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Statin Use and the Incidence of Advanced Age-Related Macular Degeneration in the Complications of Age-Related Macular Degeneration Prevention Trial

Maguire G. Maguire, PhD^{*}, Gui-shuang Ying, PhD^{*}, Colin A McCannel, MD[†], Chengcheng Liu, MS^{*}, and Yang Dai [on behalf of the Complications of Age-related Macular Degeneration Prevention Trial (CAPT) Research Group]^{*,†}

^{*}Department of Ophthalmology, School of Medicine, University of Pennsylvania, Philadelphia, PA

[†]Department of Ophthalmology, Mayo Clinic, Rochester, Minnesota

Abstract

Objective—To evaluate the impact of statin use on the incidence of advanced age-related macular degeneration (AMD) and its components, choroidal neovascularization (CNV) and geographic atrophy (GA), among patients with bilateral large drusen.

Design—Cohort study within a multicenter randomized clinical trial.

Participants—Patients enrolled in the Complications of Age-related Macular Degeneration Prevention Trial (CAPT).

Methods—Eligibility criteria for the clinical trial required that participants have ≥ 10 large ($>125\mu$) drusen and visual acuity $\geq 20/40$ in each eye. Patients scheduled for their final CAPT visit after May 2005 were interviewed on their history of use of cholesterol lowering medications, including statins. Trained readers identified CNV and endpoint GA (> 1 MPS disc area of GA) based on review of fluorescein angiograms and fundus photographs taken at annual follow-up visits and when patients reported symptoms. The risk ratio for participants developing CNV or developing GA associated with statin use was estimated with time dependent Cox proportional hazards models.

Main Outcome Measures—Development of advanced AMD, CNV, and endpoint GA.

Results—Among 764 patients eligible for the interview, 744 (97.4%) patients completed the interview on medication use. Statin use was reported by 296 (39.8%) of those interviewed, with the majority, 187 (63.2%) of the 296, beginning use after enrollment in CAPT. Among 744 patients, advanced AMD developed in 332 (22.3%) eyes of 242 (32.5%) patients, CNV in 222 (14.9%) eyes

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Reprints requests to: CAPT Coordinating Center, University of Pennsylvania, 3535 Market Street, Suite 700, Philadelphia, PA 19104-3309.

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Statins did not protect against advanced age-related macular degeneration (AMD) in the Complications of AMD Prevention Trial.

of 176 (23.7%) patients, and GA in 114 (7.7%) eyes of 80 (10.8%) patients. With adjustment for other risk factors, the estimated risk ratio for eyes (95% confidence interval) associated with statin use was 1.15 (0.87, 1.52) for advanced AMD, 1.35 (0.99, 1.83) for CNV, and 0.80 (0.46, 1.39) for GA.

Conclusion—CAPT data are not consistent with a strong protective effect (risk ratio of 0.85 or less) of statins on the development of advanced AMD among patients with bilateral large drusen.

Introduction

In 2001, Hall and colleagues reported that the prevalence of age-related macular degeneration (AMD) was markedly lower (1 in 27, 3.7%) among members of a birth cohort who reported using statins (hydroxymethyl glutaryl coenzyme A reductase inhibitors) than in those who did not use statins (76 of 352, 21.6%).¹ Because the many effects of statins include actions on processes implicated in the pathogenesis of AMD, specifically inflammation and angiogenesis, a protective effect of statins is biologically plausible.²

Several other investigators have evaluated the relationship between statin use and AMD through case-control, cross-sectional, and prospective follow-up studies with various methods for defining the drug used (any cholesterol-lowering drug or statins only), ascertaining drug use (patient interview, filled prescriptions, or medical records), ascertaining presence of AMD (photograph grading or medical record review) and defining AMD (early only, late only, early and late combined, choroidal neovascularization only, and geographic atrophy only).^{3–11} In 2004, van Leeuwen and colleagues pooled the data on incident early AMD and use of cholesterol-lowering drugs from population-based prospective studies in the United States, Netherlands, and Australia and found no association (odds ratio 1.0; 95% confidence interval (0.6, 1.6)).¹² In 2007, Chou and colleagues published results of a meta-analysis of 7 observational studies, published in 2006 or before, of statin use and early or late AMD and obtained a pooled relative risk of 0.70 (95% confidence interval (0.48, 1.03)).¹³ They concluded that statins “do not appear to lower the risk of developing AMD, although clinically significant effects cannot be excluded.”

Following the meta-analysis, published data from the cross-sectional Women’s Health Initiative Sight Examination and the prospective Beaver Dam eye study of incident AMD yielded statistically non-significant relative risks near 1.0 while the prospective Blue Mountain Study yielded relative risks of 0.33 (95% confidence interval (0.13, 0.84)) for incident soft indistinct drusen, 0.54 (95% confidence interval (0.26, 1.11)) of incident early AMD, and 0.52 (95% confidence interval (0.26, 1.04)) for early and late AMD combined.^{14–16} These later studies had larger proportions of patients taking statins, presumably for longer duration, than the studies reported earlier.

Thus, results to date have been inconsistent in supporting a protective effect of statins on development of AMD at any stage, yet not conclusive in ruling out clinically significant effects. The Complications of Age-Related Macular Degeneration Prevention Trial (CAPT) provides the opportunity to examine the effect of statins in a large group of patients at relatively high risk of progressing from having bilateral drusen to advanced AMD. In CAPT, AMD status was documented photographically for a period of five to six years and the period of statin use, if any, was ascertained through patient interview at the end of follow-up. Results of the clinical trial indicated no beneficial or harmful effect of CAPT laser treatment on visual acuity or the incidence of advanced AMD.¹⁷

Methods

Study Population

Details of the design and methods for CAPT study have been published previously.^{17–19} Only the major features of CAPT relevant to the evaluation of statin use as a risk factor for advanced AMD will be described here. Between May 1999 and March 2001, 1052 patients were enrolled through 22 clinical centers in the United States. The institutional review board associated with each center approved the study, and written informed consent was obtained from each patient. The CAPT eligibility criteria specified that each eye have ≥ 10 drusen at least $125\text{ }\mu\text{m}$ in diameter and $\text{VA} \geq 20/40$. Neither eye was to have evidence of choroidal neovascularization (CNV), serous pigment epithelial detachment, geographic atrophy (GA) within $500\text{ }\mu\text{m}$ of the foveal center or >1 Macular Photocoagulation Study disc areas in size, or other ocular conditions likely to compromise VA or contraindicate application of laser treatment. Both eyes of the patients were enrolled into the CAPT; one eye of each patient was selected randomly for laser treatment, and the contralateral eye was assigned to observation. Patients had to be ≥ 50 years old and free of conditions that would likely preclude 5 years of follow-up.

Study Procedures

During the initial visit, patients provided information on demographic characteristics, history of diabetes mellitus, history of cigarette smoking, current use of aspirin, and current use of anti-hypertensive medications. Blood pressure was measured one time while the patient was sitting. Stereoscopic, color, fundus photographs were taken of each eye and fluorescein angiography with frames from each eye was performed. During follow-up, stereoscopic, color photographs of each eye and angiograms were taken annually and color photographs also were taken at 6 months. Angiograms also were taken when patients reported symptoms between annual visits. Follow-up was scheduled for either 5 or 6 years, depending on the date of enrollment.

Beginning in May 2005, patients who were completing their final CAPT visit were interviewed on their history of use of cholesterol lowering medications including statins, bile acid sequestrants, and nicotinic acid. Patients reporting medication use were asked the starting year and ending year of their use for each cholesterol lowering medication.

Baseline photographic images were graded by trained readers in the CAPT Reading Center using a system that incorporated methods from the Wisconsin Age-Related Maculopathy Grading System and the International Classification and Grading System for Age-Related Maculopathy and Age-Related Macular Degeneration.^{20,21} Fundus features described in the grading included: number of drusen, largest drusen size, percent of area covered by drusen, drusen confluence, predominant drusen size, percent of retinal area within $3000\text{ }\mu$ of the foveal center covered by drusen, focal hyperpigmentation, and RPE depigmentation.

Determination of Choroidal Neovascularization, Endpoint Geographic Atrophy, and Advanced AMD

Readers in the CAPT Reading Center evaluated the follow-up images for the presence of CNV, endpoint GA, serous detachment of the retinal pigment epithelium (RPE). Fluorescein angiograms were used to identify CNV, defined as expansion or persistence of hyperfluorescence in the late phase of the fluorescein angiogram. GA was defined as present when the color photographs showed an area of atrophy at least $250\text{ }\mu$ and 2 of the following 3 features: visible choroidal vessels, sharp edges, and more or less circular shape. “Endpoint GA” was defined as a total of >1 MPS disc area of atrophy when all areas of geographic atrophy were combined. Serous detachment of the RPE was defined as a smooth dome-shaped elevation

of the RPE with uniform fluorescein dye pooling and well-defined borders. Advanced AMD was defined as CNV, endpoint GA, or serous detachment of the RPE.

Statistical Analyses

The patient's statin use during CAPT was based on the date of enrollment in CAPT, the calendar year statin use began, and the calendar year statin use ended. CAPT patients were scheduled for follow-up at 6 months after enrollment, 12 months, and then annually. Event times for the AMD outcomes (advanced AMD, CNV, or GA) were assigned to the closest scheduled visit. Statin use was assumed to have started, or ended, on July 1 of the reported calendar year. The association of statin use with CNV, GA and advanced AMD was analyzed using the Cox proportional hazards model with statin use defined as a time-dependent covariate. Time 0 was defined as the time of enrollment into CAPT. Both patient-specific and eye-specific analyses were performed. For patient-specific analyses, the time to an event (detection of either CNV, GA, or advanced AMD) was the time to the event in the first affected eye. Eye-specific analyses, which may be more powerful in detecting effects, used a robust variance estimator to accommodate the correlation between two eyes of the same patient.²² Because an effect of statins on AMD may not begin immediately with the initiation of use, analyses were also performed on a patient subgroup restricted to only those patients who had no change in statin use from their time of enrollment into CAPT to their last visit; i.e., patients who either started or stopped taking statins after enrollment into CAPT were excluded from the analysis.

The risk ratios for the association between statin use and events were assessed using univariate and multivariate Cox proportional hazards models. The risk factors previously identified for each event were included in the multivariate models.²³ For CNV, the factors were age, cigarette smoking status, hypertension, and level of focal hyperpigmentation. For GA, the factors were age, percent of retinal area covered by drusen, level of focal hyperpigmentation, and RPE depigmentation. For patient-specific analyses, the baseline ocular characteristics of the worse eye were used. Risk factors for either CNV or GA were included in the multivariate model for detection of advanced AMD.

All of the above analyses included treated and untreated eyes. Analyses of untreated eyes only were also performed and compared to those from the combined group of treated and untreated eyes. Statistical computations were performed with SAS 9.1 (SAS Institute, Inc., Cary, NC).

Results

Among 764 CAPT patients with a clinic visit after May 2005, 744 (97.4%) completed the interview. Baseline demographic and ocular characteristics of the 744 patients who completed the interview are presented in Table 1 and are similar to those of the entire CAPT patient group.¹⁹

A total of 296 (39.8%) of the 744 patients interviewed reported ever using statins, with the majority, 187 (63.2%) of the 296, beginning use after enrollment in CAPT. Few patients, 29 (9.8%) stopped using statins once they started them. Most, 448 (60.2%), never used statins either before CAPT enrollment or during their CAPT follow-up. Among the 1,477 eyes of 744 patients, advanced AMD developed in 332 (22.5%) eyes of 242 (32.5%) patients, CNV in 222 (15.0%) eyes of 176 (23.7%) patients, and GA in 114 (7.7%) eyes of 80 (10.8%) patients.

Table 2 provides the estimated risk ratios for AMD outcomes associated with statin use without and with adjustment of other risk factors of AMD. For development of advanced AMD, the estimated risk ratios ranged from 1.0 to 1.2 for all analysis models with 95% confidence intervals spanning 1.0 in all cases. Within CAPT patients, statin use was associated with slightly elevated risk for CNV. The estimated risk ratios associated with statin use for CNV ranged

from 1.2 to 1.4 for all analysis models with 95% confidence intervals spanning 1.0 in all cases. Statin use was associated with lower risk for GA. The estimated risk ratios ranged from 0.5 to 0.8 in the various models and with 95% confidence intervals spanning 1.0 in all cases. Overall, adjusted and unadjusted estimates of the risk ratios were similar, as were estimates from analyses conducted using both eyes of the patient and those using only the first affected eye for the patient. Analyses including only the subgroup of patients who either never used statins or who used statins continuously during their follow-up yielded risk ratio estimates that were slightly lower than in the corresponding models including all patients. Similar results were obtained when only untreated eyes were considered in each of the models in Table 2 (Data not shown).

Discussion

The established link between AMD and the Y402H genetic variant of complement factor H, the finding of elevated c reactive protein (CRP) levels among patients with all stages of AMD, and the ability of statins to reduce CRP levels create a strong biological basis for statins to lower the risk of age-related macular degeneration.^{24–29} Based on reports of a strong protective effect of statin use on AMD by Hall and some of the previous investigations;^{1,3,5,7,8,11} a few researchers have called for the initiation of clinical trials of statins as a protective treatment for AMD.^{5, 20,31} However, when all observational epidemiologic studies to date are considered, the evidence has been inconsistent on the association of statins and AMD. In addition, the feasibility of a clinical trial of statins among a group of older individuals is jeopardized by the high proportion, approaching 50%, of such people who already use statins for control of cholesterol and other cardiovascular indications.^{32,33}

The data from CAPT contain the largest number of patients with advanced AMD to date in any study of the association with statins. CAPT participants provided starting and stopping years for their statin use so that the timing of statin use could be established as preceding the development of advanced AMD, and the presence of advanced AMD was determined from review of color fundus photography and annual fluorescein angiography. The data from CAPT do not support a large effect of statins in decreasing the risk of developing advanced AMD among patients with bilateral drusen. Overall, the estimated risk ratio was slightly above 1.0 and the lower bound of the 95% confidence interval (0.87) includes only modest treatment effects. Statistical models that include the status of each eye of a patient theoretically have more precision; i.e., lower p-values and narrower confidence intervals, than models that consider only the development of advanced AMD in the first eye affected. However, they did not yield statistically significant results for statin use among the CAPT patients. Similarly, there were no statistically significant effects of statins detected for the development of CNV only or for the development of GA.

The starting and stopping dates of statin use reported by patients based on their own recall may not have been accurate. Report of never using statins and for sustained use of statins during participation in CAPT is less sensitive to errors in recalling dates. There was little impact on the risk estimates when only this second group of patients was included in the analysis. Also, information on some established risk factors, e.g. risk alleles for genes associated with complement activation, was not available for all CAPT participants. However, we have no reason to believe that statin use is associated with these genetic risk factors.

If statins have a protective effect, it is unlikely that the effect would be immediate with the initiation of use. The expected length of a possible lag period for statins to have an effect on inflammation or on another step in the causal pathway is unknown. The analyses limited to the subgroup of patients who either were taking statins at entry into CAPT and maintained their use or did not ever take statins were performed to explore whether longer-term users were at

decreased risk. Risk ratios for developing AMD, CNV, and GA did not change appreciably when only this subgroup was analyzed. However, only 12% of CAPT patients were using statins when they enrolled in CAPT.

Because of the effects of statins on both inflammation and vascular endothelial function, a more pronounced effect might be expected for protection from CNV than for GA. However, the CAPT data yielded risk ratios for statins that were lower for GA (risk ratio 0.8) than for CNV (risk ratio 1.30). Risk ratios at or above 1.0 for CNV and below 1.0 for GA were also reported from the two other studies that have examined the risk of CNV and GA separately.^{4,14} Confidence intervals for all the estimates are wide; however, it does not appear that the results for GA are masking a strong protective effect for CNV. In the Beaver Dam Eye Study, the risk ratio for prevalence of CNV was 1.50 (95% confidence interval 0.20–11.34) and of GA was 0.76 (95% confidence interval 0.10–5.78); the risk ratio for incident CNV was 1.25 (95% confidence interval 0.16–9.54) and was 0.25 for incident GA (95% confidence interval 0.05–1.22).⁴ In the Women's Health Initiative Sight Exam, the risk ratio for prevalent CNV was 0.99 (95% confidence interval 0.45–2.18) and was 0.73 (95% confidence interval 0.16–3.34) for GA.¹⁴

All of the observational studies of the effect of statins on AMD, including CAPT, suffer from the fact that statins are prescribed for primary and secondary prevention of coronary heart disease, myocardial infarction, stroke and peripheral artery disease. AMD shares some of the same risk factors as these diseases; thus, there is the possibility that a protective effect of statins for AMD is masked by the fact that only patients at high risk for AMD are prescribed statins. Only a randomized clinical trial can definitively address the impact of statin use on AMD; however, the high proportion of the older people already on statins would make recruitment and treatment compliance difficult. In addition, if the use of statins in older people continues to increase, the relevance of the question will diminish.

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Table 1**Baseline Characteristics of Patients with Completed Interviews**

<i>Patient Characteristics (N=744)</i>	
	n (%)
Age	
50–59	74 (10.0)
60–69	240 (32.3)
70–79	374 (50.3)
>79	56 (7.5)
Mean (standard deviation)	70 (7.4)
Gender	
Female	472 (63.4)
Male	272 (36.6)
Race	
White	740 (99.5)
Non-white	4 (0.5)
Cigarette smoking	
Never	343 (46.1)
Quit	362 (48.7)
Current	39 (5.2)
Hypertension	
Normal	264 (35.5)
Suspect	136 (18.3)
Definite	340 (45.7)
Unknown	4 (0.5)
<i>Eye Characteristics (N=1477)</i>	
Percent of global area covered by drusen (> 63μ)	
< 10%	958 (64.9)
10–24%	412 (27.9)
>= 25%	87 (6.0)
Cannot grade/determine/missing	20 (1.4)
Focal hyperpigmentation	
None/questionable	430 (29.1)
< 250μ	818 (55.4)
>= 250μ	206 (14.0)
Cannot grade/determine/missing	23 (1.6)
Depigmentation of the retinal pigment epithelium	
None	1387 (93.9)
Any	73 (4.9)
Cannot grade/determine/missing	17 (1.2)

Risk Ratios Associated with Statin Use from the Time Dependent Cox Proportional Hazards Model

Table 2

Outcome	Unit of Analysis	Patients Included	Number at Risk	Events	Unadjusted RR (95% Confidence Interval)	Adjusted RR (95% Confidence Interval)
Advanced Age- related Macular Degeneration	Eye	All	1477	332	1.12 (0.85, 1.47)	1.15 (0.87, 1.52)
		Subgroup	1097	231	0.99 (0.66, 1.50)	1.06 (0.69, 1.63)
		All	744	242	1.14 (0.86, 1.53)	1.19 (0.89, 1.60)
Choroidal Neovascularization	Patient	Subgroup	553	170	1.03 (0.68, 1.56)	1.14 (0.75, 1.74)
		All	1477	222	1.36 (1.00, 1.84)	1.35 (0.99, 1.83)
		Subgroup	1097	151	1.29 (0.81, 2.03)	1.30 (0.82, 2.04)
Geographic Atrophy	Patient	All	744	176	1.33 (0.96, 1.84)	1.32 (0.95, 1.84)
		Subgroup	553	122	1.25 (0.79, 1.98)	1.30 (0.82, 2.06)
	Eye	All	1468	114	0.71 (0.41, 1.23)	0.80 (0.46, 1.39)
		Subgroup	1089	85	0.58 (0.24, 1.41)	0.66 (0.26, 1.65)
	Patient	All	743	80	0.70 (0.41, 1.19)	0.75 (0.43, 1.30)
		Subgroup	552	61	0.54 (0.23, 1.27)	0.69 (0.29, 1.66)

RR = risk ratio.