Relation of Statin Use to the 5-Year Incidence and Progression of Age-Related Maculopathy

Ronald Klein, MD, MPH; Barbara E. K. Klein, MD; Sandra C. Tomany, MS; Lorraine G. Danforth, BS; Karen J. Cruickshanks, PhD

Objective: To examine the association of hydroxy-methyl glutaryl coenzyme A reductase inhibitors (statins) with the 5-year incidence of age-related maculopathy (ARM).

Design: Population-based cohort study. Participants included persons 48 to 91 years old examined March 1, 1993, through June 14, 1995, living in Beaver Dam, Wis (N=3684), of whom 2780 participated in a follow-up 5 years later.

Methods: Standardized procedures were used for physical examinations, blood sample collection, and questionnaire administration. Age-related maculopathy was determined by grading images of the posterior pole using a standard protocol. Standard univariate and multivariate analyses were performed.

Main Outcome Measures: Incidence and progression of ARM was measured over the 5-year interval.

Results: While controlling for age and sex, statin use was not found to be associated with the 5-year incidence of early ARM (odds ratio [OR], 1.12; 95% confidence interval [CI], 0.47-2.67), progression of ARM (OR, 1.22; 95% CI, 0.54-2.76), or incidence of late ARM (OR, 0.41; 95% CI, 0.12-1.45).

Conclusions: These findings do not suggest an association between statin use and incident ARM over a 5-year period. Further investigation of these relationships in larger studies over a longer period is needed.

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WHILE photocoagulation and photodynamic therapy have shown some efficacy in reducing severe visual loss in eyes with neovascular age-related macular degeneration, most eyes with advanced age-related macular degeneration do not benefit.1,2 Data from the Age-Related Eye Disease Study showed the limited efficacy of antioxidants and zinc supplements in persons with early age-related maculopathy (ARM) with a 23% rate of progression to advanced ARM in the treated group vs 28% in the control group.3 In addition, 23% of eyes receiving antioxidant and zinc treatment had a 15-letter decrease in the visual acuity score despite such treatment. No other medical interventions have been shown to reduce the incidence and progression of ARM or reduce visual loss.

Recent data from 2 studies showed an inverse association of statins and ARM.4,5 However, the few numbers of persons using statins (27 and 28, respectively) raised concerns about these findings.6 This study examined the association of statins with prevalent and incident ARM in the large population-based Beaver Dam Eye Study.

METHODS

POPULATION

Methods used to identify and describe the population have appeared previously.7-11 In brief, a private census of the population of Beaver Dam, Wis, was taken September 15, 1987, to May 4, 1988, to identify all residents in the city or township of Beaver Dam aged 43 to 84 years. Of the 5924 eligible, 4926 participated in the baseline examination between March 1, 1988, and September 14, 1990.7 Of the population, 99% was white. Of the survivors, 3684 (81.1%) participated in the 5-year follow-up examination between March 1, 1993, through June 14, 1995. Of the 3334 surviving participants in the baseline and second examination, 2764 (82.9%) participated in the second follow-up examination between March 1, 1993, through June 14, 1995. Of the 3334 surviving participants in the baseline and second examination, 2764 (82.9%) participated in the second follow-up examination between March 1, 1993, through June 14, 1995. Of the 3334 surviving participants in the baseline and second examination, 2764 (82.9%) participated in the second follow-up examination between March 1, 1993, through June 14, 1995. Comparisons between participants and non-participants at the time of the baseline and 5- and 10-year follow-up examinations have been published elsewhere.7-9 Nineteen persons (0.5%) were taking statins at the 1988-1990 examination, 143 (3.9%) at the 1993-1995 examination, and 558 (18.9%) at the 1998-2000 examination. Because few persons were taking...
statins at the 1988-1990 examination, for purposes herein, the 1993-1995 examination was considered “baseline.” Because an additional 19 people who did not participate in the first examination participated in the second and third ones, 2783 people were eligible for inclusion in the analysis. Of these, 3 persons were missing data on statin use; therefore, 2780 people contributed to this analysis.

Persons who were alive but did not participate in the 10-year follow-up (n=425) were older at the 1993-1995 examination than those who did (66.1 vs 63.5 years, P<0.001). After adjusting for age, those who were alive during the study period and did not participate were more likely to have fewer years of education completed, a lower annual income, more pack-years smoked, higher systolic blood pressure, and to be retired at the 1993-1995 examination than persons who participated. After adjusting for age and sex, participants with early ARM at baseline were as likely to participate as those in whom ARM was absent (data not shown). While controlling for age, there were no differences in participation at the 10-year follow-up examinations for men and women with a history of statin use and early ARM at the 1993-1995 examination compared with those who had a history of statin use without early ARM (data not shown).

PROCEDURES

Similar procedures have been used at both the 1993-1995 and the 5-year follow-up examinations and are described elsewhere.10-11 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.12 Participants were asked to bring to the examination all medications (prescription and over-the-counter) that they were regularly taking. The examiner asked whether there were other medications being taken but 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 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.13 In addition, subclassification information was included (eg, type of lipid-lowering agent: statin [lovastatin, simvastatin, pravastatin, fluvastatin, or atorvastatin], nicotinic acid, fibric acid derivatives [clofibrate and gemfibrozil], and bile acid sequestrants). 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).14-15 Casual blood specimens were obtained. Serum total and high-density lipoprotein cholesterol levels were determined by enzymatic procedures.14-15 Stereoscopic 30° color fundus photographs centered on the optic disc (Diabetic Retinopathy Study [DRS] standard field 1), macula (DRS standard field 2), and a nonstereoscopic 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 ARM. Grading procedures, lesion descriptions, and detailed definitions for the presence and severity, as well as the incidence of specific lesions, have been published elsewhere.16-18 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.17,18

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 1993-1995 examination, and soft indistinct drusen were present in 1 or more subfields at the 1998-2000 examination, the eye would be considered to have “incident” soft indistinct drusen.

Early ARM 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 ARM was defined by either exudative macular degeneration or pure geographic atrophy.

For each eye, a 6-level severity scale for ARM was defined as follows19:

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 pigmentary abnormalities present or soft drusen (≥125 µm in diameter) with drusen area less than 196350 µm² (equivalent to a circle with a 500-µm diameter) and no pigmentary abnormalities present.

Level 30: Soft drusen (≥125 µm in diameter) with drusen area less than 196350 µm² and pigmentary abnormalities present or soft drusen (≥125 µm in diameter) with drusen area of 196350 µm² or more with or without increased retinal pigment but no RPE depigmentation present.

Level 40: Soft drusen (≥125 µm in diameter) with drusen area of 196350 µm² or more 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 maculopathy severity in either eye by 2 or more steps from level 10 through level 30 and 1 or more steps from level 40 or level 50 from the 1993-1995 examination to the 1998-2000 examination.

Age was defined as the participant’s age at the baseline examination. The mean systolic blood pressure was the average of the 2 systolic blood pressure determinations, and the mean diastolic blood pressure was the average of the 2 diastolic blood pressures at baseline. Pulse pressure was defined as the mean systolic blood pressure minus the mean diastolic blood pressure. A person was defined as having a positive history of cardiovascular disease if at baseline he or 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 nonsmoker if he or she had smoked fewer than 100 cigarettes in his or her lifetime; as an ex-smoker if he or she had smoked more than 100 cigarettes in his or her lifetime but had stopped smoking before the baseline examination; and as a current smoker if he or she had not stopped smoking. A current heavy drinker was defined as a person consuming 4 or more servings of alcoholic beverages daily; a former heavy drinker as having consumed 4 or more servings daily in the past but not in the previous year; and a nonheavy drinker as never having consumed 4 or more servings daily on a regular basis. Participants were classified as current vitamin users if they took
at least 1 vitamin per week within 1 month prior to the baseline examination; as past users if they had ever regularly taken vitamins at least once per week, but not within the last month; and as never being users if they never took vitamins regularly at least once a week.

STATISTICAL METHODS

For these analyses, we examined the relationships between statin use at the examination in 1993-1995 and prevalence and the 5-year incidence of each specific maculopathy lesion, and 2 end points of disease severity—early and late ARM and the progression of ARM. We also looked at change in statin use between the second and third examinations and the prevalence and incidence of early and late ARM and its associated lesions at the 1998-2000 examination. A commercially available SAS software program was used to analyze these data. Multivariate odds ratios and 95% confidence intervals (CIs) were calculated using logistic regression. Age- and sex-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, sex, vitamin use, pulse pressure, total serum cholesterol level, and history of smoking and heavy drinking. Tests of trend were done treating categorical risk factors as continuous variables in the logistic model and computing the \( \chi^2 \) statistic for the parameter estimate. In these models, age was considered using 3 indicator variables, and smoking status, vitamin use, and heavy drinking status were considered using 2 variables. Total serum cholesterol level was also included as a continuous variable in the models. Change in statin use between the 1993-1995 and the 1998-2000 examinations was modeled with 3 indicator variables. When no participants taking statins developed the outcome of interest, adjusted Cochran-Haenszel estimates of the odds ratio, and the corresponding confidence limits are presented. In these cases, the \( P \) value for the odds ratio is computed using the Cochran-Mantel-Haenszel test for association.

RESULTS

Persons taking statins in 1993-1995 were more likely to be ex-smokers and to have hypertension, a greater body mass index, a higher total serum cholesterol level, a lower high-density lipoprotein cholesterol level, and a history of cardiovascular disease than those not taking statins (Table 1). The 5-year incidence and progression of ARM is given in Table 2.

Controlling for age and sex, there were no statistically significant associations of statin use at the baseline with prevalent ARM (Table 3) or with the 5-year incidence and progression of ARM (Table 4). Multivariable models including total serum cholesterol level, multivitamin use, smoking or heavy drinking status, and pulse pressure at baseline did not change these associations (data not shown). With 2780 participants and an \( \alpha \) level of .05, the power to show a 50% decrease in incidence between users and nonusers of statins was 32% for incident early ARM and 34% for progression of ARM.

While correcting for age and sex, persons who began to use statins between the 1993-1995 and 1998-2000 examinations were 32% less likely to have soft indistinct drusen, 36% less likely to have drusen 125 \( \mu \)m or greater in diameter, and 71% less likely to have late ARM present at the 1998-2000 examination compared with persons who never took statins during this period (Table 5). These relations remained while controlling for total serum cholesterol level at the beginning of the period (data not shown).

Table 1. Characteristics of the Population by Statin Use at the 1993-1995 Beaver Dam Eye Study Examination*

<table>
<thead>
<tr>
<th>Variable</th>
<th>No (n = 2862)</th>
<th>Yes (n = 118)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (range), y</td>
<td>63.5 (48-91)</td>
<td>64.1 (48-88)</td>
<td>.50</td>
</tr>
<tr>
<td>Sex, female</td>
<td>1132 (42.5)</td>
<td>49 (41.5)</td>
<td>.83</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>1280 (48.2)</td>
<td>47 (39.8)</td>
<td>.005</td>
</tr>
<tr>
<td>Past</td>
<td>1016 (38.4)</td>
<td>62 (52.5)</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>361 (13.6)</td>
<td>9 (7.6)</td>
<td></td>
</tr>
<tr>
<td>Heavy drinking</td>
<td></td>
<td></td>
<td>.83</td>
</tr>
<tr>
<td>Never</td>
<td>2218 (83.5)</td>
<td>101 (85.6)</td>
<td></td>
</tr>
<tr>
<td>Past</td>
<td>390 (14.7)</td>
<td>15 (12.7)</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>49 (1.8)</td>
<td>2 (1.7)</td>
<td></td>
</tr>
<tr>
<td>Vitamin use</td>
<td></td>
<td></td>
<td>.48</td>
</tr>
<tr>
<td>Never</td>
<td>704 (26.5)</td>
<td>37 (31.4)</td>
<td></td>
</tr>
<tr>
<td>Past</td>
<td>659 (24.8)</td>
<td>29 (24.6)</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>1292 (48.7)</td>
<td>52 (44.1)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No</td>
<td>1632 (62.6)</td>
<td>48 (42.1)</td>
<td></td>
</tr>
<tr>
<td>Yes, untreated</td>
<td>119 (4.6)</td>
<td>1 (0.9)</td>
<td></td>
</tr>
<tr>
<td>Yes, treated and controlled</td>
<td>729 (28.0)</td>
<td>58 (50.9)</td>
<td></td>
</tr>
<tr>
<td>Yes, treated and uncontrolled</td>
<td>127 (4.9)</td>
<td>7 (5.4)</td>
<td></td>
</tr>
<tr>
<td>History of cardiovascular disease</td>
<td>294 (11.1)</td>
<td>32 (27.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Body mass index, mean (range), kg/m²</td>
<td>29.6 (15.5-56.2)</td>
<td>30.7 (19.6-45.4)</td>
<td>.04</td>
</tr>
<tr>
<td>Blood pressure, mean (range), mm Hg</td>
<td>52.9 (15.5-56.2)</td>
<td>49.7 (26-85)</td>
<td>.009</td>
</tr>
</tbody>
</table>

Abbreviation: HDL, high-density lipoprotein.
SI conversion factor: To convert total and HDL cholesterol levels to milliequivalents per liter multiply by 0.02586.
*Data are given as the number (percentage) of participants unless otherwise stated. For an explanation of the various categories, see the “Procedures” subsection of the “Methods” section.
†\( \chi^2 \) test used for discrete risk factors; \( t \) test used for continuous risk factors (Satterthwaite for unequal variances, otherwise pooled \( t \) test).

Because of the discrepancy of the incidence and prevalence data, we examined whether beginning statin use during the period was associated with total serum cholesterol level and characteristics at the start of the period. Those with high total serum cholesterol levels (fourth quartile, \( \geq 267.0 \) mg/dL [6.90 mmol/L]) and drusen size of 125 \( \mu \)m or more in diameter at the start of the period were less likely to begin statin use than those who had high total serum cholesterol levels and drusen size smaller than 125 \( \mu \)m in diameter (23/106 [21.7%] vs 176/530 [33.2%], \( P = .02, \chi^2 \) test). Similar statistically significant associations were found when soft indistinct drusen were present (20/98 [20.4%]) compared with absent (175/522 [33.9%], \( P = .01 \)) and when late ARM was present (1/15 [6.7%]) compared with absent (194/606 [32.0%], \( P = .03 \), Fisher exact test).
In the Beaver Dam Eye Study, statin use was not statistically significantly associated with the prevalence, incidence, or progression of ARM. These findings are inconsistent with data from an earlier cross-sectional cohort study of 66- to 75-year-olds. In that study, 76 (22%) of the 352 persons who did not take statins and 1 (4%) of the 27 who were taking statins had signs of ARM (odds ratio, 0.14; 95% CI 0.02, 0.83). McCarty et al found a statistically nonsignificant (P = .11) 4-fold increase in progression of large drusen (≥125 μm in diameter) but to chance alone given the large number of drugs studied and the small numbers of persons taking statins compared with nonusers. *This value was estimated using logistic regression.

†This value was calculated using the Mantel-Haenszel test.
We found no consistent or significant association of statin use to the incidence or progression of ARM. Further analyses of data from other large population-based studies of longer periods are warranted before advocating a clinical trial of this class of drugs for ARM.

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<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early ARM</td>
<td>0.80 (0.60-1.06)</td>
<td>.12</td>
</tr>
<tr>
<td>Soft indistinct drusen</td>
<td>0.88 (0.59-1.32)</td>
<td>.46</td>
</tr>
<tr>
<td>Drusen &gt;/=125 μm in diameter</td>
<td>0.64 (0.45-0.86)</td>
<td>.003</td>
</tr>
<tr>
<td>Increased retinal pigment</td>
<td>0.87 (0.64-1.19)</td>
<td>.39</td>
</tr>
<tr>
<td>RPE degeneration</td>
<td>0.86 (0.59-1.26)</td>
<td>.44</td>
</tr>
<tr>
<td>Pigmentary abnormalities</td>
<td>0.84 (0.62-1.15)</td>
<td>.28</td>
</tr>
<tr>
<td>Late ARM</td>
<td>0.29 (0.09-0.95)</td>
<td>.04</td>
</tr>
<tr>
<td>Pure geographic atrophy†</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Exudative ARM</td>
<td>0.15 (0.02-1.09)</td>
<td>.06</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio; RPE, retinal pigment epithelium.
†No person developed geographic atrophy.

REFERENCES