EXTENDED REPORT

The association between statin use and age related maculopathy

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Aims: To evaluate the association between age related maculopathy (ARM) and statin use.
Methods: A nested case-control study among patients at the Veterans Affairs Medical Center in Birmingham, Alabama, with newly diagnosed ARM (cases) between 1997 to 2001 were selected and age matched to non-ARM controls.
Results: 550 incident cases of ARM were identified and matched to 5500 controls. Overall, cases were 70% (OR 0.30, 95% CI 0.21 to 0.45) less likely to have received and filled a statin prescription relative to the controls. This association was present among both current and past (OR 0.34, 95% CI 0.21 to 0.53 and OR 0.26, 95% CI 0.14 to 0.47, respectively) statin users. When considering use of statin and/or non-statin lipid lowering medications, a significant risk reduction was observed for statin only users (OR 0.30, 95% CI 0.20 to 0.45) and combined statin and non-statin users (OR 0.20, 95% CI 0.06 to 0.64); there was no significant association for non-statin only users (OR 0.47, 95% CI 0.20 to 1.13).
Conclusions: The results of this study suggest that subjects with ARM were significantly less likely to have filled a statin prescription. Future clinical research initiatives should include a clinical trial to provide direct evidence of the effectiveness of statins in lowering the incidence and progression of ARM.

Age related maculopathy (ARM) is the leading cause of irreversible vision loss among older adults in the United States.[1] Though some treatments slow the loss of visual function in later stages of ARM,[2 3] there is no effective treatment for ARM or for arresting its progression in its earliest phases. Numerous epidemiological studies have evaluated risk factors for ARM and generally focused on smoking, alcohol consumption, diet, hypertension, and diabetes among others.[4] With the exception of a consistently reported positive association between ARM and smoking, the results of existing research are equivocal. Differences in study populations and ARM definitions may contribute to this heterogeneity of findings.

The overlap in risk factors for ARM and cardiovascular disease (CVD) has led some to suggest that the pathophysiology of these diseases have similar causal pathways.[5] Positive associations between ARM and cardiovascular risk factors lend support to this proposition (blood pressure, plasma cholesterol, smoking).[4] The prominent histopathological and clinical lesions in ARM involve Bruch's membrane, a specialised vascular intima separating the photoreceptors and their support cells, the retinal pigment epithelium (RPE), from their blood supply. Because these lesions and Bruch's membrane contain abundant lipids, including cholesterol,[6–10] it is possible that ARM and CVD share common mechanisms at the level of the vessel wall.

3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors ("statins") are prescribed to help reduce low density lipoprotein (LDL) cholesterol levels by inhibiting cholesterol production and increasing LDL cholesterol removal from plasma. If cholesterol excess is a common pathway for the development of CVD and ARM, then statin use may decrease ARM risk. Some studies have suggested a protective association between use of cholesterol lowering drugs and ARM; however, others have found no association.[11–15] However, statins may reduce the risk of ARM through mechanisms other than by lowering plasma lipids.[16 17] Limitations of existing research indicate the need for additional studies of this association. The goal of this study is to evaluate the association between statin use and the risk of ARM.

PARTICIPANTS AND METHODS

Study population and data source

The Birmingham (Alabama) Department of Veterans Affairs Medical Center (BVAMC) is 134 bed acute tertiary care medical facility and serves as a Veterans Hospital Administration tertiary care referral centre for Alabama. All patients who had at least one visit (inpatient or outpatient) at the Birmingham BVAMC between 1 January 1997 and 31 December 2001 were eligible for study inclusion. Because the prevalence of ARM is low below age 50, the study population was limited to patients 50 and older. Females were also excluded as 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-9CM). 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 over the course of each patient's history with the BVAMC and not just those that occurred in 1997 to 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 ARM were defined using the ICD-9CM codes 362.50 (macular degeneration (senile), unspecified), 362.51 (non-exudative senile macular degeneration), and 362.52 (exudative senile macular degeneration). Information on the ARM diagnosis date was procured and will heretofore be referred to as the index date. Because this study addressed

Table 1 Demographic and medical characteristics among ARM cases and non-ARM controls. (Figures are numbers (%) except where otherwise indicated)

	Cases (n=550)	Controls (n=5500)	p Value
Demographic characteristics			
Age (years), mean (SD)	72.9 (6.8)	73.2 (6.7)	0.80
Race			<0.0001
White	459 (83.5)	2509 (45.6)	
African-American	22 (4.0)	864 (15.7)	
Other	5 (1.0)	20 (0.4)	
Unknown	64 (11.6)	2107 (38.3)	
Medical characteristics			
Diabetes	124 (22.6)	774 (14.1)	<0.0001
Lipid metabolism disorders	58 (10.6)	624 (11.4)	0.57
Hypertension	310 (56.4)	2128 (38.7)	<0.0001
Cardiovascular disease	167 (30.4)	1302 (23.7)	0.0005
Cerebrovascular disease	26 (4.7)	472 (8.6)	0.0017
Arterial disease	35 (6.4)	433 (7.9)	0.21

the association between statin use and the incidence of ARM, patients who had an ARM diagnosis before the observation period (1997–2001) of the study (prevalent cases) were excluded.

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

The prescription file was queried for the presence of filled statin (atorvastatin, cerivastatin, fluvastatin, pravastatin, simvastatin, lovastatin) prescriptions. Non-statin lipid lowering agents (for example, fibrates, nicotinic acid) were also extracted from the prescription file. Only those prescriptions that were filled before the index date for each matched set of cases and controls 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 more than 6 months before the index date. An analogous set of variables was created for the non-statin lipid lowering agents.

Information on the presence of the following conditions was extracted from the clinical data file because of previous research indicating their potential association with ARM[4]: ischaemic heart disease (ICD-9CM codes 410 though 414), cerebrovascular disease (ICD-9CM codes 430 though 438), lipid metabolism disorders (ICD-9CM code 272), hypertension (ICD-9CM codes 401 though 405), diseases of the arteries, arterioles, and capillaries (ICD-9CM codes 440 though 448), and diabetes (ICD-9CM code 250). For the purposes of analysis, only those diagnoses that were recorded before the index date were considered.

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 ARM. Odds ratios (ORs) and 95% confidence intervals (CIs) were also estimated for current and past statin users relative to non-users and according to time since first prescription. A similar set of analyses was conducted for non-statin lipid lowering agents. Stratified analyses were conducted to determine if ischaemic heart disease, cerebrovascular disease, lipid metabolism disorders, hypertension, diseases of the arteries, arterioles and capillaries, and diabetes modified the association between statin use and ARM. There were an insufficient number of patients using non-statin lipid lowering agents to conduct a similar set of stratified analyses. For both unstratified and stratified analyses, estimates were obtained without and with adjustment for diabetes, lipid metabolism disorders, hypertension, ischaemic heart disease, cerebrovascular disease, and arterial disease.

RESULTS

In all, 550 incident cases of ARM were identified and matched to 5500 controls. By design, the mean age of the groups was similar (Table 1). The racial distribution differed between cases and controls. The cases were more likely to be white; the frequency where race was unknown was higher among the controls. Regarding medical characteristics, the cases had a significantly higher frequency of diabetes, hypertension, cardiovascular, and cerebrovascular disease; there were no differences in lipid metabolism disorders and arterial disease.

The proportion of patients with a statin prescription filled before the index date was 6.7% among cases and 13.6% among controls (OR 0.45, 95% CI 0.32 to 0.64) (Table 2). This association persisted regardless of whether statin use was current or past (OR 0.50, 95% CI 0.33 to 0.76 and OR 0.39, 95% CI 0.22 to 0.68, respectively) and was not restricted to those with longer duration of use. When adjusted for diabetes, lipid metabolism disorders, hypertension, ischaemic heart disease, cerebrovascular disease, and arterial disease, the pattern of results was unchanged and the associations were stronger compared to the unadjusted measures. Among statin users, the use of specific types of statins did not differ between the groups (data not shown; p values >0.05).

Use of non-statin lipid lowering agents was less common among cases than controls (OR 0.55); however, the 95% CI included the null (0.28 to 1.09). Following adjustment, this association was statistically significant (OR 0.46, 95% CI 0.23 to 0.92). When considering use of both statin and non-statin medications, a significant risk reduction was observed for statin only users (OR 0.48, 95% CI 0.33 to 0.68) and combined statin and non-statin users (OR 0.32, 95% CI 0.10 to 0.99); there was no significant association for non-statin only users (OR 0.75, 95% CI 0.32 to 1.73). Adjustment for other medical conditions did not influence this pattern of results but did strengthen the magnitude of the associations.

Table 3 presents ORs and 95% CIs for the association between ARM and statin use according to the presence of specified medical conditions. With the exception of cardiovascular and cerebrovascular disease, the effect of statin use on the risk of ARM was stronger in the presence of a medical

Table 2 Statin use characteristics among ARM cases and non-ARM controls and associated odds ratios (ORs) and 95% confidence intervals (CIs) (Figures are numbers (%) except where otherwise indicated)

Statin use characteristics	Cases (n=550)	Controls (n=5500)	Crude OR (95% CI)	Adjusted* OR (95% CI)
Statin use				
No	513 (93.3)	4753 (86.4)	1.00 (Reference)	1.00 (Reference)
Yes	37 (6.7)	747 (13.6)	0.45 (0.32-0.64)	0.30 (0.21-0.45)
Non-use	513 (93.3)	4753 (86.4)	1.00 (Reference)	1.00 (Reference)
Current use	24 (4.4)	442 (8.0)	0.50 (0.33-0.76)	0.34 (0.21-0.53)
Past use	13 (2.4)	305 (5.6)	0.39 (0.22-0.68)	0.26 (0.14-0.47)
Duration of use (months)				
Non-use	513 (93.3)	4753 (86.4)	1.00 (Reference)	1.00 (Reference)
<12	11 (2.0)	238 (4.3)	0.46 (0.29-0.73)	0.32 (0.20-0.52)
12–23	11 (2.0)	161 (2.9)	0.43 (0.19-0.98)	0.29 (0.12-0.67)
>23	15 (2.7)	348 (6.3)	0.45 (0.24-0.83)	0.29 (0.15-0.56)

*Adjusted for diabetes, lipid metabolism disorders, hypertension, ischaemic heart disease, cerebrovascular disease, and arterial disease.

Table 3 Odds ratios (ORs) and 95% confidence intervals (CIs) for the association between statin use and ARM stratified according to presence of medical conditions

	Crude OR (95% CI)	Adjusted† OR (95% CI)
Diabetes		
No	0.49 (0.32 to 0.73)	0.27 (0.17 to 0.43)
Yes	0.30 (0.13 to 0.68)	0.39 (0.14 to 1.06)
Lipid metabolism disorders		
No	0.49 (0.31 to 0.78)	0.35 (0.23 to 0.55)
Yes	0.23 (0.09 to 0.59)	0.06 (0.01 to 1.18)
Hypertension		
No	0.55 (0.30 to 1.02)	0.31 (0.17 to 0.57)
Yes	0.32 (0.20 to 0.49)	0.30 (0.17 to 0.53)
Cardiovascular disease		
No	0.36 (0.19 to 0.66)	0.27 (0.15 to 0.48)
Yes	0.34 (0.20 to 0.58)	0.31 (0.16 to 0.57)
Cerebrovascular disease		
No	0.50 (0.33 to 0.69)	0.31 (0.21 to 0.46)
Yes	*	*
Arterial disease		
No	0.44 (0.30 to 0.64)	0.28 (0.19 to 0.42)
Yes	0.31 (0.03 to 3.18)	*

*Estimate not possible owing to limited number of subjects in this subcategory.
†Adjusted for diabetes, lipid metabolism disorders, hypertension, ischaemic heart disease, cerebrovascular disease, and arterial disease where appropriate.

condition (diabetes, lipid metabolism disorders, hypertension, arterial disease) than in its absence. Following adjustment, the association was generally similar for those with and without each condition. There were no statistically significant interactions noted between statin use and each of the medical conditions and ARM.

DISCUSSION

These results suggest that ARM cases were over 50% less likely to have filled a statin prescription. This association was present among those with and without specific medical conditions including diabetes, lipid metabolism disorders, hypertension, and CVD. Non-statin lipid lowering medications were less common among those with ARM but the association was not statistically significant and of lesser magnitude than that observed for statins. Whether this indicates that the association is limited to statins only or that the association also exists for non-statin lipid lowering medications, albeit weaker, will require additional research. It cannot be concluded from this study that this association represents a cause and effect relation; future research will also be required to address this issue.

To date, there have been only two studies addressing the association between statin use and ARM. Hall *et al* reported a significantly lower frequency of ARM (defined broadly as all types and severities) among statin users relative to non-users.[14] The OR reported in that study (OR 0.14) was substantially lower than that reported by us (OR 0.45); however, its 95% CI overlapped considerably with ours (95% CI 0.02 to 0.83). The limitations of the Hall *et al* study have been addressed in detail and include the small sample size and the cross sectional design.[18 19] With respect to the latter, such study designs limit the ability to evaluate the temporal relation between exposure and disease. McCarty *et al* found that the self reported use of cholesterol lowering medications was associated with a fourfold decreased risk of ARM progression in those who had ARM at baseline[15]; however, because of small sample size this finding was not statistically significant. Finally, three other studies have evaluated the impact of "lipid lowering agents"[13] and "hypocholesterolaemic drugs"[11] and found no association with early ARM[11 13] or late ARM.[11] The findings of these two studies[11 13] may not be surprising if non-statin lipid lowering medications were more weakly associated with ARM, which the results of our study suggest. Thus the aggregation of statin and non-statin medications, as was probably done in these studies, would bias any association towards the null. Finally, a third study also reported no association between self reported ever use of a cholesterol lowering medication and ARM, both early and late disease.[15] The reliance on self reported information on statin use also represents a potential limitation of this study.

HMG CoA reductase is a key enzyme not only for cholesterol biosynthesis but also for the biosynthesis of numerous non-steroidal isoprenoid compounds.[20] Numerous biological processes associated with atherosclerotic progression are modulated by HMG CoA reductase inhibition (for example, endothelial cell health, thrombosis, angiogenesis).[19 20] Statins were developed to lower plasma cholesterol levels in patients with atherosclerotic CVD. However, the benefits of statin usage may extend beyond that which can be explained by the direct effect of lowering plasma lipids concentrations.[16 17]

The eye tissues affected by ARM are photoreceptors, retinal pigment epithelium (RPE), choriocapillaris (the blood supply to the photoreceptors and the RPE), and Bruch's membrane (a thin vascular intima between the RPE and the choriocapillaris).[21 22] Prominent extracellular lesions located between the RPE and Bruch's membrane can be either focal or diffuse in form (drusen and basal deposits, respectively).

There are potentially multiple biological bases for the protective effect of statins on the risk of ARM. With regard to the potential for a lipid lowering effect, it is notable that Bruch's membrane accumulates lipids including cholesterol with normal ageing, and cholesterol is a ubiquitous component of drusen in normal and ARM eyes.[6–10] The relative contributions of plasma lipoproteins and local cells to Bruch's membrane cholesterol are still under investigation, and because of the potential non-lipid lowering effects of statins, it would be inappropriate to interpret our data as evidence for a plasma source.[7 9 10 23–25] However, apolipoprotein B, the principal protein of the atherogenic plasma lipoproteins,[26] is detectable in drusen, basal deposits, and in Bruch's membrane, where it could contribute cholesterol to lesions and/or undergo modifications with deleterious impact on surrounding cells.[27 28]

With regard to the potential for pleiotrophic effects, it is notable that many of the same processes that occur in the atherosclerotic intima probably also occur in ARM. Neovascularisation is a major complication in both conditions.[29 30] Therefore, angiogenesis and processes such as metalloproteinase activity[31] are potential points of statin modulation. Choroidal neovascular membranes associated with ARM include macrophages[32 33] and smooth muscle actin positive cells,[34] which may respond to statins. Drusen contain proteins associated with inflammation and complement activation,[35] and multiple lines of evidence point to a role for inflammatory processes in ARM progression.[36] Statins affect RPE cell survival and morphology in vitro.[37] The challenge for future laboratory research will be to determine which processes are modulated by statins in vivo and therefore are primarily responsible for the apparent beneficial effects observed in the present study.

The results of this study should be interpreted in light of its strengths and limitations. The primary strength of this study is the use of the nested case-control design that allowed for the evaluation of statin use that occurred before ARM diagnosis. Given the size of the study base, this study was able to identify a large number of ARM cases and matched controls thereby enhancing the statistical power of the study relative to other studies evaluating the relation between statin use and ARM. This study had information on actual filled prescriptions and did not rely on self reported medication use, as have other studies. Although there is no information on whether the medications were actually taken, the succession of prescription refills during the observation periods among the majority of statin users suggests that these medications were actually being taken.

There are also limitations requiring mention. Firstly, subjects with ARM were identified on the basis of ICD-9 codes and were not confirmed by a standardised comprehensive eye examination and the grading of fundus photographs. Although the ICD-9 codes allow for the classification of disease into exudative and non-exudative forms, the majority of ARM cases in the present study (>90%) were classified as "unspecified." These limitations prohibit analyses with respect to disease severity and type. Also, without confirmatory diagnostic information, there is also the possibility of misclassification with respect to ARM status. However, equivalent proportions of both cases and controls (~35%) had a visit to either the optometry or ophthalmology clinics at the BVAMC. This would suggest that for this proportion of subjects, misclassification with respect to ARM is unlikely. When the analysis is limited to those subjects who had visited optometry or ophthalmology clinics, the OR was 0.38 (95% CI 0.23 to 0.63), which is comparable to the association for all subjects (OR 0.45, 95% CI 0.32 to 0.64). For the approximately 65% in each group who did not have an optometry or ophthalmology clinic visit, misclassification remains a possibility. However, there is little reason to suspect that any such misclassification would be differential according to statin use and therefore the ultimate result would be a bias towards the null. Secondly, this study did not have the ability to evaluate the potentially confounding effects of characteristics that have been shown or hypothesised to be associated with ARM (for example, smoking). Thirdly, our study population was limited to older males. Therefore, the results of this study should only be considered generalisable to males aged 50 and older. Further research is needed to evaluate whether a similar association exists among females. Fourthly, statin use was defined on the basis of a filled prescription within the BVAMC pharmacy service. This introduces the possibility that a patient with a statin prescription record but matching fill record would be classified as a non-statin user even though the prescription may have been filled outside the BVAMC. However, because such misclassification would likely be non-differential and over 90% of prescriptions had associated fill dates, the effect of this situation would tend to be a bias towards the null. Finally, information on race was unknown for a large proportion of cases and controls thereby preventing matching according to this characteristic. However, when adjusting for race, including the unknowns, the association was similar to the overall, non-race adjusted association (ORs 0.34 and 0.45, respectively). When stratified according to race, the protective association of statin use was apparent among white people (OR 0.26) and African-Americans (OR 0.57).

The results of this study suggest that subjects with ARM were less likely to have filled a statin prescription. Further research is necessary to more fully understand the pathophysiology of ARM and the precise role, if any, of cholesterol. Future clinical research initiatives should consider a randomised clinical trial to evaluate the effectiveness of statins in lowering the risk and/or rate of progression of ARM.

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ECHO

Complex mutations of USH2A gene denote ARRP

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A study of mutations associated with non-syndromic autosomal recessive retinitis pigmentosa (ARRP) in Spanish patients will ultimately help our knowledge of events leading to blindness or deafness, or both. Before then, though, the complexities of ARRP phenotypes and how these relate to genetic make up will take some unravelling.

The study found nine cases (one homozygous, eight carriers) of missense mutation of the C759F allele of the USH2A usherin gene among 196 unrelated patients. Screening family members of six cases disclosed a further 21 carriers (seven with RP, 14 unaffected) and three homozygous cases (two unaffected). Six other mutations—three of them new—emerged after complete USH2A analysis of patients and selected family members, which uncovered compound heterozygotes with nonsense, slicing, and misssense mutations.

Huge phenotypic variation existed with C759F mutation, from symptomatic homozygosity to asymptomatic homozygosity, suggesting perhaps that another mutant allele underlies the RP phenotype in asymptomatic homozygous individuals

Patients with non-syndromic ARRP and 100 blood donor controls were screened by PCR analysis for C759F mutation. Screening was extended to family members of six patients with mutations; in three no family members were available. The USH2A gene coding region was analysed in all patients with the C759F mutation and selected family members.

Only a few gene mutations have been identified so far in a small percentage of Spanish families with ARRP, but until now did not include the recently described missense mutation in the USHA2 gene (C759F), which accounts for 4.5% of non-syndromic ARRP in North Americans.

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