Published in final edited form as:
Am J Ophthalmol. 2007 July ; 144(1): 1–6.

Statin Use and the Five-year Incidence and Progression of Age-Related Macular Degeneration

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Abstract

Purpose—To examine the association of HMG-CoA reductase inhibitors (statins) with the 5-year incidence of age-related macular degeneration (AMD).

Design—Population-based cohort study.

Setting Beaver Dam, Wisconsin

Study population Participants included persons 53 to 96 years of age at examination in 1998 to 2000 (n=2962), of whom 2204 participated in a follow-up 5 years later.

Observation procedures Standardized procedures were used for physical examinations, blood collection, and questionnaire administration. AMD was determined by grading images of the posterior pole using a standard protocol. Standard univariate and multivariate analyses were performed.

Main outcome measures Incident early and late AMD and progressed AMD

Results—There were 1347 and 1638 persons not using statins and 339 and 429 using statins at the 1998-2000 examination at risk of early and late AMD, respectively. The unadjusted 5-year incidence of early and late AMD, respectively, was 5.9% and 1.8% in those not using statins and 6.8% and 2.3% in those using statins. While controlling for age, sex, smoking status, and multivitamin use, a history of statin use was not associated with the 5-year incidence of early AMD (odds ratio [OR] 1.16, 95% confidence interval [CI] 0.71 to 1.91, p=0.55), progression of AMD (OR 1.16, 95% CI 0.75 to 1.78, p=0.51) or incidence of late AMD (OR 1.27, 95% CI 0.60 to 2.69. p=0.53).

Conclusion—These findings do not show an association between statin use and the incidence or progression of AMD over a 5-year period.

Keywords

Age-Related Macular Degeneration; Statin; Incidence

Few medical interventions prevent progression of early to late AMD. Data from the Age-Related Eye Disease Study (AREDS) showed moderate efficacy of antioxidants and zinc supplements in persons with early AMD with an absolute reduction of 5% to advanced AMD (23% rate of progression to advanced AMD in the treated group versus 28% in the control group).[1] However, 23% of eyes receiving antioxidants and zinc had a 15-letter decrease in the

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visual acuity score despite such treatment. While anti-vascular endothelial growth factor therapy has been shown to prevent and in some cases restore visual loss in eyes with neovascular AMD, these treatments may be costly and the long-term safety is not known.[2] There is no medical or surgical intervention for prevention of visual loss once signs of geographic atrophy become manifest. For these reasons, other possible medical interventions have been sought to prevent the incidence and progression of early AMD.

A protective effect of statins against AMD was suggested by findings of two studies.[3,4] The lipid lowering and anti-inflammatory properties of statins, two mechanisms hypothesized to play a role in the pathogenesis of AMD, were thought, in part, responsible for these findings.[5-7] However, data from three population-based studies did not show a protective effect of statins.[8-11] The purpose of this report is to examine the association of statins with the 5-year incidence of AMD in the Beaver Dam Eye Study cohort at a time when there is significantly higher frequency of statin use than when we previously examined this relationship five years ago.

Materials and Methods

Population

Methods used to identify and describe the population have appeared in previous reports.[12-15] In brief, a private census of the population of Beaver Dam, Wisconsin, was performed from September 15, 1987 to May 4, 1988, to identify all residents in the city or township of Beaver Dam who were 43 to 84 years of age. Of the 5 924 eligible individuals, 4 926 participated in the baseline examination between March 1, 1988 and September 14, 1990.[12] Participants were re-examined at 5-year intervals and comparisons between participants and non-participants at these examinations can be found elsewhere.[13-15] Because of the small number of persons taking statins at the 1988-90 (n=19) and 1993-1995 examinations (n=143), for purposes of this report, the 1998-2000 examination when 558 persons were taking statins is considered “baseline”.

Two thousand two hundred and four people were eligible for inclusion in the analysis. Of those eligible for inclusion, 22 persons were excluded with prevalent exudative AMD and 95 were excluded for not having incident AMD information. Therefore, 2 087 people contributed to this analysis.

Persons who were alive but did not participate in the 15-year follow-up (n=301) were more likely to higher systolic (136 vs 131 mmHg, age-adjusted $p < 0.001$) and diastolic blood pressure (75.4 vs 74.5, p=.006) than those who participated, otherwise they had similar history of smoking status, pack-years smoked, body mass index, and vitamin use (data not shown). While controlling for age, there were no differences in participation at the 15-year follow-up examinations for men and women with a history of statin use and early AMD at the 1998-2000 examination compared to those with a history of statin use without early AMD (data not shown).

Procedures

Similar procedures have been used at both the 1998-2000 and the 2003-2005 follow-up examinations and are described in detail elsewhere.[16,17] All data were collected with Institutional Review Board approval in conformity with all federal and state laws, and the study was in adherence to the tenets of the Declaration of Helsinki. Written informed consent was obtained from each participant at the beginning of the examination. Medication and vitamin use was assessed using a standardized questionnaire administered by the examiners at each examination. Participants were asked to bring all medications (prescription and over-the-

counter) that they were regularly taking to the examination. The examiner asked whether there were other medications that were being taken but were not brought. If there were, the subject was asked to call the study examiner with the medication name. In addition, at the baseline examination participants were asked if they had used specific classes of drugs in the past. Information on duration of use was not obtained. Participants were asked to list the pharmacy or pharmacies where they usually obtained their medications. Participants, their physicians, and their pharmacies were called when necessary to verify medication and reason for use.

The name of the drug was entered into a drug database where the record number assigned was associated with the drug use section of the questionnaire through a code table structure. With the drug record, each active ingredient was assigned the appropriate American Hospital Formulary Service code.[18] In addition, sub classification information was included (e.g., type of lipid lowering agent: statin (e.g., lovastatin, simvastatin, prevastatin, fluvastatin, atorvastatin), nicotinic acid, fibric acid derivatives (clofibrate and gemfibrozil) and bile acid sequesterants). Because the use of non-statin lipid lowering agents was low at the 1998-2000 examination, the analyses were limited to statins. The examination at baseline and follow-up included measuring weight, height, pulse rate, and blood pressures (using a random-zero sphygmomanometer following the Hypertension Detection and Follow-up Program protocol).[19] Stereoscopic 30° color fundus photographs centered on the disc (Diabetic Retinopathy Study [DRS] standard field 1), macula (DRS standard field 2), and a non-stereoscopic color fundus photograph temporal to but including the fovea of each eye were taken.

The Wisconsin Age-Related Maculopathy Grading System was used to assess the presence and severity of lesions associated with AMD. Grading procedures, lesion descriptions, and detailed definitions for the presence and severity, as well as the incidence of specific lesions, have appeared elsewhere.[20-22] Incidence implies the appearance of a lesion at follow-up when it was absent at baseline in any of the subfields that could be graded at baseline and follow-up examinations. Progression implies the presence of a lesion at baseline with a worsening at follow-up.[21,22]

Incidence was determined for maximum size and type of each specific drusen class, increased drusen area, increased retinal pigment, retinal pigment epithelial (RPE) depigmentation, pigmentary abnormalities (defined as RPE depigmentation or increased retinal pigment), signs of exudative macular degeneration, and pure geographic atrophy. For example, if none of the subfields had soft indistinct drusen at the 1998-2000 examination and soft indistinct drusen were present in one or more subfields at the 2003-05 examination, the eye would be considered to have “incident” soft indistinct drusen.

Early AMD was defined by the presence of either soft indistinct drusen or the presence of any type of drusen associated with RPE depigmentation or increased retinal pigment. Late AMD was defined by either exudative macular degeneration or pure geographic atrophy.

For each eye, a six-level severity scale for AMD was defined as follows:[23]

Level 10	No drusen of any type or hard drusen or small soft drusen (<125 μm in diameter) only, regardless of area of involvement, and no pigmentary abnormality (increased retinal pigment or RPE depigmentation) present
Level 20	Hard drusen or small soft drusen (<125 μm in diameter), regardless of area of involvement, with increased retinal pigment present but no RPE depigmentation present or soft drusen (≥ 125 μm in diameter) with drusen area <196,350 μm^2 (equivalent to a circle with a diameter of 500 μm) and no pigmentary abnormalities present
Level 30	Soft drusen (≥ 125 μm in diameter) with drusen area <196,350 μm^2 and RPE depigmentation present or soft drusen (≥ 125 μm in diameter) with drusen area ≥196,350 μm^2 with or without increased retinal pigment but no RPE depigmentation present
Level 40	Soft drusen (≥ 125 μm in diameter) with drusen area (≥ 196,350 μm^2 involvement and RPE depigmentation present with or without increased retinal pigment

Level 50	Pure geographic atrophy in absence of exudative macular degeneration
Level 60	Exudative macular degeneration with or without geographic atrophy present

Progression for a participant was defined as an increase in the AMD severity in either eye by two steps or more from level 10 through 30 and one step or more from level 40 or level 50 from the 1998-2000 examination to the 2003-2005 examination.

Age was defined as the age at the time of the baseline examination. The mean systolic blood pressure was the average of the two systolic blood pressure determinations, and the mean diastolic blood pressure was the average of the two diastolic blood pressures at baseline. A person was defined as having a positive history of cardiovascular disease if at baseline he/she responded affirmatively to the questions regarding history of angina, heart attack, or stroke. Cigarette smoking status at the time of the baseline examination was determined as follows. A subject was classified as a non-smoker if he/she had smoked fewer than 100 cigarettes in his/her lifetime; as an ex-smoker if he/she had smoked more than this number of cigarettes in his/her lifetime but had stopped smoking before the baseline examination; and as a current smoker if he/she had not stopped smoking.

Statistical Methods

For these analyses, we examined the relationships between statin use at the examination in 1998-2000 and the 5-year incidence or progression of each specific AMD lesion and two endpoints of disease severity, early and late AMD. In a secondary analysis, we investigated past use of statins at the 1993-95 examination as well as present use at the 2003-05 examination to create a 5-level variable (1: never used statins; 2: used statins only at the 4^{th} examination; 3: used statins only at the 3^{rd} examination; 4: used statins at only the 3^{rd} and 4^{th} examinations; and 5: used statins at the 2^{nd}, 3^{rd} and 4^{th} examinations).

SAS was used for analyzing the data.[24] Multivariate odds ratios (OR) and 95% confidence intervals (CI) were calculated from logistic regression models for 5-year incidence and progression.[25] Age- and gender-adjusted models were constructed by outcome for each of the potential risk factors. A final model was then built by outcome for each risk factor, adjusting for age, gender, history of smoking, and vitamin use.

Results

Persons taking statins in 1998-2000 were more likely to be men, ex-smokers or have a greater number of pack years smoked, to have hypertension, a greater body mass index, and a history of cardiovascular disease than those not taking statins (Table 1). The 5-year incidence and progression of AMD increased with age (Table 2).

Controlling for age and sex, there were no statistically significant associations of statin use with the 5-year incidence and progression of AMD (Table 3). Multivariable models including a history of vitamin use and smoking status at baseline did not change these associations (Table 3). Further addition of serum total cholesterol levels, a history of cardiovascular disease or antioxidant supplement use to the multivariable models did not change these associations (data not shown). There was no relation of duration of statin use (5-step scale as described in Methods) and any AMD endpoint (data not shown). Statin use was not related to the 5-year incidence of early or late AMD or progression of AMD in men or women, in those with or without hypertension, and those who never smoked, were former smokers or were current smokers at the 1998-2000 examination (data not shown).

Discussion

In Beaver Dam, statin use was not associated with the incidence or progression of AMD in contrast to some other studies.[3,4,26,27] We are not alone in our findings as data from other case control or large population-based studies also did not show a protective effect of statins.[8-11,28-30] While adjusting for smoking, alcohol intake, body mass index, atherosclerotic disease, hyperlipidaemia, heart failure, diabetes mellitus, hypertension, use of other cardiovascular drugs, and fibrates, no relationship (OR 0.93, 95% CI 0.81 to 1.07, p=0.33) was found between exposure to statins and AMD in a large case-control study (18 007 cases, 86 169 controls).[29] In that study, there was no evidence that the risk varied by dose of statin, duration of use, or specific type of statin. In two large cross-sectional studies, the Cardiovascular Health Study and the POLA study, history of statin use was not found to be related to the presence of AMD.[28,30] In the Rotterdam Study, during 26 781 person years of follow-up in 457 persons, those using cholesterol lowering drugs had a similar incidence of AMD as those not using these drugs (hazard ratio 1.0, 95% CI 0.7 to 1.5).[10] Controlling for other confounders did not change this association. The duration of use of statins was not associated with risk of developing AMD. In the Blue Mountains Eye Study, while controlling for age, sex, smoking, and total serum cholesterol, persons who had used statins at baseline had an insignificant increase in the odds of 5-year incidence of neovascular AMD.[11]

Care must be taken in interpreting the results of our study. Though we report no association of statins to incident or progressed AMD, we have relatively limited power to assure that such a relation does not exist, especially for late AMD. Furthermore, we have no data regarding the dosage of statin use, although it is not known whether this would influence these associations. Five or fewer years of use might not be a long enough interval to see a protective effect of statins against AMD. There was also no specific information on duration of use, although there were persons taking statins at either 2 or 3 examinations, they were not more likely to have less incident or progressed AMD than those on it for five or fewer years. Finally, while it is possible that selective survival may have affected our conclusions for those at risk, we had no evidence that a person's AMD status and statin use were related to survival.

In summary, we found no consistent or significant association of statin use to the 5-year incidence or progression of AMD. The consistency of the prospective findings from the Beaver Dam, Rotterdam, and the Blue Mountains Eye Studies suggest that statin use is not associated with the incidence of early AMD.[10,11] Further data from large long-term population-based studies are needed to examine the association of statin use and incidence of late AMD.

Acknowledgements

A. FUNDING/SUPPORT

The National Eye Institute provided funding for entire study including collection and analyses and of data (Grant No. EY06594; R Klein, BEK Klein); RPB provided further additional support for data analyses (R. Klein, BEK Klein, Senior Scientific Investigator Awards, New York, NY).

B. FINANCIAL DISCLOSURES

None (RK, BEKK, MK)

C. CONTRIBUTIONS OF AUTHORS

Design of the study (RK and BEK); Conduct of the study (RK, BEKK, MK); Collection (RK, BEKK); Management (RK, BEKK); Analysis and interpretation of data (RK, BEKK, MK); Preparation, review, and final approval of manuscript (RK, BEKK, MK).

D. CONFORMITY WITH AUTHOR INFORMATION

Written informed consent for the use and disclosure of protected health information was obtained from all subjects before being enrolled in the study and Institutional Review Board approval was granted by the Health Sciences Institutional Review Board at the University of Wisconsin, Madison.

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Biography

Dr. Ronald Klein is a Professor of Ophthalmology and Visual Sciences at the University of Wisconsin Medical School interested in ocular epidemiology of age-related eye disease and hypertensive and diabetic retinopathy.

Table 1

Characteristics of the population by statin use at the 1998-2000 examination.

	Not taking statins		Taking statins		
	N	**Mean ± SD or %**	**N**	**Mean ± SD or %**	***P****
Age, years	1756	66.8 ± 9.0	448	67.4 ± 8.2	0.20
Women	1061	60.4	232	51.8	<0.001
Men	695	39.6	216	48.2	
History of smoking					
Never	859	48.9	180	40.2	<0.001
Past	695	39.6	245	54.7	
Current	202	11.5	23	5.1	
Pack-years smoked, years	1749	13.7± 23.0	448	17.8 ± 25.5	0.002
Body mass index, kg/m^2	1698	29.9 ± 5.7	430	31.3 ± 6.3	<0.001
Systolic blood pressure, mmHg	1715	130.7 ± 18.7	436	132.1 ± 18.4	0.23
Diastolic blood pressure, mmHg	1715	74.8 ± 10.1	435	73.4 ± 10.5	0.02
Hypertension, present	928	53.5	307	69.1	
History of CVD, present	170	9.7	147	32.8	<0.001
Vitamin use					
None	592	33.7	117	26.1	0.09
Other†	369	21.0	124	27.7	
Multi-vitamin	795	45.3	207	46.2	

N=number of observations; SD=standard deviation; CVD=cardiovascular disease;

*adjusted for age (where appropriate)

†includes single or other non-standard combination (e.g., B-complex) vitamins

Table 2

Relation of 5-Year Incidence and Progression of Age-Related Macular Degeneration (AMD) by Age in Beaver Dam Eye Study 1998-2000 and 2003-2005.

	Incidence of Early AMD		Incidence of Late AMD		Progression of AMD	
Age, year	**N at risk**	**%**	**N at risk**	**%**	**N at risk**	**%**
53-64	882	3.7	969	0.2	968	1.5
65-74	539	5.0	687	2.2	684	6.7
75-84	224	15.6	361	4.7	371	17.5
85+	21	23.8	50	10.0	54	24.1
Total	1686	6.1	2067	1.9	2077	6.7

Table 3

Relation of statin use to 5-year incidence or progression of age-related macular degeneration (AMD) in Beaver Dam Eye Study, 1998-00 to 2003-05

			Unadjusted		Age and gender adjusted			Multivariate adjusted *		
Outcome	**History of Statin use**	**N**	**%**	***P***	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Incidence of Early AMD	No	1347	5.9	0.53	1.00			1.00		
	Yes	339	6.8		1.11	(0.68, 1.82)	0.67	1.16	(0.71, 1.91)	0.55
Incidence of Late AMD	No	1638	1.8	0.43	1.00			1.00		
	Yes	429	2.3		1.32	(0.63, 2.78)	0.47	1.27	(0.60, 2.69)	0.53
Incidence of Exudative AMD	No	1653	1.0	0.30	1.00			1.00		
	Yes	434	1.6		1.56	(0.63, 3.86)	0.33	1.51	(0.61, 3.77)	0.37
Incidence of Pure Geographic Atrophy	No	1624	0.9	1.00	1.00			1.00		
	Yes	422	0.7		0.89	(0.25, 3.20)	0.86	0.84	(0.23, 3.06)	0.79
Progression of AMD	No	1650	6.5	0.45	1.00			1.00		
	Yes	427	7.5		1.13	(0.74, 1.74)	0.56	1.16	(0.75, 1.78)	0.51
Incidence of large drusen (≥ 125 μm)	No	1349	9.2	0.35	1.00			1.00		
	Yes	364	7.4		0.74	(0.47, 1.16)	0.19	0.80	(0.51, 1.25)	0.32
Incidence of soft indistinct drusen	No	1439	7.2	1.00	1.00			1.00		
	Yes	370	7.0		0.95	(0.60, 1.51)	0.84	0.93	(0.59, 1.49)	0.78
Incidence of pigmentary abnormalities	No	1424	3.3	0.21	1.00			1.00		
	Yes	365	4.7		1.40	(0.78, 2.51)	0.25	1.49	(0.83, 2.69)	0.18

OR=odds ratio, CI=confidence interval

* Adjusted for age (categorically), sex, smoking history and vitamin use