the number of treatments with the age of the participants. Older participants were less likely to receive anti-VEGF therapies. Interestingly, a study from the Veterans Health Administration[41] of men 55 years or older with a diagnosis of AMD evaluated mortality among those who received anti-vascular endothelial growth factor agents vs. those who did not. The twelve-month all-cause mortality were 3.5% in the treated vs. 4.5% in the untreated. The adjusted analyses showed the hazards ratio of 0.89 (95% CI: 0.74–1.06), with the point estimate also not in the direction of harm but this was not statistically significant. The all-cause mortality risk was

similar for both administration of bevacizumab and ranibizumab. In the Inhibition of VEGF in Age-related choroidal Neovascularisation (IVAN) trial where these two anti-VEGF therapies were compared, using different treatment regimens, there was reduced mortality in those participants who had continuous (monthly) administration of the anti-VEGF therapies compared with those who had greater intervals between their “discontinuous” therapies (OR: 0.47, 95% CI: 0.22–1.03, p=0.05). Again, there was no difference in mortality between the two anti-VEGF drugs (OR 0.96, 95% CI: 0.46–2.02, p=0.91). A possible explanation for the reduced mortality in those who received anti-VEGF therapies may reflect a selection bias of administering the therapy to healthier and more active participants in AREDS2. Contributing to this selection bias is the increased mortality of those with more severe or late AMD that may have further resulted in a more robust younger group who received additional anti-VEGF therapies as death is truly a competing risk for this cohort. These interesting findings warrant further studies designed to evaluate among persons with AMD the impact of anti-VEGF therapies on mortality.

There were no statistically significant associations with all-cause mortality in participants assigned to the AREDS2 treatment interventions. The AREDS nutritional supplement treatment modifications of zinc and beta-carotene also showed no statistically significant effect on mortality. Prior observational follow-up in the AREDS cohort suggested a protective association with either zinc alone or in combination with antioxidants and decreased all-cause mortality. No statistically significant association was found with oral zinc supplementation at a high (80mg) or low (25mg) dose. Addition of lutein and zeaxanthin, omega-3 fatty acids, individually or combined as well as the removal of beta-carotene from the original AREDS formulation did not have an apparent effect on survival.

Strengths of the current study include a large cohort enrolled at 82 clinical centers across various regions of the United States, low attrition rate, standardized gradings of fundus photographs for reproducible study endpoints, a relatively long follow-up, almost complete registry of deaths, and data on a variety of covariates. This study also enrolled a large portion of participants with late AMD, increasing our power and allowing us to evaluate the impact of late AMD on mortality independent of significant confounders. Like any other clinical trial, the current AREDS2 participants tend to be well-educated, health-conscious individuals are considerably more likely to volunteer in clinical trials.[33,37] In this observational portion of the study, adjustment for significant covariates may not have been complete, as AMD shares several risk factors for many confounding comorbidities. Participants with a history of cataract surgery at baseline may be inherently different from those who did not undergo surgery, further confounding mortality outcomes. However, AMD category was more evenly distributed among the cataract surgery and non-surgery groups. Inclusion of AMD category as a significant covariate in fully-adjusted models diminished the impact of bias on study findings.

In summary, increased mortality was associated with late AMD, bilateral cataract surgery and visual acuity <20/40. This may indeed reflect an aging process and residual confounding is difficult to eliminate. There was no increased mortality in those participants who received anti-VEGF therapies throughout the study. Oral supplementation with AREDS2 treatment modifications did not have a significant effect on survival outcomes. The impact of ocular

disorders on long-term mortality may be related to common factors for both increased risk of eye disease and mortality, suggesting systemic rather than local involvement. The clinical assessment and management in older persons with intermediate to advanced ocular disease status may present with challenges. Early detection of age-related eye diseases in this population may prevent deterioration of visual acuity and improve quality of life.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. The Eye Diseases Prevalence Research Group*. Causes and Prevalence of Visual Impairment Among Adults in the United States. Arch Ophthalmol. 2004; 122(4):477–485. [PubMed: 15078664]
2. Wang JJ, Mitchell P, Simpson JM, Cumming RG, Smith W. Visual Impairment, Age-Related Cataract, and Mortality. Arch Ophthalmol. 2001; 119(8):1186–1190. [PubMed: 11483087]
3. Knudtson MD, Klein BEK, Klein R. Age-Related Eye Disease, Visual Impairment, and Survival. The Beaver Dam Eye Study. Arch Ophthalmol. 2006; 124(2):243–249. [PubMed: 16476894]
4. Lee DJ, Gómez-Marín O, Lam BL, Zheng DD. Visual Acuity Impairment and Mortality in US Adults. Arch Ophthalmol. 2002; 120(11):1544–1550. [PubMed: 12427070]
5. McCarty C, Nanjan M, Taylor H. Vision impairment predicts 5 year mortality. The British Journal of Ophthalmology. 2001; 85(3):322–326. [PubMed: 11222339]
6. Thompson JR, Gibson JM, Jagger C. The association between visual impairment and mortality in elderly people. Age Ageing. 1989; 18(2):83–88. [PubMed: 2729011]
7. Pedula KL, Coleman AL, Yu F, et al. Age-Related Macular Degeneration and Mortality in Older Women: The Study of Osteoporotic Fractures. Journal of the American Geriatrics Society. 2015; 63(5):910–917. [PubMed: 25941039]
8. AREDS Research Group. Associations of Mortality With Ocular Disorders and an Intervention of High-Dose Antioxidants and Zinc in the Age-Related Eye Disease Study. AREDS Report No.13. Arch Ophthalmol. 2004; 122(5):716–726. [PubMed: 15136320]
9. Tseng VL, Yu F, Lum F, Coleman AL. Cataract Surgery and Mortality in the United States Medicare Population. Ophthalmology. 2016; 123(5):1019–26. [PubMed: 26854033]
10. Cugati S, Cumming RG, Smith W, Burlutsky G, Mitchell P, Wang JJ. Visual Impairment, Age-Related Macular Degeneration, Cataract, and Long-term Mortality. The Blue Mountains Eye Study. Arch Ophthalmol. 2007; 125(7):917–924. [PubMed: 17620571]
11. Fisher DE, Jonasson F, Eiriksdottir G, et al. Age-related macular degeneration and mortality in community-dwelling elders: The Age, Gene/Environment Susceptibility-Reykjavik Study. Ophthalmology. 2015; 122(2):382–390. [PubMed: 25264026]
12. Wang J, Xue Y, Thapa S, Wang L, Tang J, Ji K. Relation between Age-Related Macular Degeneration and Cardiovascular Events and Mortality: A Systematic Review and Meta-Analysis. BioMed Research International. 2016; 2016:8212063. [PubMed: 28070519]
13. Borger P, Leeuwen R, Hulsman C, et al. Is there a direct association between age-related eye diseases and mortality? The Rotterdam Study. Ophthalmology. 2003; 110(7):1292– 1296. [PubMed: 12867381]

14. Vingerling JR, Dielemans I, Bots ML, Hofman A, Grobbee DE, de Jong PTVM. Age-related macular degeneration is associated with atherosclerosis. The Rotterdam Study. Am J Epidemiol. 1995; 142:404–409. [PubMed: 7625405]
15. Hyman L, Schachat AP, He Q, Leske MC. Hypertension, cardiovascular disease, and age-related macular degeneration. Arch Ophthalmol. 2000; 118:351– 35. [PubMed: 10721957]
16. Sperduto RD, Hiller R. Systemic hypertension and age-related maculopathy in the Framingham Study. Arch Ophthalmol. 1986; 104:216– 219. [PubMed: 3947296]
17. Snow KK, Seddon JM. Do age-related macular degeneration and cardiovascular disease share common antecedents? Ophthalmic Epidemiol. 1999; 6:125– 143. [PubMed: 10420212]
18. Siantar RG, Cheng C-Y, Gemmy Cheung CM, et al. Impact of Visual Impairment and Eye diseases on Mortality: The Singapore Malay Eye Study (SiMES). Scientific Reports. 2015; 5:16304.doi: 10.1038/srep16304 [PubMed: 26549406]
19. Wang YX, Zhang JS, You QS, Xu L, Jonas JB. Ocular diseases and 10-year mortality: the Beijing Eye Study 2001/2011. Acta Ophthalmol. 2014; 92(6):424–428.
20. Hennis A, Wu SY, Li X, Nemesure B, Leske MC. the Barbados Eye Studies Group. Lens opacities and mortality: The Barbados Eye Studies. Ophthalmology. 2001; 108:498–504. [PubMed: 11237904]
21. West SK, Munoz B, Istre J, et al. Mixed lens opacities and subsequent mortality. Arch Ophthalmology. 2000; 118(3):393–397.
22. Taylor HR, McCarty CA, Nanjan MB. Vision impairment predicts five-year mortality. Transactions of the American Ophthalmological Society. 2000; 98:91–99. [PubMed: 11190044]
23. Ariyo AA, Haan T, Tangen CM, et al. Depressive symptoms and risks of coronary heart disease and mortality in elderly Americans: Cardiovascular Health Study Collaborative Research Group. Circulation. 2000; 102:1773– 1779. [PubMed: 11023931]
24. The Age-Related Eye Disease Study Research Group. The Age-Related Eye Disease Study (AREDS): design implications: AREDS Report No. 1. Control Clin Trials. 1999; 20:573– 600. [PubMed: 10588299]
25. The Age-Related Eye Disease Study Research Group. The Age-Related Eye Disease Study (AREDS) system for classifying age-related macular degeneration from stereoscopic color fundus photographs: AREDS Report No. 6. Am J Ophthalmol. 2001; 132:668– 681. [PubMed: 11704028]
26. Benson WH, Farber ME, Caplan RJ. Increased mortality rates after cataract surgery: a statistical analysis. Ophthalmology. 1988; 95:1288–1292. [PubMed: 3211506]
27. Hirsch RP, Schwartz B. Increased mortality among elderly patients undergoing cataract extraction. Arch Ophthalmol. 1983; 101:1034– 1037. [PubMed: 6870624]
28. Thiagarajan M, Evans JR, Smeeth L, Wormald RPL, Fletcher AE. Cause-Specific Visual Impairment and Mortality Results from a Population-Based Study of Older People in the United Kingdom. Arch Ophthalmol. 2005; 123(10):1397–1403. [PubMed: 16219731]
29. Fong CS, Mitchell P, et al. Correction of visual impairment by cataract surgery and improved survival in older persons: The Blue Mountains Eye Study cohort. Ophthalmology. 2013; 120(9): 1720–1727. [PubMed: 23664468]
30. Fong CS, Mitchell P, et al. Visual impairment corrected via cataract surgery and 5-year survival in a prospective cohort. Am J Ophthalmology. 2014; 157(1):163–170.
31. Ninn-Pedersen K, Stenevi U. Cataract patients in a defined Swedish population 1986–90: VII Inpatient and outpatient standardized mortality ratios. British Journal of Ophthalmology. 1995; 79:1115–1119. [PubMed: 8562547]
32. Street DA, Javitt JC. National five-year mortality after inpatient cataract extraction. Am J Ophthalmol. 1992; 113:263– 268. [PubMed: 1543218]
33. Ederer F, Church TC, Mandel JS. Sample sizes for prevention studies have been too small. Am J Epidemiol. 1993; 137:787–976. [PubMed: 8484370]
34. Chew EY, Clemons T, SanGiovanni JP, et al. The Age-Related Eye Disease Study 2 (AREDS2): Study Design and Baseline Characteristics (AREDS2 Report Number 1). Ophthalmology. 2012; 119(11):2282–2289. [PubMed: 22840421]

35. Age-Related Eye Disease Study Research Group. A Simplified Severity Scale for Age-Related Macular Degeneration: AREDS Report No. 18. Archives of Ophthalmology. 2005; 123(11):1570–1574. [PubMed: 16286620]

36. Whooley MA, Browner WS. for the Study of Osteoporotic Fractures Research Group. Association Between Depressive Symptoms and Mortality in Older Women. Arch Intern Med. 1998; 158(19): 2129–2135. [PubMed: 9801180]

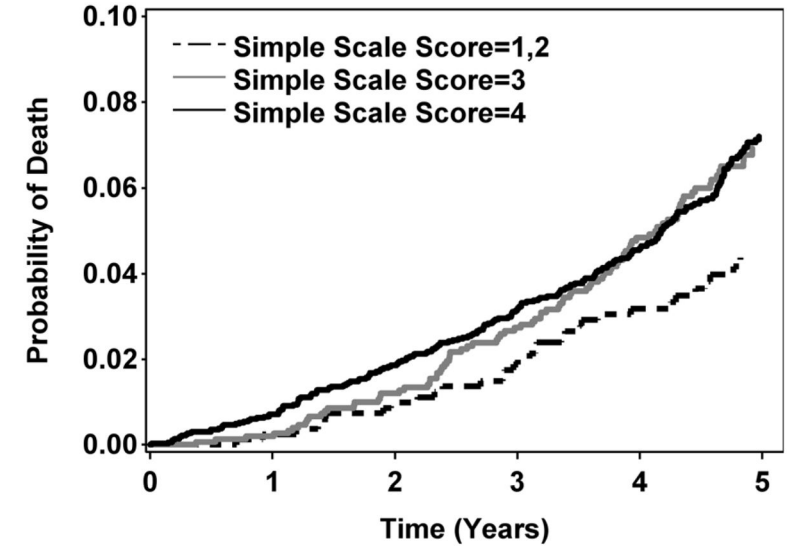
37. Ganguli M, Lytle ME, Reynolds MD, Dodge HH. Random versus volunteer selection for a community-based study. J Gerontol A Biol Sci Med Sci. 1998; 53(1):M39–46. [PubMed: 9467432]

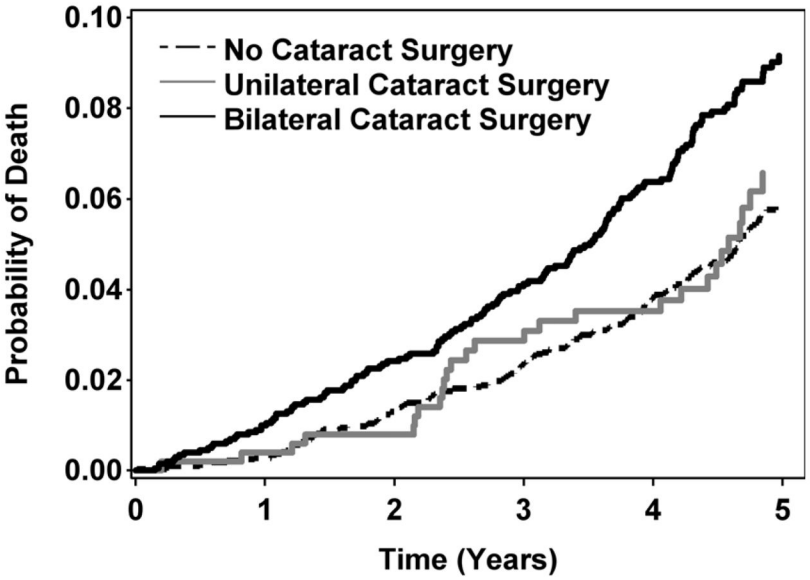
38. Age-Related Eye Disease Study 2 Research, Group. Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: The Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. JAMA. 2013; 309(19):2005–2015. [PubMed: 23644932]

39. Wong TY, Tikellis G, Sun C, Klein R, Couper DJ, Sharrett AR. Age-related macular degeneration and risk of coronary heart disease: The Atherosclerosis Risk in Communities Study. Ophthalmology. 2007; 114(1):86–91. [PubMed: 17198851]

40. Tan JS, Wang JJ, Liew G, Rochtchina E, Mitchell P. Age-related macular degeneration and mortality from cardiovascular disease or stroke. Br J Ophthalmol. 2008; 92(4):509–512. [PubMed: 18310310]

41. French DD, Margo CE. Age-related macular degeneration, anti-vascular endothelial growth factor agents, and short-term mortality: a postmarketing medication safety and surveillance study. Retina. 2011; 31(6):1036–1042. [PubMed: 21836410]





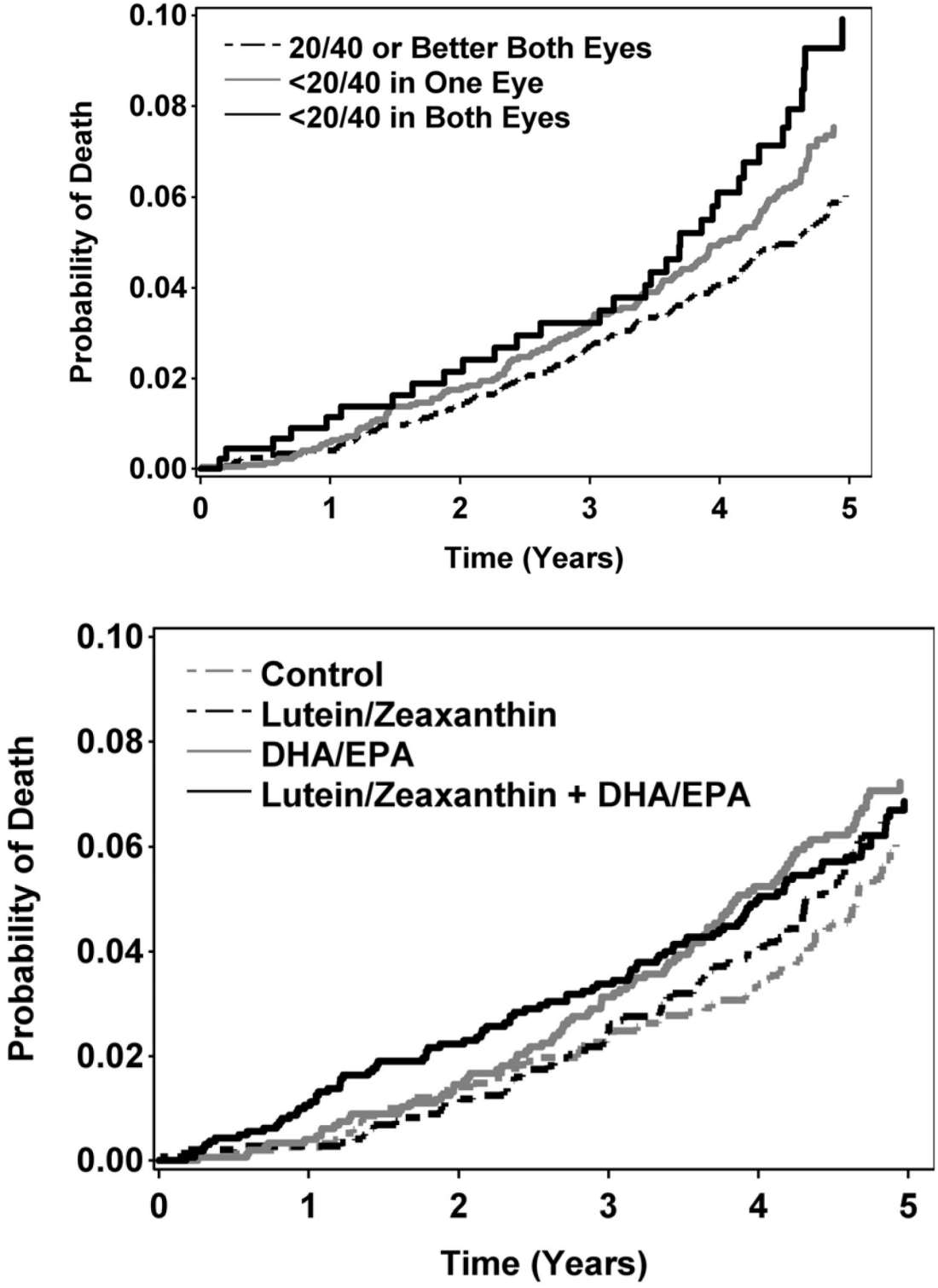


Figure 1.

Figure 1A: The rates of mortality (Kaplan-Meier curve) by baseline severity of age-related macular degeneration (AMD), using the AREDS AMD simple score scale, based on

presence of large drusen, retinal pigmentary changes, and late AMD. The more severe AMD cases (simple scale score of 3 and 4) were associated with greater mortality rates.

Figure 1B: The rates of mortality (Kaplan-Meier curve) by baseline cataract surgery (none, 1 eye, or both eyes). The AREDS2 participants who had bilateral cataract surgery had a greater rate of mortality compared to those without cataract surgery.

Figure 1C. The rates of mortality (Kaplan-Meier curve) by baseline visual impairment, (none, one eye, or both eyes with visual acuity worse than 20/40). Having vision worse than 20/40 in either or both eyes was associated with increased mortality.

Figure 1D. The rates of mortality (Kaplan-Meier curve) by the Age-Related Eye Disease Study 2 (AREDS2) study supplements: control, lutein plus zeaxanthin, omega-3 fatty acids and the combination of lutein/zeaxanthin and omega-3 fatty acids. There were no statistically significant differences in the mortality rates between these treatment arms.

Table 1

All-Cause Mortality by Baseline Characteristics

Characteristic	No. of subjects n=4,203, (%)	No. of deaths (%)	Mortality⊥%	Hazard Ratio* (95% Confidence Interval)
Age, yrs.				
< 65	683 (16.3)	16 (2.3)	2.4	1.00
65 – 74	1545 (36.8)	83 (5.4)	5.0	2.25 (1.32 – 3.85)
75 – 79	1115 (26.5)	122 (10.9)	10.6	4.64 (2.75 – 7.81)
≥ 80	860 (20.4)	147 (17.1)	16.8	7.79 (4.65 – 13.06)
Gender				
Male	1816 (43.2)	205 (11.3)	9.1	1.00
Female	2387 (56.8)	163 (6.8)	5.6	0.61 (0.50 – 0.75)
Race				
Non-Hispanic White	3997 (95.1)	361 (9.0)	7.1	1.00
Other	206 (4.9)	7 (3.4)	3.4	0.42 (0.20 – 0.89)
Education ✞				
High school or less	1337 (31.8)	148 (11.1)	8.0	1.00
More than High school	2788 (66.3)	213 (7.6)	6.4	0.73 (0.59 – 0.90)
Smoking Status				
Never	1824 (43.4)	132 (7.2)	5.9	1.00
Former	2097 (49.9)	198 (9.4)	7.1	1.18 (0.94 – 1.48)
Current	282 (6.7)	38 (13.5)	13.5	2.46 (1.71 – 3.55)
Diabetes				
No	3657 (87.0)	292 (8.0)	6.4	1.00
Yes	546 (13.0)	76 (13.9)	10.8	1.81 (1.41 – 2.34)
Aspirin Use				
No	2146 (51.1)	162 (7.6)	6.6	1.00
Yes	2057 (48.9)	206 (10.0)	7.5	1.16 (0.94 – 1.43)
NSAID Use				
No	3747 (89.2)	340 (9.1)	7.2	1.00
Yes	456 (10.8)	28 (6.1)	5.7	0.79 (0.53 – 1.16)
CES-Depression score ≥ 16 **				
No	2201 (63.9)	173 (7.9)	6.7	1.00
Yes	1246 (36.1)	115 (9.2)	8.0	1.24 (0.98 – 1.58)
History of High Blood Pressure§				
No	1733 (41.2)	105 (6.1)	5.2	1.00
Yes	2469 (58.7)	263 (10.7)	8.2	1.57 (1.25 – 1.97)
History of Congestive Heart Failure§				
No	4055 (96.5)	334 (8.2)	6.7	1.00
Yes	147 (3.5)	34 (23.1)	15.4	2.43 (1.71 – 3.47)
History of Coronary Heart Disease§				
No	3797(90.3)	300 (7.9)	6.7	1.00

Characteristic	No. of subjects n=4,203, (%)	No. of deaths (%)	Mortality⊥%	Hazard Ratio* (95% Confidence Interval)
Yes	405 (9.6)	68 (16.8)	10.2	1.62 (1.24 – 2.13)
History of Angina§				
No	4004 (95.3)	338 (8.4)	6.9	1.00
Yes	198 (4.7)	30 (15.2)	9.2	1.43 (0.98 – 2.08)
History of MI§				
No	3909 (93.0)	307 (7.9)	6.6	1.00
Yes	293 (7.0)	61 (20.8)	12.4	2.09 (1.58 – 2.77)
History of Stroke§				
No	3991 (95.0)	330 (8.3)	6.7	1.00
Yes	211 (5.0)	38 (18.0)	12.2	1.80 (1.29 – 2.53)
History of High Cholesterol§				
No	1796 (42.7)	160 (8.9)	7.4	1.00
Yes	2406 (57.2)	208 (8.7)	6.7	0.93 (0.76 – 1.15)

⊥Age- and sex adjusted mortality for median follow-up (4.8 years)

*Age- and sex-adjusted risk ratios

✞ 78 participants refused to answer (education)

§1 participant with missing data (history of high blood pressure, congestive heart failure, coronary heart disease, angina, MI, stroke, and high cholesterol)

756 participants with missing CES-D score, **CES-D: Center for Epidemiologic Studies' Depression Scale

Table 2

Association of All-Cause Mortality with Ocular Characteristics and AREDS2 Treatment Characteristics

Characteristic	No. of subjects (%)	No. of deaths (%)	Mortality-1 %	Risk Ratio* (95% CI)	Hazard Ratio** (95% CI)
Simple Scale Score					
Score: 1, 2	635 (15.1)	33 (5.2)	4.8	1.00	1.00
Score = 3	1065 (25.3)	94 (8.8)	7.4	**1.58 (1.06 – 2.35)**	**1.60 (1.07 – 2.40)**
Score = 4	2490 (59.2)	240 (9.6)	7.4	**1.63 (1.13 – 2.34)**	**1.72 (1.19 – 2.50)**
AMD status					
Intermediate AMD	2790 (66.4)	201 (7.2)	6.8	1.00	1.00
Geographic Atrophy	135 (3.2)	19 (14.1)	10.1	1.46 (0.91 – 2.34)	1.31 (0.81 – 2.10)
Neovascular AMD	1278 (30.4)	148 (11.6)	8.6	**1.31 (1.01 – 1.63)**	**1.56 (1.21 – 2.01)**
Cataract Surgery					
None	2876 (68.4)	175 (6.1)	5.8	1.00	1.00
Unilateral	283 (6.7)	29 (10.3)	7.0	1.20 (0.80 – 1.79)	1.12 (0.75 – 1.67)
Bilateral	1044 (24.8)	164 (15.7)	10.4	**1.87 (1.48 – 2.34)**	**1.63 (1.29 – 2.06)**
Visual Acuity					
20/40 or better OU	2647 (63.0)	178 (6.7)	6.1	1.00	1.00
20/40 or worse in one eye	1326 (31.5)	157 (11.8)	8.2	**1.35 (1.09 – 1.68)**	**1.32 (1.05 – 1.66)**
20/40 or worse OU	227 (5.4)	33 (14.5)	10.1	**1.57 (1.08 – 2.29)**	**1.57 (1.07 – 2.31)**
Anti-vascular endothelial growth factor (VEGF) therapy					
No	2597 (61.8)	230 (8.9)	7.5	1.00	1.00
Yes	1606 (38.2)	138 (8.6)	7.3	**0.78 (0.63 – 0.97)**	**0.71 (0.57 – 0.88)**
No. of anti-vascular endothelial growth factor (VEGF) therapies					
None	2597 (61.8)	230 (8.9)	7.5	1.00	1.00
No. of injections unknown	659 (15.7)	87 (13.2)	12.1	1.28 (1.00 – 1.64)	1.20 (0.93 – 1.54)
1–5 injections	519 (12.3)	35 (6.7)	5.7	**0.59 (0.41 – 0.84)**	**0.52 (0.36 – 0.74)**
6–10 injections	255 (6.1)	12 (4.7)	3.2	**0.40 (0.22 – 0.71)**	**0.35 (0.19 – 0.64)**
> 10 injections	173 (4.1)	4 (2.3)	3.2	**0.21 (0.08 – 0.55)**	**0.20 (0.07 – 0.53)**
AREDS2 Treatment					
DHA/EPA Main Effect					
No DHA/EPA	2056 (48.9)	168 (8.2)	6.6	1.00	1.00

Characteristic	No. of subjects (%)	No. of deaths (%)	Mortality⊥ %	Risk Ratio* (95% CI)	Hazard Ratio** (95% CI)
DHA/EPA	2147 (51.1)	200 (9.3)	7.4	1.17 (0.95 – 1.43)	1.19 (0.97 – 1.46)
Lutein/Zeaxanthin Main Effect					
No Lutein/Zeaxanthin	2080 (49.5)	177 (8.5)	6.9	1.00	1.00
Lutein/Zeaxanthin	2123 (50.5)	191 (9.0)	7.1	1.05 (0.85 – 1.28)	1.04 (0.85 – 1.28)
Individual Treatment Groups					
Control	1012 (24.1)	81 (8.0)	6.3	1.00	1.00
Lutein/Zeaxanthin Alone	1044 (24.8)	87 (8.3)	6.9	1.02 (0.75 – 1.38)	1.09 (0.80 – 1.49)
DHA/EPAAlone	1068 (25.4)	96 (9.0)	7.5	1.14 (0.85 – 1.53)	1.24 (0.92 – 1.68)
Lutein/Zeaxanthin + DHA/EPA	1079 (25.7)	104 (9.6)	7.2	1.22 (0.91 – 1.63)	1.24 (0.92 – 1.66)
AREDS2 Secondary Randomization ✟					
Low Zinc Main Effect					
High Zinc	1522 (36.2)	140 (9.2)	7.7	1.00	1.00
Low Zinc	1514 (36.0)	141 (9.3)	7.5	1.02 (0.81 – 1.29)	0.97 (0.76 – 1.23)
No Beta-Carotene Main Effect§					
No Beta-Carotene	1341 (31.9)	116 (8.7)	6.9	1.00	1.00
Beta-Carotene	1348 (32.1)	118 (8.8)	6.8	0.99 (0.77 – 1.28)	1.03 (0.80 – 1.34)

⊥ Age- and gender-adjusted mortality for median follow-up (6.5 years)

* Age- and gender-adjusted risk ratios

** Adjusted for significant covariates: age, gender, race, education, smoking status, diabetes, history of high blood pressure, history of congestive heart failure, history of coronary heart disease, history of MI, history of stroke, and anti-angiogenic treatment

✟ Includes N = 3036 participants who agreed to AREDS2 2nd tier randomization

§ Excludes smokers and former smokers not randomized to beta-carotene

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Table 3

Associations of Cause-Specific Mortality with Baseline Ocular and Treatment Characteristics

	Circulatory System	Neoplasms	Other Causes
Characteristic	**Hazard Ratio* (95% CI)**	**Hazard Ratio* (95% CI)**	**Hazard Ratio* (95% CI)**
Simple Scale Score			
Score: 1, 2	1.00	1.00	1.00
Score = 3	1.45 (0.69 – 3.03)	1.34 (0.63 – 2.84)	**1.90 (1.01 – 3.56)**
Score = 4	1.56 (0.79 – 3.07)	1.11 (0.55 – 2.24)	**2.30 (1.28 – 4.12)**
AMD status			
Intermediate AMD	1.00	1.00	1.00
Geographic Atrophy	1.35 (0.57 – 3.17)	`	0.64 (0.26 – 1.59)
Neovascular AMD	**1.68 (1.04 – 2.71)**	**1.87 (1.08 – 3.24)**	1.38 (0.97 – 1.98)
Cataract Surgery			
None	1.00	1.00	1.00
Unilateral	1.21 (0.61 – 2.40)	0.98 (0.41 – 2.34)	1.15 (0.63 – 2.10)
Bilateral	1.23 (0.78 – 1.93)	1.29 (0.77 – 2.14)	**2.11 (1.51 – 2.97)**
Visual Acuity			
20/40 or better OU	1.00	1.00	1.00
20/40 or worse in one eye	**1.60 (1.04 – 2.44**)	1.29 (0.80 – 2.08)	1.19 (0.85 – 1.67)
20/40 or worse OU	1.08 (0.46 – 2.57)	0.69 (0.21 – 2.26)	**2.17 (1.35 – 3.50)**
Anti-VEGF therapy			
No	1.00	1.00	1.00
Yes	**0.58 (0.38 – 0.89)**	0.95 (0.61 – 1.49)	**0.70 (0.52 – 0.95)**
No. of anti-vascular endothelial growth factor (VEGF) therapies			
None	1.00	1.00	1.00
Number of injections unknown	1.00 (0.62 – 1.63)	1.61(0.96 – 2.68)	1.17 (0.82 – 1.68)
1– 5 injections	**0.48 (0.24 – 0.96)**	0.74 (0.36 – 1.53)	**0.46 (0.27 – 0.79)**
6–10 injections	**0.10 (0.01 – 0.73)**	0.49 (0.15 – 1.58)	**0.44 (0.21 – 0.95)**
> 10 injections	0.17 (0.02 – 1.22)	--	**0.26 (0.09 – 0.89)**
AREDS2 Treatment			
DHA/EPA Main Effect			
No DHA/EPA	1.00	1.00	1.00
DHA/EPA	1.09 (0.73 – 1.60)	1.07 (0.69 – 1.66)	1.31 (0.97 – 1.77)
Lutein/Zeaxanthin Main Effect			
No Lutein/Zeaxanthin	1.00	1.00	1.00
Lutein/Zeaxanthin	1.34 (0.90 – 1.99)	0.97 (0.63 – 1.51)	0.93 (0.70 – 1.25)
Individual Treatment Groups			
Control	1.00	1.00	1.00
Lutein/Zeaxanthin Alone	1.80 (1.00 – 3.24)	1.06 (0.56 – 1.98)	0.80 (0.51 – 1.27)
DHA/EPAAlone	1.50 (0.82 – 2.76)	1.16 (0.63 – 2.15)	1.16 (0.77 – 1.76)
Lutein/Zeaxanthin + DHA/EPA	1.52 (0.84 – 2.77)	1.04 (0.56 – 1.96)	1.20 (0.80 – 1.80)

	Circulatory System	Neoplasms	Other Causes
Characteristic	**Hazard Ratio* (95% CI)**	**Hazard Ratio* (95% CI)**	**Hazard Ratio* (95% CI)**
AREDS2 Secondary Randomization ✞			
Low Zinc Main Effect			
High Zinc	1.00	1.00	1.00
Low Zinc	1.21 (0.77 – 1.91)	1.16 (0.69 – 1.96)	0.79 (0.56 – 1.10)
No Beta-Carotene Main Effect§			
No Beta-Carotene	1.00	1.00	1.00
Beta-Carotene	0.62 (0.38 – 1.02)	0.92 (0.51 – 1.66)	1.44 (1.00 – 2.08)

*Adjusted significant covariates: age, gender, race, education, smoking status, diabetes, history of high blood pressure, history of congestive heart failure, history of coronary heart disease, history of MI, history of stroke, and anti-angiogenic treatment

Table 4

Cause specific mortality

Cause of Death (Total: N=368)	**N**
Cardiovascular Deaths (Subtotal: 88/368 [23.9%])	
Cardiovascular Disease	74
Cerebrovascular Disease	14
Malignancy (Subtotal: 90/368 [24.4%])	
Lung	24
Pancreatic	6
Prostate	4
Leukemia	5
Lymphoma	3
Brain	4
Breast	2
Bladder	5
Kidney	2
Ovarian	2
Esophagus	3
Liver	6
Skin	5
Gastric (Stomach)	2
Other neoplasms	17
Miscellaneous/Other/Unknown (190/368 [51.6%])	
Accident or trauma related	11
Musculoskeletal disorders or orthopedic procedure	2
Diabetes mellitus	3
Liver Disease	3
Pneumonia/Influenza	22
Chronic obstructive pulmonary/other respiratory diseases	38
Mental Health Disorders	12
Genitourinary Problems	10
Other	46
Unknown	43