Statins, incident Alzheimer disease, change in cognitive function, and neuropathology

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ABSTRACT

Objective: To examine the relation of statins to incident Alzheimer disease (AD) and change in cognition and neuropathology.

Methods: Participants were 929 older Catholic clergy (68.7% women, mean baseline age 74.9 years, education 18.2 years, Mini-Mental State Examination 28.5) free of dementia, enrolled in the Religious Orders Study, a longitudinal clinical-pathologic study of AD. All agreed to brain autopsy at time of death and underwent annual structured clinical evaluations, allowing for classification of AD and assessment of cognition (based on 19 neuropsychological tests). Statins were identified by direct medication inspection. Neuropathologic data were available on 262 participants. All macroscopic chronic cerebral infarctions were recorded. A measure of global AD pathology was derived from silver stain, and separate measures of amyloid and tangles were based on immunohistochemistry. We examined the relation of statins to incident AD using Cox proportional hazards, change in cognition using mixed effects models, and pathologic indices using logistic and linear regression.

Results: Statin use at baseline (12.8%) was not associated with incident AD (191 persons, up to 12 follow-up years), change in global cognition, or five separate cognitive domains (all *p* values > 0.20). Statin use any time prior to death (17.9%) was not related to global AD pathology. Persons taking statins were less likely to have amyloid (*p* = 0.02). However, among those with amyloid, there was no relation of statins to amyloid load. Statins were not related to tangles or infarction.

Conclusions: Overall, statins were not related to incident Alzheimer disease (AD) or change in cognition, or continuous measures of AD pathology or infarction. *Neurology* 2008;70:1795–1802

GLOSSARY

AD = Alzheimer disease; **CERAD** = Consortium to Establish a Registry for Alzheimer's Disease; **MMSE** = Mini-Mental State Examination; **PHF** = paired helical filament.

Statins are 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, which block a key enzyme in the cholesterol synthesis pathway, and are known to have multiple actions.[1] They are among the most widely prescribed medications in the United States, yet their relation to Alzheimer disease (AD), one of the most common neurologic problems in old age, remains unclear. Several studies have suggested that statin users were less likely to have AD,[2-6] while others have not.[7-10] Further, little is known about the relation of statins to the principal manifestation of AD, cognitive decline.[4,11] Although cell and animal studies have suggested a protective effect of statins against pathogenic mechanisms important in AD,[12] little data are available on the relation of statins to AD pathology using human postmortem brain tissue from persons well-characterized during life.

This study tests hypotheses that statins are associated with lower risk of AD, slower rate of cognitive decline, and decreased AD pathology, using data from the Religious

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Orders Study, an ongoing prospective clinical-pathologic study of dementia. Analyses were conducted on more than 900 older persons free of dementia at baseline, who were followed annually for up to 12 years. We first examined relations of statins to clinical outcomes of incident AD and change in cognition, including global cognition and five different cognitive domains. Next, we examined relations of statins to AD pathology and cerebral infarction, two common pathologic causes of dementia, in more than 250 persons who died during the study and on whom neuropathologic data were available.

METHODS **Subjects.** Older Catholic clergy, from >40 groups across the United States, enrolled in the Religious Orders Study, a clinical-pathologic study of dementia, approved by the IRB of Rush University Medical Center. Subjects agreed to annual clinical evaluations and brain donation at time of death and each signed an informed consent and anatomic gift act.

Of 1,096 persons enrolled between January 1994 and November 2006, 82 had baseline dementia and were excluded from analyses. Of the remaining 1,011, clinical data from 929 with at least 1 year of follow-up were available for analyses. Of 1,011 persons without baseline dementia, 314 died, of whom 294 (94%) underwent brain autopsy. Analyses of neuropathologic data were conducted on the first consecutive 262 persons with available data.

Clinical evaluations. Clinical evaluations followed procedures recommended by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD),[13] as previously described in detail.[14] Each subject underwent a baseline uniform structured evaluation. Annual follow-up evaluations were identical to baseline in all essential details, and were performed blinded to previously collected data.

Cognition was evaluated at baseline and each follow-up evaluation using neuropsychological tests that were selected to assess a broad range of abilities, as reported previously.[14-16] Neuropsychological data were reviewed by a neuropsychologist. The Mini-Mental State Examination (MMSE)[17] was used for descriptive purposes. Nineteen tests were used to form summary measures of global cognition and five separate cognitive domains (seven tests for episodic memory, four for semantic memory, four for working memory, two for perceptual speed, and two for visuospatial ability), as previously described.[14] The global cognition measure was based on all 19 tests.[14] Summary measures, derived by converting the raw scores of individual tests to z scores and averaging the z scores, allow for decreased floor and ceiling artifacts.

Dementia and AD[18] were identified by clinicians experienced in diseases of aging, after review of all available clinical data from that year. At time of death, a neurologist, blinded to pathologic data, reviewed all clinical information to render a classification of dementia status proximate to death.

Clinical evaluations documented medications at baseline and at each follow-up examination, by direct visual inspection of all containers for prescription and over-the-counter agents. Medications were recorded and subsequently coded using the Medi-Span Drug Data Base,[19] as previously reported.[20] Statin use was determined using several approaches. A dichotomous variable (use vs nonuse) was created for core analyses: statins were identified at baseline for analyses of clinical outcomes, and at any time during the study (baseline or follow-up) for pathologic outcomes. Statins were further grouped according to lipophilic properties,[9] as lipophilicity affects blood–brain barrier penetration and may relate differentially to outcomes. We also constructed a time-varying measure of cumulative use, by dividing the number of annual visits with statins by number of annual study visits, providing an estimate of duration of exposure to statins during the study.

Clinical evaluations also allowed for assessment of factors with the potential to affect relations of statins to outcomes of interest. Comprehensive medical histories and established tools[21] included questions pertaining to vascular factors. Medication inspection allowed for identification of antidiabetic agents.[22] Clinical examinations documented signs suggestive of stroke. For these analyses, a summary score of vascular diseases was based on the presence or absence of myocardial infarction, congestive heart failure, claudication, and stroke (range 0 to 4) and a score of vascular risk factors on hypertension, diabetes, and smoking (range 0 to 3). Blood specimens were used to perform ApoE genotyping.[23]

Autopsy and neuropathologic measures. Brain autopsies were performed using standard techniques and blinded to clinical data, as previously described.[23,24] Hemispheres were cut coronally into 1 cm slabs. Slabs not designated for freezing were fixed. A uniform examination for cerebral infarctions was conducted. For these analyses, we included all chronic macroscopic infarctions, which were dichotomized as present (one or more) vs absent, as published elsewhere.[24]

Brains were examined for AD pathology. A modified Bielschowsky silver stain was used to visualize pathologic markers of AD in four cortical regions (midfrontal, middle or superior temporal, inferior parietal, entorhinal cortices).[24] The number of neuritic plaques, diffuse plaques, and neurofibrillary tangles in 1 mm^2 area ($\times100$ magnification) in each region were counted. Counts were standardized separately in each region and averaged across the regions to create summary scores of the three markers for each subject. A global AD pathology measure was created, by averaging the summary scores of the three markers.[23] A neuropathologic diagnosis of no, possible, probable, or definite AD was based on semiquantitative estimates of neuritic plaque density as recommended by CERAD.[25] These criteria were modified such that the diagnosis was blinded to age and clinical data. Braak scores were based upon the staging of neurofibrillary tangle pathology.[26]

AD pathology was further characterized by immunohistochemistry and computer-assisted sampling, as previously described.[27] Briefly, we used tissue from six regions (entorhinal, CA1/subiculum, dorsolateral prefrontal, inferior temporal, angular gyrus/supramarginal, calcarine cortices). Amyloid-β was labeled with MO0972 (DAKO, 1:100). Immunohistochemical analysis was performed using diaminobenzidine as the reporter. Amyloid-β was quantified by

image analysis, using systematic random sampling, an Olympus BX60 microscope, a computer-controlled motorized stage, and high sensitivity video camera. A custom algorithm for quantitative analysis of amyloid was used.[28] Averaging values across all six regions yielded a summary measure of amyloid-β-immunoreactive plaque load. To quantify tangles, paired helical filament (PHF)-tau was labeled with AT8 (Innogenetics, 1:1000) using tissue from the same six cortical regions. Tangles were quantified by stereology, using systematic sampling and a stereologic mapping station, with a Leica DMBRE or Olympus BX60 microscope.[27] Averaging values across all regions yield a summary measure of PHF tau-immunoreactive neurofibrillary tangle density. StereoInvestigator software version 5 was used for both immunohistochemical measures.

Statistical analyses. We used a Cox proportional hazards model[29] adjusted for age, sex, and education, to examine the relation of baseline statin use (vs no statin use at baseline) to incident AD. In additional separate analyses, we added terms for vascular diseases, vascular risk factors, ApoE ε4, and their interaction with statins. We also examined the relations of more or less lipophilic statins at baseline (vs no statin), and the cumulative statin variable, to incident AD. Next, the relations of baseline statins to baseline level and change in cognition were examined using separate mixed effects models, adjusted for age, sex, and education.[30]

We examined the relation of statin use at any time point in the study (vs no statin use at any time point) to neuropathologic outcomes. All models adjusted for age at death, sex, and education. Multiple linear regression analyses examined the relation to global AD pathology by silver stain. Because this measure was skewed, it was transformed using the square root. Additional analyses controlled for the presence of cerebral infarction and tested for an interaction between statins and infarctions. More or less lipophilic statins (vs no statin use at any time point) were also examined separately.

We then examined the relation of statins to amyloid and tangles. Because these measures of pathology were skewed, even with square root transformation, we used a two-step analytic approach. The first step was a logistic regression analysis examining the relation of statins to presence vs absence of pathology (using 0.1 unit as the cut-off score for tangles, as the distribution was curvilinear with a large number of cases with near zero values). We performed separate analyses adding terms for infarction and the interaction of statins with infarction, and analyses examining relations for more and less lipophilic statins separately. The second step was a linear regression analysis, in those with pathology, examining the relation of statins to level of pathology (transformed using the square root). Analyses were repeated for more or less lipophilic statins.

Finally, multiple logistic regression analysis examined odds of infarction in statin users vs nonusers.

Analyses were carried out using SAS/STAT software version 8 on a SunUltraSparc workstation. Model assumptions were adequately met.[31]

RESULTS Clinical characteristics at baseline. Of 929 persons, 119 (12.8%) were statin users at baseline and 810 (87.2%) were not. Statin users were younger (72.7 years, SD = 6.1) compared to nonusers (75.2 years, SD = 7.1), with $p < 0.01$.

Gender, education level, and MMSE were similar in both groups (users: 74% women, 18.3 [SD = 3.2] years of education, MMSE 28.7 [SD = 1.6]; nonusers: 67.9% women, 18.1 [SD = 3.4] years of education, MMSE 28.5 [SD = 1.7]; all $p > 0.11$). Among statin users, 67 were taking one with more lipophilic (34 simvastatin and 33 lovastatin) and 52 with less lipophilic (35 atorvastatin, 12 pravastatin, 5 fluvastatin) properties.

Relation of statins to incident AD and cognitive function. During the follow-up period (up to 12 years of annual clinical evaluations), 191 persons developed AD, of whom 16 (8.4%) were statin users at baseline. In a Cox proportional hazards model adjusted for age, sex, and education, baseline statin use was not associated with risk of AD compared to nonuse (HR = 0.91; 95% CI 0.54, 1.52). In separate analyses, the presence of vascular diseases or risk factors (separately) did not change this finding and, in additional analyses, there were no interactions between statins and either vascular diseases or risk factors (all $p > 0.05$). Similarly, the presence of ApoE ε4 did not change the finding and there was no interaction of statins with ApoE ε4. We conducted additional separate analyses of the relations of more and less lipophilic statins, and no effects were observed (HR = 1.05; 95% CI 0.57, 1.95 for more lipophilic and HR = 0.71; 95% CI 0.29, 1.74 for less lipophilic statins). Finally, there was no relation of the cumulative statin variable to incident AD (HR = 0.93; 95% CI 0.56, 1.55).

As the principal manifestation of AD is decline in cognition, we next examined the relation of statins to cognition. Because cognition is a multidimensional process and statins may affect some cognitive domains but not others, after examining the relation of statins to global cognition, we examined relations to summary measures of five separate cognitive domains. Statins were not associated with level (all $p > 0.08$) or change (all $p > 0.20$) in global cognition or any of the cognitive domains, as shown in table 1. Further, among persons who developed dementia, there was no relation of statins to change in global cognition ($p = 0.32$).

Pathologic characteristics of deceased subjects. Pathologic data were available for 262 subjects (mean time from enrollment to death, 5.9 years), with a mean age at death of 85.4 years (SD = 6.8), 148 (56.5%) women, and mean educational level 18.2 years (SD = 3.6). The mean MMSE was 23.5 at the last clinical evaluation (mean time interval to death, 6.5 months). A third (36.3%) had clinical dementia proximate to death. Statin users at any time point during the course of the study (n = 47; 17.9%

Table 1	The relation of statin use to change in cognition in 929 persons*		
Cognitive function	Regression coefficient	Standard error	p Value
Global cognition	−0.014	0.012	0.245
Episodic memory	−0.017	0.016	0.290
Semantic memory	−0.008	0.013	0.529
Working memory	−0.009	0.009	0.321
Perceptual speed	−0.006	0.013	0.617
Visuospatial ability	−0.009	0.010	0.329

*Analyses were adjusted for age, sex, and education.

Table 2	The relation of statin use to Alzheimer disease (AD) pathology in 262 deceased persons*		
Pathologic marker	Regression coefficient	Standard error	p Value
Global AD pathology[†]	−0.06	0.06	0.30
Amyloid load[‡]	−1.02	0.42	0.02
Tangle density[‡]	−0.09	0.58	0.88

*Analyses were adjusted for age at death, sex, and education.
[†] Linear regression analysis using the square root transformation of the global AD pathology score.
[‡] Logistic regression analysis using the presence or absence of pathology as the outcome measure.

of deceased subjects) and nonusers (n = 215; 82.1%) were similar in sex, education, and MMSE, but users were younger (82.6 vs 86.1 years, $p = 0.02$) and less likely to have clinical dementia (12.8% vs 41.4%, $p < 0.001$) at time of death. Nearly all 262 subjects had at least some AD pathology, and the mean global AD pathology score was 0.59 (range 0 to 1.50) in statin users and 0.70 (range 0 to 1.59) in nonusers ($p = 0.07$). More than half of 262 subjects (61.5%) had a CERAD plaque density rating diagnosis of probable or definite AD, and 48.1% had a Braak score of V or VI.

Of 199 persons with amyloid data, the mean age was 85.1 years (SD = 6.5), 104 (52.3%) were women, the mean education was 18.3 years (SD = 3.5), and MMSE 27.9 (SD = 2.0) at the last clinical evaluation. Statin users (16.6%) were younger (81.9 vs 85.7 years, $p < 0.01$) but similar to nonusers (83.4%) for other characteristics (sex, education, MMSE). Most of the 199 persons had amyloid immunoreactivity, with a mean value of 1.79 units (range 0 to 10.33), and statin users had less immunoreactivity compared to nonusers (0.92 vs 1.97 units, $p < 0.01$).

Of 231 persons with tangle data, the mean age was 85.5 years (SD = 6.7), 125 (54.1%) were women, the mean educational level was 18.3 years (SD = 3.6), and MMSE 27.9 (SD = 2.0). Statin users (16.9%) were younger (82.7 vs 86.1 years, $p < 0.01$) but similar to nonusers (83.1%) for other characteristics. Most of the 231 persons had tangle immunoreactivity, with a mean value of 5.96 units (range 0 to 39.19), and there was no difference between statin users and nonusers.

Eighty-one of 262 subjects (30.9%) had cerebral infarctions, present in 23.4% of statin users and 32.6% of nonusers ($p = 0.22$).

Relation of statins to neuropathology. All models adjusted for age at death, sex, and education. In a linear regression analysis, statins were not associated with the global AD pathology score, as shown in table 2. In this analysis, there was 80% power to detect a difference in pathology score as small as 0.17 unit, which represents about one quarter of the interquartile range. The finding was unchanged after controlling for the presence of cerebral infarction and, in a separate model, there was no interaction between statins and infarctions. Compared to no statin use, more or less lipophilic statin use was not associated with global AD pathology ($p = 0.28$ for more lipophilic and $p = 0.76$ for less lipophilic statins). Additional analyses did not show a relation of statins to CERAD plaque density rating ($\chi^2[1] = 0.54$, $p = 0.46$) or Braak staging ($\chi^2[1] = 0.83$, $p = 0.36$).

In addition to using a silver-stain measure, we used quantitative measures of amyloid and tangles based on immunohistochemistry, to further examine the relation of statins to AD pathology. Using a logistic regression analysis, we found that statin users were less likely to have amyloid (table 2). The presence of cerebral infarction did not change this relation (regression coefficient = −1.00, SE = 0.43, $p = 0.02$). In a separate model, there was no interaction between statins and infarctions ($p = 0.19$). More lipophilic statins were associated with a lower likelihood of amyloid (regression coefficient = −1.14, SE = 0.53, $p = 0.03$), and there was no effect with less lipophilic statins (regression coefficient = −0.73, SE = 0.52, $p = 0.16$). Next, restricting analyses to those with amyloid pathology present (n = 155), we conducted linear regression analyses to further examine these relations. We did not find relations of all statins ($p = 0.13$), more lipophilic ($p = 0.73$) or less lipophilic statins ($p = 0.09$), with the continuous measure of amyloid load. Further, there was no relation of statins to amyloid in persons with ($p = 0.20$) or without ($p = 0.61$) clinical dementia.

Similarly, we examined the relation of statins to tangles. First using a logistic regression analysis, we found no relation (table 2). This was unchanged when a term for cerebral infarction was added to the model ($p = 0.81$), and there was no interaction of statins with infarctions. No relations were found with either more ($p = 0.38$) or less lipophilic statins ($p = 0.87$). Finally, restricting analyses to those with tangle pathology (n = 210), we did not find relations of all statins, or more or less lipophilic statins, with tangles in separate linear regression analyses (all $p > 0.38$).

Because persons taking statins may be at lower risk for cerebral infarction, we examined the relation of statins to infarction. Using a logistic regression model adjusted for age, sex, and education, we did not find a relation (OR = 0.9, 95% CI: 0.4, 1.8).

DISCUSSION In this study of more than 900 older persons without baseline dementia and up to 12 years of annual follow-up, we did not find a relation of statins to incident AD, or change in global cognition or five separate cognitive domains. In more than 250 deceased subjects with neuropathologic data, we did not find a relation of statins with continuous measures of AD pathology, but we found an inverse relation with one of the amyloid measures. Statin use was not related to cerebral infarction. Overall, these results do not support a relation between statins and AD or cognitive decline among older persons.

Results from observational studies of statins and clinically diagnosed AD have been mixed, with cross-sectional studies differing markedly from longitudinal studies. Three cross-sectional studies have found that statin users were less likely to have AD.[2,4,6] Also, two nested case-control studies suggested that statins have a protective effect against the development of AD.[3,5] On the other hand, four recent prospective longitudinal studies failed to show a relation of statins to incident AD.[7-10] In the study with the highest number of follow-up evaluations, authors found that statin users had a similar risk of developing AD compared to those who never used a lipid-lowering agent.[9] By contrast, when authors analyzed data cross-sectionally, they found that current statin users had about half the odds of AD, underscoring the challenges of interpreting results from cross-sectional data. Our study supports the substantial amount of data derived from longitudinal studies that statins are not protective against the development of AD. However, re-

sults concerning the relation of statins to AD may be affected by a variety of factors other than study methodology. Statins may have a direct action on AD pathogenesis[32,33] and statins' effects may differ by their lipophilicity.[34] We are aware of only one other prospective study examining this issue, and there was no evidence of a relation of either more lipophilic or less lipophilic statins to incident AD.[9] Our study is in keeping with these findings. However, interpretation needs to be done with caution, as the number of persons taking a statin who later developed AD was small. Examining these and other factors may help better understand the relation of statins to clinical AD.

Another approach to understanding the relation of statins to AD is to examine the relation of statins to the principal manifestation of AD, namely decline in cognition. To our knowledge, only two observational studies in older persons have examined the relation of statins to cognition, with one study suggesting a relation[4] and the other not.[11] Both studies assessed cognition at only two time points. With this approach, differences in cognition reflect much of the initial cross-sectional level. By contrast, studies using three or more data points on cognition can more accurately separate cross-sectional from longitudinal effects, and allow for a better estimate of change in cognition.[35] Our study took advantage of annual measures of cognitive performance over a long follow-up period. Power was further enhanced by analyzing the outcomes as continuous measures, and by using composite measures of cognition. However, our null findings will need to be replicated in more diverse cohorts.

Little data are available regarding the relation of statins to measures of AD pathology. We are aware of only one other study of statins and AD pathology using human postmortem tissue.[36] Using data from 110 persons, representing about 20% of deceased persons of a subset of those under 80 years of age at enrollment in a large prospective study, authors found no relation of statins to Braak staging or CERAD plaque density rating in models adjusting for age, gender, and cognition at enrollment. When controlling for additional factors including microvascular lesions, statins were associated with lower Braak staging. By contrast, our study did not suggest a relation of statins to AD pathology, whether by Braak staging or a more sophisticated measure of tangles by quantitative immunohistochemistry, and findings were not affected by vascular factors, in particular cerebral infarction. The basis for the discrepancy between the two studies is uncertain. Our

study had an autopsy rate >90%, decreasing the possibility of selection bias, and more than double the sample size. Contrary to Braak staging for which pathology assessment is limited to the temporal lobe, we also assessed tangles in six separate cortical regions and conducted analyses with tangles as both categorical and continuous measures. Although both studies did not find a relation of statins to CERAD plaque density rating, our data of an inverse association of statins with amyloid (dichotomized as present vs absent), and noted only in those using more lipophilic but not less lipophilic statins, may be supportive of a possible protective effect of statins against the other key pathologic marker of AD, amyloid. However, we did not find a relation of statins with a continuous measure of amyloid, raising the possibility of a spurious finding. Nevertheless, nonclinical studies in the field have yielded provocative findings,[37] including that statins may modulate metabolism of the amyloid-precursor protein, by activation of α-secretase activity,[12] and have other modulatory effects that decrease production of amyloid-β and decrease amyloid-β load.[38] Further, several other mechanisms may play a role in the possible protective effect of statins in AD. Statins have been found to attenuate cerebral inflammatory pathways by inhibiting glial production of cytokines,[39,40] reduce oxidative stress,[41] increase cerebral circulation,[42,43] and reduce plasma membrane cholesterol.[44] Statins may also decrease risk for cerebrovascular disease,[45] which in turn may decrease the likelihood of clinical expression of AD.[46] However, we did not find a relation of statins with cerebral infarction in our study. Although the diverse actions of statins suggest potential therapeutic effects in AD, large clinical-pathologic studies using human tissue are needed to examine these questions further. With the advent of sophisticated brain imaging techniques that allow in vivo imaging of amyloid and hopefully soon tangles, imaging may provide a complementary means to further assess the relation of statins to AD.

Weaknesses of this study are derived from several factors. First, this study is limited by the likely possibility of indication bias (statin exposure is nonrandom). Second, we cannot rule out the possibility that limited power may have contributed to the null results. In particular, because there were relatively few statin users among those who died, we had limited power to detect a weak association between statins and AD pathology. Third, the findings may not be generalizable. Finally, the possibility of associations of statins with other pathologic/biologic changes of AD not assessed here need to be explored in future human postmortem studies.

This study has several strengths. Importantly, we examined incident AD, change in cognition, and neuropathology in the same large cohort, while taking advantage of the long follow-up period and high follow-up and autopsy rates. These rates minimize selective attrition effects and information bias, and contribute to high internal validity of the study. Further, the number of annual evaluations provided power to detect relations of interest, particularly that of statins with change in cognition. Next, the cohort homogeneity may, in fact, control for effects of potential confounding factors (e.g., access to health care). Finally, the study benefited from detailed neuropathologic data (including silver stain and immunohistochemistry) on a large number of well-characterized deceased persons, allowing to assess for relations of statins to neuropathologic causes of dementia.

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