AMERICAN ACADEMY OF OPHTHALMOLOGY®

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

Age-Related Eye Disease Study 2 Report Number 13

*The Age-Related Eye Disease Study 2 Research Group**
Writing Committee: Chandana Papudesu, BSc,[1] Traci E. Clemons, PhD,[2] Elvira Agrón, MA,[1] Emily Y. Chew, MD[1]

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

Design: Cohort study.

Participants: 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 on the basis of the International Classification of Diseases 9th or 10th Revision 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 with participants with no or few drusen (hazard ratio [HR], 1.56; 95% confidence interval [CI], 1.21−2.01; $P < 0.001$). Poorer survival was associated with bilateral cataract surgery before 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 significant covariates. Participants who received antivascular 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 VA less than 20/40 was 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. *Ophthalmology 2017;■:1−10 Published by Elsevier on behalf of the American Academy of Ophthalmology*

Supplemental material available at www.aaojournal.org.

Age-related eye 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.[2−13] Although the relationship between AMD or cataract with survival has been less clear, AMD was associated with decreased survival in some studies,[7−9,13] but others reported no statistical significance after adjustment for appropriate confounders.[3,10,14−16] 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 lead to shorter survival.[9,17−20] However, few studies have evaluated the impact of late AMD (nonfoveal 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 versus cortical or subcapsular, in some[2,3,10,13,21−24] but not all studies.[14−16] The association of mortality and a clinical history of cataract surgery has not

https://doi.org/10.1016/j.ophtha.2017.10.028
ISSN 0161-6420/17

been well established.[12,25–29] Although reasons for shorter survival in persons with cataracts or cataract surgery are not known, the presence of cataract may be a possible marker for biological aging. The role of oxidative stress and inflammatory processes also may be suggested by previous studies of decreased survival with cataract.[3,13,25,26]

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, and they were followed for a median follow-up of 5 years.[30] 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 a total of 4203 men and women aged 50 to 80 years with bilateral intermediate AMD or late AMD in 1 eye. The study concluded in October 2012 with a median follow-up of 5 years. This 2 × 2 factorial trial evaluated the addition of high-dose antioxidants lutein (10 mg) and zeaxanthin (2 mg) and/or omega-3 long-chain polyunsaturated fatty acids: docosahexaenoic acid (DHA [350 mg]) and eicosapentaenoic acid (EPA [650 mg]) to the original AREDS formulation in reducing the primary outcome of AMD and cataract progression. The original AREDS formulation consisted of vitamin C (500 mg), vitamin E (400 IU), beta-carotene (15 mg), zinc (80 mg as zinc oxide), and copper (2 mg as cupric oxide). The AREDS2 participants underwent primary randomization to 4 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 (15 mg) and high-dose (80 mg) or low-dose (25 mg) zinc formulations.[30]

Participants eligible for the study included those who were willing and able to undergo yearly examination for at least 5 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 who 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 photographs, 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 1 eye and late AMD in the fellow eye. This translates to the AREDS AMD Simple Scale of 2, 3, and 4.[31] The Simple Scale was a person-scale that included both eyes, and the scale was based on the presence of large drusen or retinal pigment epithelial hypopigmentary/hyperpigmentary changes or the presence of late AMD.[31,32] The reading center also evaluated the progression to late AMD (central geographic atrophy or neovascular AMD) on the basis of 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 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 the World Health Organization 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 before 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 or nonsteroidal anti-inflammatory drugs/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, because this covariate has been strongly associated with risk of developing AMD and mortality.[7,8] All analyses were conducted using SAS version 9.2 (SAS Institute Inc, Cary, NC).

Results

Between 2006 and 2008, AREDS2 enrolled 4203 participants aged 50 to 80 years with bilateral intermediate AMD or late AMD in 1 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