# Statins and Other Cholesterol-Lowering Medications and the Presence of Glaucoma

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**Objective:** To explore whether oral statin and other antihyperlipidemic medications are associated with open-angle glaucoma.

**Methods:** The administrative clinical databases maintained at the Veterans Affairs Medical Center, Birmingham, Ala, were used to conduct a matched case-control study. Cases were all male patients aged 50 years and older with a new diagnosis of glaucoma on an outpatient or inpatient visit during the period January 1, 1997, through December 31, 2001. Ten control subjects were matched to each case according to age (within 1 year). Prescription files were assessed for statin use as well as additional medications to lower cholesterol levels. Information on comorbid medical conditions was also obtained. Conditional logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs).

**Results:** Longer duration of statin use was associated with a lower risk of open-angle glaucoma (*P* for trend=.04) primarily among subjects with 24 months or more of use (OR, 0.60; 95% CI, 0.39-0.92). When stratified by comorbid medical condition, among those with cardiovascular disease (OR, 0.63; 95% CI, 0.42-0.97), lipid metabolism disorders (OR, 0.63; 95% CI, 0.41- 0.99), and the absence of cerebrovascular disease (OR, 0.76; 95% CI, 0.58-0.99), statins demonstrated a protective effect on open-angle glaucoma. Finally, a protective association was also observed among those who used nonstatin cholesterol-lowering agents (OR, 0.59; 95% CI, 0.37-0.97).

**Conclusions:** Initial examination of an administrative clinical database indicates the intriguing possibility that long-term use of oral statins may be associated with a reduced risk of open-angle glaucoma, particularly among those with cardiovascular and lipid diseases. Nonstatin cholesterol-lowering agents were also associated with a reduced risk of having open-angle glaucoma. Additional investigation is warranted as to whether these classes of agents may provide an additional therapeutic addition for glaucoma.

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THE USE OF STATINS HAS BEEN associated in some studies with a diminished risk of developing age-related macular degeneration as well as a potential for reducing risk for several medical conditions related to cardiovascular disease.[1-4] The presumed direct causal mechanisms have centered on the effect of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors in reducing cholesterol production and enhancing low-density lipoprotein cholesterol removal from plasma. To the extent that excess total cholesterol or low-density lipoprotein cholesterol is implicated in these conditions, use of the statins would reduce the risk of developing these conditions, or at least delay their onset. Another potential mechanism may be their inhibition of nonsteroidal isoprenoid production, in which processes associated with atherosclerotic progression may be likewise inhibited.[5-7] Many statins also inhibit rho-kinase activity, which has been shown to increase aqueous outflow.[8] Finally, there may be as yet undiscovered or indirect effects of these compounds to help explain their protective associations.

With a greater understanding of the multiple mechanisms that could potentially affect the outflow system or the optic nerve in glaucoma, there are plausible means by which statin use could be associated with a reduced risk of developing glaucoma. By reducing atherosclerotic processes and subsequent vascular diseases, statins may directly protect optic nerve head vasculature or may indirectly improve ocular blood flow. Since the trabecular meshwork has endothelial cells that share many attributes of vascular endothelial cells, statins may also exert a pro-

tective effect in enhancing trabecular endothelial cell function. Thus, in this article, we seek to address the issue of whether in a large cohort of patients the use of statins is associated with open-angle glaucoma.

## METHODS

### STUDY POPULATION AND DATA SOURCE

The Birmingham (Alabama) Department of Veterans Affairs Medical Center (BVAMC) is a 134-bed acute tertiary care medical facility and serves as a Veterans Hospital Administration tertiary care referral center for Alabama. All patients who had at least one visit (inpatient or outpatient) to the BVAMC between January 1, 1997, and December 31, 2001, were eligible for study inclusion. Because the prevalence of glaucoma is low in individuals younger than 50 years, the study population was limited to patients aged 50 years and older. Women were also excluded because they represented such a small proportion of the patient population (10.8%) that meaningful analyses were impossible.

The BVAMC provided data files containing demographic information (age, sex, race) and clinical and medication information for each patient. The clinical file contained a description of each diagnosis made at the BVAMC during inpatient and outpatient visits and the diagnosis date. All diagnoses were coded using the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*).[9] The medication file contained information on each medication prescribed during each patient visit. This file also contained the prescription date and the date the prescription was filled. For both the clinical and medication files, the information provided pertained to all diagnoses and medications during the course of each patient's history with the BVAMC and not just 1997 through 2001. All data received from the BVAMC contained no information that would allow patients to be identified. The institutional review board of the BVAMC approved the protocol.

### STUDY DESIGN

Within the study population, a nested case-control study was conducted. Cases of glaucoma were defined using the *ICD-9-CM* codes 365.1 (open-angle glaucoma), 365.8 (other specified forms of glaucoma), and 365.9 (unspecified glaucoma). Information on the glaucoma diagnosis date was procured and will heretofore be referred to as the index date. Because this study addressed the association between statin use and the new diagnosis of glaucoma, patients who had a glaucoma diagnosis prior to the observation period of the study (prevalent cases) were excluded.

Control subjects were randomly selected from the study population who did not have a glaucoma diagnosis by the end of the observation period. To be considered an eligible control subject for a given case, the control subject must have had an encounter with the BVAMC (inpatient or outpatient) on or before the index date of the matched case. Ten control subjects were selected for each case and matched on age (±1 year). Each control subject was assigned the index date associated with their matched case.

The prescription file was queried for the presence of filled statin (atorvastatin calcium, cerivastatin sodium, fluvastatin sodium, pravastatin sodium, simvastatin, lovastatin) prescriptions. Nonstatin lipid-lowering agents (eg, fibrates, nicotinic acid) were also extracted from the prescription file. Only those prescriptions that were filled prior to the index date for each matched set of cases and control subjects were considered. Time since first statin use was calculated as the time between the first statin prescription and the index date. Statin users were also classified as being current or past users with the former being those who had a statin prescription filled within 6 months before the index date and the latter being those whose last prescription fill date was greater than 6 months before the index date. An analogous set of variables was created for the nonstatin lipid-lowering agents.

Information on the presence of the following conditions was extracted from the clinical data file: ischemic heart disease (*ICD-9-CM* codes 410-414); cerebrovascular disease (*ICD-9-CM* codes 430-438); lipid metabolism disorders (*ICD-9-CM* code 272); hypertension (*ICD-9-CM* codes 401-405); diseases of the arteries, arterioles, and capillaries (*ICD-9-CM* codes 440-448); and diabetes (*ICD-9-CM* code 250). For the purposes of analysis, only those diagnoses that were recorded prior to the index date were considered.

**Table 1. Demographic and Medical Characteristics Among Glaucoma Cases and Control Subjects***

| | Cases (n = 667) | Control Subjects (n = 6667) | *P* Value |
|---|---|---|---|
| Demographic characteristics | | | |
| Age, y, mean | 69 | 69 | .93 |
| Race, | | | <.001 |
| White | 252 (37.8) | 3162 (47.4) | |
| African American | 193 (28.9) | 939 (14.1) | |
| Other | 9 (1.4) | 26 (0.4) | |
| Unknown | 213 (31.9) | 2540 (38.1) | |
| Medical characteristics | | | |
| Diabetes | 172 (25.8) | 818 (12.3) | <.001 |
| Lipid metabolism disorders | 100 (15.0) | 545 (8.2) | <.001 |
| Hypertension | 341 (51.1) | 1811 (27.2) | <.001 |
| Cardiovascular disease | 130 (19.5) | 1312 (19.7) | .91 |
| Cerebrovascular disease | 50 (7.5) | 453 (6.8) | .49 |
| Arterial disease | 41 (6.2) | 368 (5.5) | .50 |

*Values are expressed as number (percentage) of individuals unless otherwise indicated.

### STATISTICAL ANALYSIS

Conditional logistic regression was used to calculate an odds ratio (OR) and 95% confidence interval (CI) for the association between any statin use and the risk of developing glaucoma. The ORs and 95% CIs were also estimated for current and past statin users relative to nonusers and according to time since first prescription. A similar set of analyses was conducted for nonstatin lipid-lowering agents. Stratified analyses were conducted to determine if diabetes, lipid metabolism disorders, hypertension, cardiovascular disease, cerebrovascular disease, and arterial disease modified the association between statin use and glaucoma. There was an insufficient number of patients using nonstatin lipid-lowering agents to conduct a similar set of stratified analyses.

## RESULTS

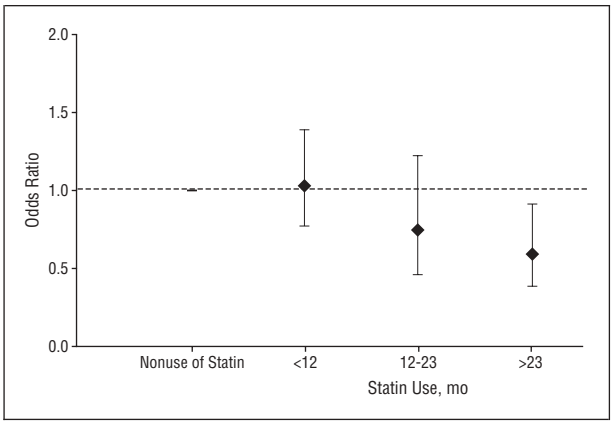
We selected 667 cases; 170 had a diagnosis of open-angle glaucoma (*ICD-9-CM* code 365.1), 31 had other specified forms of glaucoma (*ICD-9-CM* code 365.8), and 466 had unspecified glaucoma (*ICD-9-CM* code 365.9).

**Table 1** presents the demographic and medical characteristics among the glaucoma cases and control subjects. By design, the mean age of both cases and control subjects was equivalent. There were twice as many Af-

**Table 2. Statin and Nonstatin Medication Use Characteristics Among Glaucoma Cases and Control Subjects and Associated Odds Ratios (ORs) and 95% Confidence Intervals (CIs)***

| | Cases (n = 667) | Control Subjects (n = 6667) | OR (95% CI) | OR (95% CI)† |
|---|---|---|---|---|
| Statin use characteristics | | | | |
| Statin use | | | | |
| No | 548 (82.2) | 5663 (84.9) | 1.00 | 1.00 |
| Yes | 119 (17.8) | 1004 (15.1) | 1.23 (0.99-1.51) | 0.85 (0.66-1.09) |
| Current use | 71 (10.6) | 535 (8.0) | 1.37 (1.06-1.78) | 0.94 (0.70-1.27) |
| Past use | 48 (7.2) | 469 (7.0) | 1.06 (0.78-1.44) | 0.74 (0.53-1.04) |
| Duration of use, mo | | | | |
| No use | 548 (82.2) | 5663 (84.9) | 1.00 | 1.00 |
| <12 | 68 (10.2) | 507 (7.6) | 1.39 (1.06-1.81) | 1.03 (0.77-1.39) |
| 12-23 | 21 (3.2) | 191 (2.9) | 1.14 (0.72-1.80) | 0.75 (0.46-1.23) |
| >23 | 30 (4.5) | 306 (4.6) | 1.01 (0.69-1.49) | 0.60 (0.39-0.92) |
| Nonstatin cholesterol-lowering medication use characteristics | | | | |
| Nonstatin agent use | | | | |
| No | 647 (97.0) | 6441 (96.6) | 1.00 | 1.00 |
| Yes | 20 (3.0) | 226 (3.4) | 0.88 (0.55-1.40) | 0.59 (0.37-0.97) |
| Current use | 8 (1.2) | 91 (1.4) | 0.88 (0.42-1.81) | 0.60 (0.29-1.27) |
| Past use | 12 (1.8) | 135 (2.0) | 0.89 (0.49-1.61) | 0.59 (0.32-1.09) |
| Duration of use, mo | | | | |
| Non use | 647 (97.0) | 6441 (96.6) | 1.00 | 1.00 |
| <12 | 8 (1.2) | 138 (2.1) | 0.58 (0.28-1.18) | 0.38 (0.18-0.79) |
| = 12 | 12 (1.8) | 88 (1.3) | 1.36 (0.74-2.50) | 0.95 (0.50-1.79) |
| Statin and nonstatin use characteristics | | | | |
| Neither statin nor nonstatin | 538 (80.7) | 5558 (83.4) | 1.00 | 1.00 |
| Statin use only | 109 (16.3) | 883 (13.2) | 1.28 (1.03-1.59) | 0.86 (0.66-1.11) |
| Nonstatin use only | 10 (1.5) | 105 (1.6) | 0.98 (0.51-1.89) | 0.60 (0.30-1.18) |
| Statin and nonstatin use | 10 (1.5) | 121 (1.8) | 0.85 (0.45-1.64) | 0.52 (0.26-1.04) |

*Values are expressed as number (percentage) of individuals unless otherwise indicated.
†Adjusted for diabetes, lipid metabolism disorders, hypertension, cardiovascular disease, cerebrovascular disease, and arterial disease.




Association between glaucoma and duration of statin use.

rican American individuals among the cases compared with control subjects. Those with glaucoma were more likely to also have diabetes, lipid metabolism disorders, and hypertension.

**Table 2** demonstrates the statin and nonstatin medication use characteristics among glaucoma cases and control subjects, as well as the unadjusted and adjusted ORs. While cases were more likely to have filled a statin prescription (OR, 1.23; 95% CI, 0.99-1.51), following adjustment for diabetes, lipid metabolism disorders, hypertension, cardiovascular disease, cerebrovascular disease, and arterial disease, a protective association was observed (OR, 0.85; 95% CI, 0.66-1.09), albeit not a statistically significant one. This association, although not significant, was also observed for past (OR, 0.74; 95% CI, 0.53-1.04) but not current (OR, 0.94; 95% CI, 0.70-1.27) statin use. There was a significant trend toward a reduced risk of glaucoma with longer-term statin use ($P$=.04) (**Figure**). Indeed, use of statins for greater than 23 months was associated with a statistically significant reduction in the risk of glaucoma (OR, 0.60; 95% CI, 0.39-0.92).

Use of nonstatin lipid-lowering medications was also associated with a significantly reduced risk of glaucoma (OR, 0.59; 95% CI, 0.37-0.97) that was also apparent among both current and past users, although neither association was statistically significant. However, this association was limited to those with less than 12 months of use (OR, 0.38; 95% CI, 0.18-0.79). When considering the joint effect of statin and nonstatin medications, the largest risk reduction was associated with use of both types of medications (OR, 0.52), followed by nonstatin use only (OR, 0.60), and statin use only (OR, 0.86). However, none of these associations were statistically significant.

**Table 3** presents ORs and 95% CIs for the association between statin use and glaucoma stratified according to the presence of comorbidities. Once the other medical characteristics were controlled for, significant associations between statin use and glaucoma were observed among those with lipid metabolism disorders, cardiovascular disease, and those without cerebrovascular disease.

## COMMENT

The results of this analysis demonstrate a significant and meaningful association between glaucoma and long-term statin use. Evaluating larger datasets with longer follow-up periods, such as those with managed care companies or with insurance company claims files where both disease and pharmacy data are maintained, would allow a more definitive evaluation of the possibility of statins being an additional therapy for glaucoma or its prevention.

Such an endeavor is clearly worthwhile, based not only on the results of the current study but also on some plausible potential mechanisms whereby such a protective effect might occur. First, many statins inhibit the activity of rho kinase; such inhibition has been shown to enhance aqueous outflow and thereby presumably lower intraocular pressure.[8] Since we did not have access to medical record data in this study, it would be interesting for other investigators to examine the effect of statin use on the level of intraocular pressure, controlling for the status of glaucoma and the intensity of treatment. Second, the ability of statins to reduce cardiovascular disease may directly or indirectly protect the vascular supply to the optic nerve or eye. Interestingly, statin use is associated with a higher, albeit not statistically meaningful, elevation of risk of glaucoma among those with cerebrovascular disease compared with a lower risk among those with cardiovascular disease. This may indicate that the direct and indirect mechanisms have opposing effects or that there are additional factors at work that have yet to be identified.

If the trend and the magnitude of effect seen with statin use of greater than 23 months is upheld with larger sample sizes in future studies, the protective effect will rival that of lowering intraocular pressure through the use of medications discussed in the Ocular Hypertension Treatment Study[10] and of other treatments discussed in other studies.[11] This would also imply that a new therapeutic class of agents might be effective for the care and treatment of patients with glaucoma.

The adverse effects of statins on ocular structures have been studied to a limited degree. While animal models might indicate a higher risk of cataract development because of the rho-kinase inhibition of statins, human studies have demonstrated no elevated risk of cataracts among those taking statins.[12,13] Obviously, longer-term follow-up across many years will be needed to be able to conclude that such long-term use is completely safe for the eye. In addition, the potential systemic adverse effects of statins need to be carefully considered, as do the costs of the medications. Lastly, the ability to topically administer statins or statin-like compounds has yet to be investigated.

The intriguing finding of some protective association with nonstatin use also raises the possibility that lipid diseases as a whole may be associated with the presence of glaucoma, as seen in the higher proportion of cases with lipid disorders compared with control subjects. There have been no studies to suggest this is the case in population-based evaluations to date. Nevertheless, the associations found here, both in the protective association with cholesterol-lowering agents and the higher rate of lipid disorders seen in those with glaucoma compared with control subjects, suggest that such inquiry is warranted. Thus, additional work is also needed to clarify the nature of the association between the presence of lipid disorders and the use of medications to lower lipids. The evidence in favor of an independent role for treatment, however, is found in the significant OR of 0.63 among those with lipid disorders who have received statin treatment compared with those who have not, even after adjusting for comorbid conditions.

**Table 3. Odds Ratio (ORs) and 95% Confidence Intervals (CIs) for the Association Between Statin Use and Glaucoma Stratified According to Presence of Medical Conditions**

| | OR (95% CI) | Adjusted OR (95% CI)* |
|---|---|---|
| Diabetes | | |
| No | 1.12 (0.87-1.46) | 0.79 (0.58-1.07) |
| Yes | 0.97 (0.67-1.40) | 0.97 (0.63-1.50) |
| Lipid metabolism disorders | | |
| No | 1.11 (0.85-1.46) | 0.97 (0.73-1.30) |
| Yes | 0.57 (0.37-0.88) | 0.63 (0.41-0.99) |
| Hypertension | | |
| No | 1.40 (1.01-1.95) | 1.05 (0.72-1.53) |
| Yes | 0.71 (0.54-0.94) | 0.75 (0.54-1.03) |
| Cardiovascular disease | | |
| No | 1.59 (1.23-2.06) | 0.98 (0.73-1.33) |
| Yes | 0.81 (0.55-1.18) | 0.63 (0.42-0.97) |
| Cerebrovascular disease | | |
| No | 1.17 (0.94-1.47) | 0.76 (0.58-0.99) |
| Yes | 1.65 (0.89-3.06) | 2.01 (0.99-4.10) |
| Arterial disease | | |
| No | 1.26 (1.01-1.57) | 0.86 (0.66-1.11) |
| Yes | 0.87 (0.42-1.80) | 0.74 (0.32-1.72) |

*Adjusted for diabetes, lipid metabolism disorders, hypertension, cardiovascular disease, cerebrovascular disease, and arterial disease where appropriate.

Among those without cerebrovascular disease, there was a protective association between statin use and glaucoma (OR, 0.76; 95% CI, 0.58-0.99), whereas those with cerebrovascular disease demonstrated a positive association between statin use and glaucoma (OR, 2.01; 95% CI, 0.99-4.10). This result is difficult to interpret. This could be a spurious association or an anomaly in the data or results. Alternatively, it may reflect the more general state of vascular supply to the central nervous system. Those without a history of cerebrovascular disease have a statin association similar to the other subpopulations and the population as a whole in this study. Those with a history may reflect a strong difficulty in vascular flow that overrides the effects of statins because even those who do not use statins have an elevated, albeit not significant, risk of glaucoma (OR, 1.65). Further, those who have such conditions and who have been placed on statins may have cerebrovascular disease of greater severity than those who do not.

The study has several limitations that should be kept in mind. First, the study population consisted entirely of men because it was an older veteran population. Additional research on the association between statin use and glaucoma among women is necessary. Second, the diagnoses of glaucoma were made by individual physi-

cians without the use of standardized criteria, which could introduce significant differences relative to other studies and study populations. However, there is no reason to expect the diagnosis of glaucoma to have been biased by the use of statins. Third, the diagnoses were subject to miscoding into *ICD-9-CM* codes; again, however, there is no reason to suspect that bias would result from this. Also, we included nonspecified forms of glaucoma assuming these were likely to reflect open-angle glaucoma that was imprecisely coded. To the extent that they truly represent other forms of glaucoma that are not associated with statin use, the bias so introduced would be toward the null. It should also be noted that while the majority of cases had visited the optometry and/or ophthalmology clinics at the BVAMC, only 40% of the control subjects had made such a visit, thus introducing the potential for misclassification of glaucoma. Fourth, no clinical data was available, so we could not comment on the severity of glaucoma. Fifth, statin use was defined on the basis of a filled prescription within the BVAMC pharmacy service. This suggests that a patient with a statin prescription record but no matching fill record would be classified as a nonstatin user even though he did indeed use statins by filling the prescription outside the BVAMC system. Such misclassification, however, would only bias to the null. Additionally, since more than 90% of statin prescriptions were filled at the BVAMC, this is unlikely to have produced a significant effect. We also did not have information on statin use outside the veteran affairs system. Thus, we may have underestimated some subjects' duration of use. As long as such misclassification is not differential according to case status, then the effect on the study results is likely to be minimal. Finally, race was unknown for a large proportion of our study population (both cases and control subjects). However, the race distribution among those with known data was similar to what would be expected given population-based studies and thus unlikely to introduce spurious results in the analyses. When stratified according to race, the protective association of statin use was apparent among white individuals (OR, 0.56) and African American individuals (OR, 0.76) as well as those with unknown race (OR, 0.58). Given the consistency of the associations, even if race had been known for all subjects, adjustment would likely have had little effect on the observed results. Information on additional potentially confounding characteristics (eg, smoking) was similarly not available.

An important methodological issue is the possibility of left-censored data in that many patients with preexisting glaucoma would have been captured in the first or second year of the study, because case identification was made on the basis of the first visit at which an open-angle or unspecified type of glaucoma was diagnosed. Thus, we fully expect that many of the new diagnosis cases of glaucoma were actually prevalent cases that were first seen at the BVAMC and recorded into the database and captured by our selection algorithm as a new diagnosis case because of the enrollment intervals. To address this issue, the analyses were also conducted including the prevalent cases, and the results were highly consistent with those reported herein.

In summary, the results of the current study thus suggest that the association between statin use and the risk of glaucoma deserves further investigation. Any such study should address the difficulties faced when using administrative data sources such as in the present study. If confirmation is forthcoming, a randomized clinical trial of the use of statins or other antilipid/cholesterol-lowering agents may lead to the application of a new class of medications for the treatment of glaucoma.

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