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# The Association of Statin Use with Cataract Progression and Cataract Surgery The Age-Related Eye Disease Study 2 Report Number 8

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## Introduction

Numerous epidemiologic studies have evaluated the association of statin use and cataracts but the results have been inconsistent.[1, 2,.3] Statins, or 3-hydroxy-3methylglutaryl-coenzyme A reductase inhibitors, are currently the most common lipid-lowering class of drugs. The Age-Related Eye Diseases Study 2 (AREDS2) was a prospective, multi-centered clinical trial that evaluated the progression of age-related macular degeneration (AMD) and cataract in participants aged 50 to 85 with at least intermediate AMD.[4] In this report, we investigated the association of statin use with cataract progression or cataract surgery in AREDS2.

## Methods

The AREDS2, sponsored by the National Eye Institute, evaluated the safety and efficacy of adding lutein and zeaxanthin and/or omega-3 long-chain polyunsaturated fatty acids to the AREDS supplements in reducing the primary outcome of progression of age-related macular degeneration (AMD) and the secondary outcome of cataract progression. As reported, the supplementation had no effect on lens opacity progression.[5] The study enrolled 4203 participants aged 50 through 85 between 2006 and 2008 at 82 clinical centers in the United States. The study concluded in October 2012 with a median follow-up of five years. Institutional review board approval was obtained at each clinical site, and participants signed informed consent for the study.

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Participants included in these analyses were bilaterally phakic at baseline and had cortical and posterior subcapsular (PSC) lens opacities involving less than 5% of the area in the central 5 mm diameter zone of the lens as documented on red reflex lens photographs. Progression to 5% or more was considered an outcome for both cortical and PSC opacities. Cataract surgery was used as a surrogate of moderate to severe lens opacity of unspecified type. Slit-lamp examination at annual study visits documented the presence of pseudophakia and an interim history of cataract surgery was obtained during study telephone calls that occurred every six months between the study visits. Statin use was self-reported at baseline.

## Statistical analyses

The 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. 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 upon the risk factors at baseline. Values closer to 1 indicate a higher likelihood of a participant using statins.

We then conducted age and sex-adjusted Cox regression using the propensity score, with and without matching of these scores, to evaluate the association of statin use with progression of lens opacities in either eye. Finally, adjustment was made for the competing risk of death. The unit of analysis is by person.

## Results

Of the 2771 participants who were bilaterally phakic at baseline with less than 5% center subfield cortical or PSC opacity, 1184 (42.7%) were statin users. E-Table 1 (Supplementary table) displays the baseline characteristics of these two groups. Statin users tended to be older, male, former or current smokers, with history of diabetes, and aspirin use. Statin users were also more likely to have a history of hypertension, congestive heart failure, coronary heart disease, angina, myocardial infarction, and stroke. The progression rates at 5 years were: 18.0% (499/2771) for cataract surgery, 42.6% (1111/2609) cortical lens opacities, and 30.6% (819/2673) PSC lens opacities.

In age and sex-adjusted analyses that included propensity scores, statin users had an increased risk of cataract surgery [hazard ratio (HR), 1.90; 95% confidence interval (CI), 1.17–3.10], cortical lens opacity progression (HR, 1.52; 95% CI, 1.08–2.12) and PSC lens opacity progression (HR, 1.84; 95% CI, 1.25–2.71) (Table 2). Female statin users had increased risk of cataract progression and cataract surgery. Statin users under the age of 75 years also had an increased risk of PSC lens opacity progression and cataract surgery.

Matching statin users and non-users by the propensity scores resulted in 904 matched pairs. Differences in the covariates were then no longer statistically significantly different (E-Table 1). However, the age difference between each propensity-matched pair could still range between 0–30 years despite the matching. The analyses of the propensity-matched cohort were adjusted for age in the subsequent Cox regression analysis. Results for the matched analyses and the competing risks analysis were similar to those seen for the unmatched analyses (E-Table 3).

## Discussion

The use of statins in AREDS2 participants was associated with cataract surgery and progression of both cortical and PSC lens opacities. Risk of these outcomes appeared to be greater for females and persons younger than 75 years who used statins.

The current study has limitations. While propensity matching is designed to reduce bias by balancing the covariates between those choosing and not choosing to take statins, the propensity technique can adjust only for factors that were measured in AREDS2. Whether unknown or unmeasured factors influenced our findings or the findings of previously conducted observational studies cannot be determined. Of particular concern, given the widespread use of statins in patients with cardiovascular disease, is incomplete adjustment for risk factors associated with both CVD and cataract,

Our study was subject to potential recall bias as statin use was self-reported. Both statin dosage and duration of use were not ascertained but 86% of participants who reported using statins at baseline continued to report statin use at their close-out visit. Our study results are not necessarily generalizable because our study cohort was a select population of patients with intermediate to late AMD.

Important strengths of this study include the longitudinal prospective nature, large sample size, standardized examinations, and the centralized grading of the lens photographs. An additional strength of the study was the collection and analyses of data on a large number of potentially important covariates.

Our study raises important questions about some of the most commonly used drugs in the population. Additional studies in other populations are needed to determine whether use of statins increases the risk of cataract and whether cataract outcomes with statin use are influenced by sex or age group. Currently, patients should be encouraged to take statins when medically indicated and maintain regular eye exams.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Table 2

Results of the Age-Adjusted Cox Regression of the Effect of Statins on Cataract Progression: Hazard Ratios and 95% Confidence Limits using Unmatched Statin-Use Propensity Scores.

| | N | HR | 95% CI |
|---|---|---|---|
| **Cataract surgery incidence** | | | |
| All participants | 2771 | **1.90** | **1.17–3.10** |
| Stratified by sex: | | | |
| Females | 1540 | **2.46** | **1.25–4.85** |
| Males | 1231 | 1.48 | 0.74–2.93 |
| Stratified by age group: | | | |
| Age < 75 years | 1824 | **2.52** | **1.20–5.33** |
| Age ≥ 75 years | 947 | 1.41 | 0.74–2.68 |
| **Progression of cortical lens opacity** | | | |
| All participants | 2609 | **1.52** | **1.08–2.12** |
| Stratified by sex: | | | |
| Females | 1438 | **1.67** | **1.03–2.71** |
| Males | 1171 | 1.40 | 0.89–2.20 |
| Stratified by age group: | | | |
| Age < 75 years | 1738 | 1.49 | 0.94–2.36 |
| Age ≥ 75 years | 871 | 1.57 | 0.96–2.58 |
| **Progression of posterior subcapsular lens opacity** | | | |
| All participants | 2673 | **1.84** | **1.25–2.71** |
| Stratified by sex: | | | |
| Females | 1480 | **2.27** | **1.31–3.94** |
| Males | 1193 | 1.51 | 0.89–2.58 |
| Stratified by age group: | | | |
| Age < 75 years | 1768 | **2.11** | **1.22–3.65** |
| Age ≥ 75 years | 905 | 1.54 | 0.88–2.68 |

HR = hazard ratio; CI = confidence interval**. Boldface** hazard ratios and confidence intervals are significant ($P < 0.05$). Analyses of all participants are age and sexadjusted. The analyses stratified by sex are adjusted for age, and the analyses stratified by age are adjusted for age and sex.