

The Association of Statin Use with Age-Related Macular Degeneration Progression

The Age-Related Eye Disease Study 2 Report Number 9

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Purpose: To evaluate the association of statin use with progression of age-related macular degeneration (AMD).

Design: Preplanned, prospective cohort study within a controlled clinical trial of oral supplementation for age-related eye diseases.

Participants: Age-Related Eye Disease Study 2 (AREDS2) participants, aged 50 to 85 years.

Methods: Factors, including age, gender, smoking status, aspirin use, and history of diabetes, hypertension, heart disease, angina, and stroke—all known to be associated with statin use—were included in a logistic regression model to estimate propensity scores for each participant. Age-adjusted proportional hazards regression models, with and without propensity score matching, were performed to evaluate the association of statin use with progression to late AMD. Analyses adjusting for the competing risk of death were also performed.

Main Outcome Measures: Baseline and annual stereoscopic fundus photographs were assessed centrally by masked graders for the development of late AMD, either neovascular AMD or geographic atrophy (GA).

Results: Of the 3791 participants (2462 with bilateral large drusen and 1329 with unilateral late AMD at baseline), 1659 (43.8%) were statin users. The overall analysis, with no matching of propensity scores and no adjustment for death as a competing risk, showed that statin use was not associated with progression to late AMD (hazard ratio [HR], 1.08; 95% confidence interval [CI], 0.83–1.41; $P = 0.56$). When matched for propensity scores and adjusted for death as a competing risk, the result was not statistically significant (HR, 0.81; 95% CI, 0.55–1.20; $P = 0.29$). Furthermore, subgroup analyses of persons with or without late AMD at baseline and the various components of late AMD (neovascular AMD, central GA, or any GA) also showed no statistically significant association of statin use with progression to AMD.

Conclusions: Statin use was not statistically significantly associated with progression to late AMD in the AREDS2 participants, and these findings are consistent with findings in the majority of previous studies. Statins have been demonstrated to reduce the risk of cardiovascular disease, but our data do not provide evidence of a beneficial effect on slowing AMD progression. *Ophthalmology* 2015;■:1–7 © 2015 Published by Elsevier on behalf of the American Academy of Ophthalmology.



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Age-related macular degeneration (AMD), a progressive disease that results in central vision loss, is the leading cause of blindness among people aged older than 60 years of age in the United States.¹

The pathogenesis of AMD is unknown. Associated risk factors include increasing age, cigarette smoking, hypertension, increased body mass index, lower educational level, presence of lens opacities, and others.^{2–5} The use of antioxidant vitamins and minerals, known as the Age-Related Eye Disease Study supplement, reduces the risk of progression to late AMD, suggesting that oxidative stress may play a role in AMD.⁶ The association of genetic polymorphism in the

complement pathway involving complement factor H and many other complement factors suggest that local or systemic inflammatory pathways also may be important in the pathogenesis of AMD.^{7–11} This potential inflammatory pathway is further supported by the statistically significant association of elevated serum C-reactive protein with AMD in the Women's Health Study, Rotterdam Study, and Age-Related Eye Disease Study.^{4,7,8,12,13}

Statins, or 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, currently the most commonly prescribed class of lipid-lowering drugs,¹⁴ are proven to lower serum lipids and reduce cardiovascular morbidity and mortality.¹⁵

The main role of statins is to inhibit 3-hydroxy-3-methylglutaryl-CoA reductase in the liver, downregulating lipid metabolism.¹⁶ However, this class of drugs has exhibited unexpected anti-inflammatory, antioxidative, and anti-angiogenic effects.^{17–20} Pathologic studies of AMD have also demonstrated the accumulation of lipids in Bruch's membrane similar to the atherosclerotic changes of cardiovascular disease,^{21–23} suggesting that statins might have an effect on AMD. Previous observational studies demonstrated that statin use was associated with a protective effect on AMD^{24–33}; however, other studies were not confirmatory.^{34–37} Lipid lowering with 40 mg of simvastatin in a small proof-of-concept study was associated with a possible beneficial effect, especially for persons with bilateral intermediate AMD and those with genotype of the risk alleles for complement factor H for progression to late AMD.³⁸

The Age-Related Eye Disease Study 2 (AREDS2) was a prospective, multicenter clinical trial that tested oral supplements of omega-3 fatty acids and lutein/zeaxanthin for the treatment of AMD and cataract.³⁹ These participants were followed for a median of 5 years, and the observational data from this study provided an opportunity to investigate the effect of statins on progression to late AMD.

Methods

Study Population

The study design for AREDS2 is detailed in a previous report³⁹ but briefly summarized as follows. Between 2006 and 2008, 4203 participants aged 50 to 85 years were enrolled at 82 retinal specialty clinics in the United States. At enrollment, participants were included if they had bilateral large drusen or unilateral late AMD in 1 eye and large drusen in the fellow eye. Institutional review board approval was obtained at each clinical site, and written informed consents for the research were obtained from all study participants.

The AREDS2 participants were randomly assigned to placebo, lutein/zeaxanthin, docosahexaenoic acid (DHA) plus eicosapentaenoic acid (EPA), or the combination of lutein/zeaxanthin and DHA plus EPA. At the baseline visit and each annual study visit, comprehensive eye examinations were performed, including stereoscopic fundus photographs by certified photographers. These images were assessed by trained graders using a standardized protocol at the University of Wisconsin Fundus Photograph Reading Center. The main study outcome is the development of late AMD as graded from annual fundus photographs.

In AREDS2, late AMD was defined as having at least 2 features of neovascularization, including serous detachment of the sensory retina, hemorrhage, retinal pigment epithelial detachment, fibrous tissue, or hard exudates; or geographic atrophy (GA) of an area of 360 μ m or greater in diameter, involving the center of the macula; or a history of treatment for neovascular AMD. In this study, we used the recently recommended and more inclusive definition of "late AMD," which includes any definite GA in the definition, not just central GA.¹²

Questionnaires administered at the baseline and annual study visits were used to collect information on nutrition, medications, adverse events, and treatment compliance, among others. Telephone calls were performed twice in the first year of randomization and annually thereafter to collect information about adverse events, treatment for AMD, and incidence of cataract surgery between the study visits.

Statistical Methods

We included only participants who had no missing values to evaluate the effect of statins in eyes with intermediate AMD on the progression to late AMD. Baseline patient characteristics were compared between statin users and nonusers using the *t* test for continuous variables (age) and chi-square test for categorical variables, including gender, race, education level, smoking status, diabetes, nonsteroidal anti-inflammatory drug use, acetaminophen use, hypertension (defined as >140 mmHg systolic and/or >90 mmHg diastolic blood pressures), congestive heart failure, coronary heart disease, angina, history of myocardial infarction, and history of stroke.

A propensity score approach can be used to reduce or eliminate the effects of confounding when using observational data (e.g., statin use) to estimate treatment effects.⁴⁰ To reduce the effects of confounding for statin use, we used logistic regression to estimate propensity scores, which range from 0 to 1 and indicate the probability that a participant is a statin user, based on the risk factors listed previously. Values closer to 1 indicate a higher likelihood of a participant using statins. After developing the propensity score for statin users and nonusers, we matched statin users to nonusers using the propensity scores to mimic characteristics of a controlled clinical trial.⁴¹ Applied in the context of statin use in AREDS2, the propensity matching approach consisted of forming match sets of statin users and nonusers who share a similar value for the propensity score. Baseline characteristics were included in the matching model that excluded data that could not be matched.

This propensity score matching is a second method to attempt to control for the confounding from the variables in the propensity score that are associated with both statin use and progression of AMD. The matching was done using a greedy matching technique (Parsons LS. Reducing bias in a propensity score matched-pair sample using greedy matching techniques. Paper presented at: Proceedings of the 26th Annual SAS Users Group International Conference, 2001; Long Beach, CA).

Age-adjusted proportional hazards regression models were used to evaluate the effect of statin use on progression to any late AMD, including neovascular AMD and GA, in the entire cohort. Additional analyses were conducted separately for the development of neovascular AMD and GA. To fit a proportional subdistribution hazards model,⁴² the competing risk of death was taken into account using the macro developed by Kohl and Heinze.⁴³ Hazard ratios (HRs) were calculated with 95% confidence intervals (CIs), with *P* < 0.05 being considered significant for all analyses.

Analyses were performed both matching and not matching statin users and nonusers by the propensity scores, in addition to adjusting for death as a competing risk. Analyses were also performed separately for the 2 groups: participants with bilateral large drusen and participants with unilateral late AMD. No adjustments were made for multiplicity of analyses. All analyses were conducted using SAS version 9.3 (SAS Inc, Cary NC).

Results

Of the 3791 participants included in this analysis, progression to late AMD by the end of the study occurred in 1650 (869 with any GA, 479 with central GA, and 998 with neovascular AMD). Each participant could have any combination of the late forms of AMD.

Associations of possible confounders with statin use are shown in Table 1. The result from the proportional hazards regression model on the entire cohort, adjusting for the propensity scores,

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