3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase Inhibitors and the Presence of Age-Related Macular Degeneration in the Cardiovascular Health Study

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Objective: To evaluate both the use of cholesterol-lowering medications as a group and the use of statins specifically with regard to the risk of age-related macular degeneration (AMD).

Methods: A case-control study was conducted using data from the Cardiovascular Health Study, a population-based prospective study of adults enrolled from 4 communities in the United States in 1989 and 1990. Individuals with AMD (cases) and those without AMD (controls) were compared with regard to their use of cholesterol-lowering medications and statins.

Results: Nearly equal proportions of cases and controls used cholesterol-lowering medications, both before adjustment (odds ratio, 0.92; 95% confidence interval, 0.70-1.21) and after adjustment for selected confounding variables (age, sex, and race) (odds ratio, 1.35; 95% confidence interval, 0.98-1.87). Statin use was also found to be similar among cases and controls (odds ratio, 0.98; 95% confidence interval, 0.73-1.30). After controlling for the aforementioned 3 confounders (odds ratio, 1.40; 95% confidence interval, 0.99-1.98), we noted a modest trend for statin users to have an increased risk of AMD.

Conclusion: The results suggest that no association exists between having used cholesterol-lowering medications and AMD. However, there was a suggestion that statin use might increase the risk of AMD.


Recent recommendations for the aggressive use of antihyperlipidemic medications to lower low-density lipoprotein (LDL) cholesterol levels have contributed to a rising trend in the prescription of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors or statins to reduce the risk of cardiovascular disease (CVD) and CVD-related outcomes such as myocardial infarction and stroke.1-4 The main mechanism thought to account for the reduced risk of CVD and CVD-related outcomes is lowered serum cholesterol levels and the subsequent prevention or possible reversal of atherosclerotic plaques. Reports have also emerged suggesting that statin use may reduce the risk of other diseases (eg, osteoporosis, dementia, and depression), although findings have been inconsistent.5-11 Included among the list of conditions reportedly associated with statin therapy is age-related macular degeneration (AMD). As with other noncardiovascular outcomes, the mechanism of protection and the evidence for a protective association between statin use and AMD has been equivocal. While some studies observed a clinical benefit,12-14 at least an equal number found no association,15-17 and 1 study suggested an increased risk of AMD with statin use.18

One of the factors believed to potentially play an etiological role in the development of AMD is cholesterol. Although the mechanism by which cholesterol may contribute to AMD is not well defined, studies have found larger deposits of cholesterol within the extracellular lesions of AMD, known as drusen, in older adults compared with younger adults.19,20 Furthermore, the lipids involved in the pathogenesis of atherosclerosis, such as apolipoprotein B and E, are also located within these lesions.21,22 and clinical measures of atherosclerotic severity (eg, carotid artery thickness and ankle-arm index) have shown that the pathological lesions of atherosclerosis (atherosclerotic plaques) are positively correlated with AMD.23 These findings have led to the hypothesis that statins may slow, stabilize, or reverse the progression of AMD in a manner similar to CVD, ie, by lowering serum and/or ocular cholesterol concentrations. However,
several epidemiologic studies have reported that no association between plasma cholesterol levels and AMD exists. While others have found that lower plasma cholesterol levels increased the risk of AMD. Apart from lowering cholesterol levels, there is evidence that other statin effects, ie, restoration of endothelial cell function, enhancement of atherosclerotic plaque stability, and reduction of oxidative stress and vascular inflammation, may influence the natural history of AMD. Thus, the pleiotropic effects of statins, though well characterized for cardiovascular outcomes, have yet to be definitively linked to a reduction in AMD risk.

METHODS

STUDY POPULATION

The current study seeks to address the relationship between the use of statins and other cholesterol-lowering medications and AMD in the Cardiovascular Health Study, a population-based prospective study designed to identify modifiable risk factors related to the onset of coronary heart disease and stroke in older adults. The study population has been described in detail elsewhere. In brief, participants were sampled from Health Care Financing Administration Medicare eligibility lists in 1 of 4 communities: Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pennsylvania. Eligibility was contingent on the following inclusion criteria: individuals were aged 65 years or older; were not institutionalized at the time of examination; were expected to remain in the area for the next 3 years; were able to provide informed consent; and did not require a proxy respondent at baseline. Potentially eligible individuals who were wheelchair-bound or receiving hospice treatment, radiation therapy, or chemotherapy for cancer at baseline were excluded. A bialennial cohort of 5201 men and women was ultimately enrolled and evaluated annually for previously described physical and laboratory health parameters. Characteristics of those who did and did not participate in the study have also been described previously.

STUDY DESIGN

We employed a case-control design to evaluate the association between cholesterol-lowering medication use in general, statin use specifically, and the presence of AMD. Fundus photographs to classify study participants as cases (AMD) or controls (no AMD) were taken at 1 visit in 1997 or 1998. In this time frame, 4249 participants (95.5% of survivors) returned for a clinic examination. Photographs for 1494 participants were either unavailable or unreadable, leaving 2755 participants with photographs available for analysis.

CASE AND CONTROL DEFINITION

Retinal photography procedures in the Cardiovascular Health Study were similar to those reported for the Atherosclerosis Risk in Communities Study. After 5 minutes of dark adaptation, a single 45° retinal photograph centered on the region of the optic disk and macula of a randomly selected eye was taken using an autofocus camera. Trained graders at the Fundus Photograph Reading Center (University of Wisconsin, Madison), who were masked to participant characteristics, evaluated the photographic slides for signs of AMD according to standardized protocols.

The participants' AMD status was assessed according to the modified Wisconsin Age-Related Maculopathy grading system. Measures used to evaluate AMD included presence of soft drusen, depigmentation of the retinal pigment epithelium (RPE), 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). Soft drusen was defined as a diameter larger than 63 mm. Depigmentation of the RPE, increased retinal pigment associated with AMD, and pigmentary abnormalities were defined as present, absent, or questionable. 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 geography atrophy. Those who participated in the 1997 and 1998 study visit who had gradable photographs but no signs of early or late AMD were classified as controls.

VARIABLE SELECTION AND DEFINITION

The primary independent risk factors of interest in the current study were use of any statin or other cholesterol-lowering medication. As instructed, participants brought to each annual visit all medications taken within the preceding 2 weeks. Medication use was ascertained by abstracting the name and concentration of each medication directly from the medication container. Study nurses or clinicians also conducted interviews with participants for the purpose of verification. Cholesterol-lowering medications were coded as statins, antihyperlipidemics, bile sequestrants, gemfibrozil, cholestyramine, clofibrate, colestipol, or vitamin B3. In classifying participant use of cholesterol-lowering medications, information from all annual visits leading up to the retinal photograph visit was considered. That is, participants were classified as users if they reported using cholesterol-lowering medications at 1 or more study visits.

Data on demographic characteristics (ie, age, sex, race), behavioral characteristics (ie, cigarette smoking, alcohol consumption), medical characteristics (ie, systolic and diastolic blood pressure, body mass index, high-density lipoprotein levels, LDL levels, total serum cholesterol levels), and information about selected chronic diseases (diabetes, hypertension, stroke, CVD) that might confound the association between cholesterol-lowering medications and AMD were also collected and included in the analysis. Smoking, alcohol consumption, and body mass index were defined using data from the retinal photograph visit, whereas we considered plasma lipid levels, blood pressure, and the presence of selected chronic medical conditions from all visits.

STATISTICAL ANALYSIS

Cases and controls were compared with respect to demographic, behavioral, and medical characteristics using χ² and t tests for categorical and continuous variables, respectively. Logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between AMD and the use of cholesterol-lowering medications. Odds ratios were calculated with and without consideration of potential confounding factors. In the multivariable analysis, we took 2 approaches. The first included all demographic, behavioral, and medical variables, regardless of their impact on the magnitude or statistical significance of the association between AMD and...
cholesterol-lowering medication use. A second, more parsimonious approach retained only those variables that appeared on bivariate analysis to be confounders, thus allowing for more precise estimates of the association between AMD and cholesterol-lowering medications. Determination of which confounding variables should be retained was based on change-in-estimate criteria. Two-sided P values of \( \leq 0.05 \) were considered statistically significant.

### RESULTS

Of the 2755 participants included in this study, 390 exhibited AMD (cases) and 2365 did not (controls). Among the cases, 360 had early AMD and 30 had late AMD. Table 1 presents the demographic, behavioral, and medical characteristics among cases and controls. Cases were more likely to be older (\( P < 0.001 \)) and white (\( P < 0.001 \)) than controls. Moreover, cases were significantly more likely to have a lower body mass index (\( P = 0.02 \)) and a lower total cholesterol level (\( P = 0.04 \)) than the controls. Otherwise, case and control groups were similar with regard to sex, smoking status, alcohol consumption, and medical conditions. However, there was a modest trend for cases to have diabetes less often than controls (\( P = 0.08 \)) and lower levels of LDL cholesterol (\( P = 0.07 \)).

In the univariate analysis, we found that nearly equal proportions of cases and controls used cholesterollowering medications (OR, 0.92; 95% CI, 0.70–1.21) (Table 2). The absence of a significant association remained after adjusting for all other variables (OR, 1.06; 95% CI, 0.81–1.40) and selected variables (age, sex, and race) (OR, 1.35; 95% CI, 0.98–1.87). Likewise, when the OR was calculated for statin use and risk of AMD, statin use was found to be similar among cases and controls (OR, 0.98; 95% CI, 0.73–1.30). However, after controlling for all demographic, behavioral, and medical variables (OR, 1.13; 95% CI, 0.84–1.51) or the aforementioned 3 confounders (OR, 1.40; 95% CI, 0.99–1.98), a modest trend of increased risk for AMD in the cases appeared.

When cases were limited to early AMD, after adjusting for age, sex, and race, no significant association was observed for the use of any cholesterol-lowering medication (OR, 1.10; 95% CI, 0.83–1.46) or statin use specifically (OR, 1.18; 95% CI, 0.88–1.59). For late AMD, a protective association was observed for both any cholesterol-lowering medication and statin use (OR, 0.58; 95% CI, 0.17–1.95, and OR, 0.46; 95% CI, 0.11–1.99, respectively), yet neither association was statistically significant (Table 2). Yet neither association was statistically significant.

### COMMENT

The results of the present study suggest that persons with AMD are equally likely as those without AMD to have ever used any cholesterol-lowering medication or statin. Several studies to date have evaluated the relationship between lipid-lowering agents and AMD and found conflicting results. Three prospective population-based cohort studies from the United States, the Netherlands, and Australia consistently found no association between the use of a lipid-lowering agent and the risk of developing AMD. Conversely, 2 cross-sectional studies from the United Kingdom and Australia and 1 nested case-control study from the United States reported that individuals with AMD were less likely to have used statins. The reason for the variability in reported associations is likely to be multifactorial. In most of the prior studies, measurement of drug use was largely based on information obtained from standardized interviews. In some instances, responses about medication usage were verified by physical inspection of prescription bottles. Nonetheless, reliance on self-report creates a potential for misclassification of exposure that can vary across studies in magnitude and direction.

The primary exposure of interest also differs among studies. The 3 population-based cohort studies that found no effect evaluated the overall association between any lipid-lowering medication and AMD while the 3 studies that observed a significant association focused specifically on statins. Therefore, a potential effect of statin...
therapy on the incidence of AMD in the former studies could have been attenuated by weaker associations with other types of antihyperlipidemic medications. In fact, McGwin et al. found a protective association for statins that did not extend to other classes of lipid-lowering drugs. The present study also evaluated the association between AMD and cholesterol-lowering agents generally or statins specifically but found no effect with respect to either. A key difference between the current and prior case-control studies is that the latter restricted its study population to incident cases. By including prevalent cases of AMD in the present study, we are limited in making inferences about the temporal relationship between drug exposure and disease. The 2 studies also differed in the proxy measures used to assign exposure. In the present study, drug exposure was measured according to the same methods employed by the aforementioned studies. McGwin et al., however, studied a Veterans Administration hospital–based cohort and were therefore able to assess dates and dosages of statin use by examining prescription files from hospital databases. The greater possibility for nondifferential misclassification of exposure category in the current study may partially explain a potential bias toward a null result.

The current debate about the utility of cholesterol-lowering agents, particularly statins, as preventive measures against developing AMD draws not only on the current pharmacoepidemiological literature but also on research into the role of lipids in the pathogenesis of AMD. Our finding that total serum cholesterol levels were lower in patients with AMD corroborates several similar studies including the first National Health Examination and Nutrition Survey. Such evidence may seem contrary to the proposed atherosclerotic-like theory of AMD wherein statins are expected to be protective. However, Klein et al. recently proposed the idea that an atherogenic lipid profile (high LDL levels and low high-density lipoprotein levels) may actually offer protection from AMD by reducing the contribution of cholesterol to drusen. Interestingly, this line of reasoning implies that by lowering serum cholesterol levels with statins, an increased amount of cholesterol may be taken up by the RPE cells with a subsequent increased deposition in drusen and an increased risk of AMD. Evaluating the complex relationship between serum cholesterol, statin use, and AMD based on existing data sources has been problematic because of the retrospective nature of most studies to date.

Whether statins represent a viable mechanism for preventing or slowing AMD is still an issue of current debate that can best be resolved by designing adequately powered observational studies specifically to evaluate the impact of statins on the incidence of AMD. These studies should pay particular attention to the limitations inherent across published studies to date such that these issues are sufficiently resolved.

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