The Use of Cholesterol-Lowering Medications and Age-Related Macular Degeneration

Gerald McGwin, Jr, MS, PhD,[1,2] *Aiyuan Xie, MS,*[2] *Cynthia Owsley, MSPH, PhD*[2]

Purpose: To evaluate the association between cholesterol-lowering medications and age-related macular degeneration (AMD).

Design: Case–control study.

Participants: The Atherosclerosis Risk in Communities study is a prospective, population-based, cohort study conducted in 4 communities across the United States. A total of 15792 individuals aged 45 to 65 years were enrolled between 1987 and 1989; fundus photographs were added to the study protocol at the 6-year follow-up (1993–1995). Cases were subjects who were identified as having AMD after applying a standard definition to their fundus photographs; controls did not have AMD.

Methods: The use of cholesterol-lowering medications at any time during the study was determined and compared between cases and controls, adjusting for the potentially confounding effect of demographic, behavioral, and medical characteristics.

Main Outcome Measures: Presence of AMD and the use of cholesterol-lowering medications.

Results: A total of 871 AMD cases and 11 717 controls were identified. Of the AMD cases, 11% made use of cholesterol-lowering medications, as compared with 12.3% of controls (odds ratio [OR], 0.89; 95% confidence interval [CI], 0.71–1.11). Adjusting for the confounding influence of age, gender, and race revealed a statistically significant relationship between AMD and use of cholesterol-lowering medications (OR, 0.79; 95% CI, 0.63–0.99).

Conclusions: The results of this study add to the growing body of evidence that cholesterol-lowering medications may reduce the risk of developing AMD. Additional research is needed to document the mechanism responsible for this association. A clinical trial of the impact of statins on AMD deserves consideration. *Ophthalmology 2005;112:488–494*

3-hydroxy-3-methylgluatryl coenzyme A reductase inhibitors (statins) reduce low-density lipoprotein cholesterol levels, elevations of which are associated with an increased risk of cardiovascular disease (CVD) and associated CVD-related outcomes, including myocardial infarction and stroke.[1] Statin use has also shown to reduce the risk of other conditions, including Alzheimer's disease[2] and fractures[3]; however, studies have not produced consistent findings. Despite this inconsistency, clinical trials on the use of statins to prevent these conditions have been proposed or conducted.[2,3] The association between the use of cholesterol-lowering medications, including statins, and age-related macular degeneration (AMD) has also been evaluated. Although some studies have reported a reduced risk,[4–6] others have found no association,[7–10] and one study has reported an increased risk,[11] which has sparked debate on the appropriateness for a clinical trial on statins and AMD.[12]

The mechanism by which statins might reduce the risk of developing AMD is unknown. Their lipid-lowering effect is an attractive hypothesis because of the accumulation of lipids, including cholesterol, in Bruch's membrane of older eyes and the ubiquitous presence of cholesterol in drusen.[13,14] Epidemiological studies on the association between plasma cholesterol and AMD risk have had inconsistent results.[15–18] However, recent research suggests that cholesterol in the retina may have a local rather than a serum source.[13] Statins have also been shown to have many ancillary properties, such as improving or restoring endothelial function, enhancing the stability of atherosclerotic plaques, and decreasing oxidative stress and vascular inflammation.[19] Thus, it remains open to debate whether the mechanism underlying any association between statin use and

Originally received: July 22, 2004.
Accepted: October 4, 2004. Manuscript no. 240574.

[1] Department of Epidemiology and International Health, School of Public Health, University of Alabama at Birmingham, Birmingham, Alabama.

[2] Department of Ophthalmology, School of Medicine, University of Alabama at Birmingham, Birmingham, Alabama.

This research was supported by the National Eye Institute, Bethesda, Maryland (grant no.: R21-EY14071); the EyeSight Foundation of Alabama, Birmingham, Alabama; and Research to Prevent Blindness, Inc., New York, New York. Dr Owsley is a Research to Prevent Blindness Senior Scientific Investigator.

Correspondence to Gerald McGwin, Jr, MS, PhD, Department of Ophthalmology, School of Medicine, University of Alabama at Birmingham, 700 South 18th Street, Suite 609, Birmingham, AL 35294-0009. E-mail: mcgwin@uab.edu.

ISSN 0161-6420/05/$–see front matter
doi:10.1016/j.ophtha.2004.10.027

AMD is attributable to cholesterol lowering and/or some other ancillary property of statins.

The objective of this study is to evaluate the association between the use of cholesterol-lowering medications and AMD in the Atherosclerosis Risk in Communities (ARIC) study, a large, prospective, population-based cohort study conducted in 4 communities across the United States. This study has several strengths compared with the previous research on this topic,[4–10] including a larger sample size, the availability of retinal photographs for the documentation of AMD, and more information on confounding variables.

Materials and Methods

Study Population

The ARIC study is a prospective epidemiologic study conducted in 4 U.S. communities: Forsyth County, North Carolina; the city of Jackson, Mississippi; the suburbs of Minneapolis, Minnesota; and Washington County, Maryland.[20] The study is designed to investigate the etiology and natural history of atherosclerosis; the etiology of clinical atherosclerotic diseases; and variation in cardiovascular risk factors, medical care, and disease by race, gender, location, and date. Beginning in 1987, each ARIC field center randomly selected and recruited a cohort sample of approximately 4000 individuals aged 45–64 years from a defined population in their community. A total of 15 792 participants received an extensive examination, including medical, social, and demographic data. These participants were reexamined every 3 years, with the first screen (baseline) occurring in 1987–1989, the second in 1990–1992, and the third in 1993–1995. Follow-up occurred yearly by telephone to maintain contact with participants and to assess the health status of the cohort. Of those examined at baseline, 14 346 (93%) and 12 887 (86%) of surviving participants returned for the second and third screenings, respectively. The characteristics of those who did and did not participate in the study have been described previously.[21] This study was approved by the institutional review board of the University of Alabama at Birmingham.

Study Design

A case–control design was used to evaluate the association between the use of cholesterol-lowering medications and AMD. Fundus photographs necessary to classify study participants as having AMD (cases) or not (controls) were taken only at the time of the third screening (1993–1995). Thus, of the 15 972 original study participants, only 12 830 (82% of survivors) returned for the third screening and thus were potentially eligible for inclusion in this study. Retinal photographs were unavailable for 242 of these participants, and thus they were excluded, yielding a total of 12 588 participants for this study.

Case and Control Definitions. Details of the retinal photography procedures are described in detail elsewhere.[22–24] Briefly, after 5 minutes of dark adaptation, a single 45° retinal photograph of one randomly selected eye was taken, centered on the region of the optic disc and macula, using an autofocus camera. Photographs were sent to a centralized reading center in the department of ophthalmology at the University of Wisconsin in Madison, Wisconsin, where trained graders masked to the participant characteristics evaluated the photographic slides for signs of AMD according to a standardized protocol. Extensive quality control procedures were in place to ensure the consistency and quality of the grading and associated data. Specifically, the presence of soft drusen, retinal pigment epithelium (RPE) depigmentation, increased retinal pigment, pure geographic atrophy, and signs of exudative macular degeneration (subretinal hemorrhage, subretinal fibrous scar, RPE detachment, and/or serous detachment of the sensory retina) were determined using a modification of the Wisconsin Age-Related Maculopathy Grading System.[25,26] Soft drusen were defined as having a diameter larger than 63 mm. Depigmentation of the RPE, increased retinal pigment associated with AMD, and pigmentary abnormalities were defined as present or as absent or questionable. For the purposes of quality control, assessment of photographs for 520 participants was repeated; intrarater and interrater agreement was generally good to excellent.

For the purposes of this study, cases were defined as those participants with early or late AMD. Early AMD was defined as the presence of soft drusen alone, RPE depigmentation alone, or a combination of soft drusen with increased retinal pigment and/or depigmentation in the absence of late AMD. Late AMD was defined as the presence of signs of exudative AMD degeneration or pure geographic atrophy. Those who participated in the third screening and had gradable photographs but no signs of early or late AMD were classified as controls.

Variable Selection and Definition. The primary independent variable or risk factor of interest for this study is the use of cholesterol-lowering medications. The use of prescription and nonprescription medications was assessed at each of the 3 screening visits. Those medications used within the 2 weeks preceding the screening visit were ascertained. Participants were instructed to bring all medications taken within the last 2 weeks to the screening visit. The names and concentrations of each medication were abstracted directly from the medication containers. Interviews with participants were also conducted by a study nurse or clinician to verify the use of each medication and to determine if the participant had not brought in all medications. If the participant did not bring in any or all medications, alternative methods of obtaining the necessary medications were pursued (e.g., telephone interview, review of medical data). Interviewers and medication coding specialists were centrally trained and were responsible for providing local staff training in the transcription and coding of medications. For each person certified to code medications, a 10% sample of medication coding records was identified by the Coordinating Center for blinded repeat coding at the field center.

Although medications were collected individually in the ARIC study, they were coded into classes or groups. The primary independent variable of interest is the use of cholesterol-lowering medications. This classification includes the following specific medications: statin, cholestyramine, clofibrate, colestipol, gemfibrozil and others related to bile sequestrants, antihyperlipidemic medications, and vitamin B_3. The coding of medication information into classes in the ARIC study precludes analyses according to specific medications (e.g., statins) because this information was not noted in the coding process. In classifying participants as users or nonusers of cholesterol-lowering medications, information from all 3 screening visits was considered. That is, those participants who reported using cholesterol-lowering medications during at least 1 study screening were classified as users; the remaining participants were classified as nonusers.

Because of the observational nature of this study, it is necessary to evaluate the association between cholesterol-lowering medications and AMD independent of the potentially confounding effect of demographic, behavioral, and medical characteristics. In addition to demographic characteristics (i.e., age, gender, race), information on behavioral and medical characteristics was also obtained. With respect to behavioral characteristics, information pertaining to cigarette smoking and alcohol consumption was noted, and participants were classified as current or former users or those who never used. The medical characteristics of interest