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Statin Use and the Risk of Incident Dementia

The Cardiovascular Health Study

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Background: Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) reduce cardiovascular risk through mechanisms that might affect the development of dementia.

Objective: To evaluate whether statin use is associated with a lower risk of dementia compared with never use of lipid-lowering agents (LLAs).

Design: Cohort study of community-dwelling adults 65 years and older. The analysis included 2798 participants free of dementia at baseline.

Main Outcome Measures: Using Cox proportional hazards regression analysis, we estimated the risk of incident all-cause and type-specific dementia associated with time-dependent statin therapy compared with never use of LLAs. The primary analyses incorporated a 1-year lag between exposure and outcome. Secondary analyses included the final year of exposure and modeled statin use as current use vs nonuse to simulate a case-control approach.

Results: Compared with never use of LLAs, ever use of statins was not associated with the risk of all-cause dementia (multivariable-adjusted hazard ratio [HR], 1.08; 95% confidence interval [CI], 0.77-1.52), Alzheimer disease alone (HR, 1.21; 95% CI, 0.76-1.91), mixed Alzheimer disease and vascular dementia (HR, 0.87; 95% CI, 0.44-1.72), or vascular dementia alone (HR, 1.36; 95% CI, 0.61-3.06). In contrast, in secondary analyses, current use of statins compared with nonuse of LLAs was associated with HRs of 0.69 (95% CI, 0.46-1.02) for all-cause dementia and 0.56 (95% CI, 0.35-0.92) for any Alzheimer disease.

Conclusions: In this cohort study, statin therapy was not associated with a decreased risk of dementia. Methodological differences may explain why results of this cohort investigation differ from those of prior case-control studies. Additional investigation is needed to determine whether and for whom statin use may affect dementia risk.

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DEMENTIA IS ASSOCIATED with excess morbidity and mortality.[1] The most common causes of dementia are Alzheimer disease (AD) and cerebrovascular changes that produce vascular dementia (VaD). Although each type may evolve from distinct pathophysiologies, evidence suggests that the 2 may exist along a spectrum.[2] For both causes, many demographic, socioeconomic, genetic, and clinical risk factors have been identified, perhaps reflecting different pathological processes.[2,3] In particular, some evidence supports a role of lipid metabolism or inflammation in the development of dementia, specifically AD.[4]

The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, or statins, prevent cardiovascular disease in at-risk populations. These agents may reduce cardiovascular risk by inhibiting cholesterol synthesis or through anti-inflammatory effects.[5] Statin use could therefore affect the development of dementia. In vivo, in vitro, and epidemiological investigations have reported a possible protective association between statin use and the dementia process, specifically AD.[6-12] In contrast, results from trials designed to assess the cardiovascular effects of statin use, in which a surrogate measure was used to assess dementia, have not shown a protective statin association.[13] Using data from the Cardiovascular Health Cognition Study, an ancillary study of the Cardiovascular Health Study, we assessed the risk of incident all-cause and type-specific dementia associ-

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Table 1. Proportions of Person-years of Characteristics According to Use of Lipid-Lowering Agents*

Characteristic	No Lipid-Lowering Therapy (13 209 Person-years)	Statin Therapy (1284 Person-years)	Other Lipid-Lowering Therapy (537 Person-years)
Age >80 y	7199 (54.5)	728 (56.7)	243 (45.3)
Female sex	7825 (59.2)	864 (67.3)	316 (58.8)
White race	11 925(90.3)	1165 (90.7)	492 (91.6)
Educational level			
<High school	2617 (19.8)	263 (20.5)	123 (22.9)
High school or vocational school	5020 (38.0)	523 (40.7)	244 (45.4)
College or graduate school	5572 (42.2)	498 (38.8)	170 (31.7)
Current smoker	1035 (7.8)	103 (8.0)	52 (9.7)
Alcohol use, drinks/wk			
0	6700 (50.7)	743 (57.9)	308 (57.3)
1-7	4888 (37.0)	413 (32.2)	205 (38.2)
≥8	1621 (12.3)	128 (10.0)	24 (4.5)
Baseline Mini-Mental State Examination score <95	6474 (49.0)	557 (43.4)	250 (46.6)
Diabetes mellitus	2384 (18.0)	262 (20.4)	130 (24.2)
Diastolic blood pressure ≥90 mm Hg or systolic blood pressure ≥140 mm Hg	4566 (34.6)	446 (34.7)	156 (29.1)
Coronary heart disease	2426 (18.4)	531 (41.4)	168 (31.3)
Stroke	540 (4.1)	85 (6.6)	43 (8.0)
Total cholesterol level >200 mg/dL	7614 (57.6)	980 (76.3)	372 (69.3)
Baseline C-reactive protein level >2.0 mg/dL	5539 (41.9)	655 (51.0)	271 (50.5))
≥1 *APOE* ε4 allele	2684 (20.3)	359 (28.0)	94 (17.5)

SI conversion factor: To convert cholesterol to millimoles per liter, multiply by 0.0259.
*Data are given as number (percentage) of person-years.

ated with statin therapy. We hypothesized that statin therapy would be associated with a lower risk of dementia compared with never use of lipid-lowering therapy.

METHODS

SETTING, SUBJECTS, AND DESIGN

The Cardiovascular Health Study[14] is a prospective population-based cohort study of risk factors for cardiovascular disease among community-dwelling older adults. The Cardiovascular Health Cognition Study included the subset of Cardiovascular Health Study participants 65 years and older who underwent magnetic resonance imaging from 1991 to 1994 and a concurrent Mini-Mental State Examination. The present analyses include 2798 participants who were free of dementia at the time of the baseline magnetic resonance imaging. The study was approved by appropriate institutional review boards.

At baseline, the Cardiovascular Health Study collected data on demographics, clinical characteristics, medication use, diagnostic testing, laboratory assessments, and clinical outcomes. The clinical assessment included functional health status, cognitive function, smoking status, alcohol intake, blood pressure, diabetes mellitus status, and clinical and subclinical measures of cardiovascular disease. The laboratory assessment included baseline fasting lipid profile, *APOE* ε4 genotype, and C-reactive protein level. To assess medication use, participants brought all prescription medications used within the prior 2 weeks to each annual study visit.[15] Participants were followed up annually with regard to functional health status, symptoms, physical examination, clinical characteristics, and medication use.

MAIN OUTCOME MEASURES

The criteria and process used to identify dementia in the Cardiovascular Health Cognition Study[16] have been detailed previously. The main outcomes of the present analysis were incident all-cause dementia and dementia due solely to AD as defined by the criteria of the National Institute of Neurological and Communicative Diseases and Stroke.[17] The State of California Alzheimer's Disease Diagnostic and Treatment Centers criteria[18] were used to identify VaD.

EXPOSURES

The main exposure was the use of lipid-lowering agents (LLAs), specifically statins, as assessed by the annual medication inventory. Lipid-lowering agents were grouped according to statin and nonstatin classifications. Statins were further classified as more lipophilic (lovastatin, simvastatin, and cervistatin) or less lipophilic (atorvastatin calcium, pravastatin sodium, and fluvastatin sodium).[19] Nonstatin LLAs included fibrates, niacin, bile acid sequestrants, and probucol, with fibrate use constituting three quarters of nonstatin use. The baseline cognitive assessment was performed using the Modified Mini-Mental State Examination.[20]

STATISTICAL ANALYSIS

For the main analyses, the use of LLAs was modeled as a time-dependent covariate and categorized as never use, statin use, or nonstatin LLA use. The use of statins and nonstatin LLAs was modeled as ever use, current use, or former use. Time-dependent Cox proportional hazards regression analysis was used to compute multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the association of LLA use with dementia, using never users as the referent group.

For the primary analyses, follow-up started at the date of the baseline magnetic resonance imaging and extended to 1 year before the date of dementia diagnosis or censoring. The main models a priori incorporated this 1-year lag because dementia typically manifests in a gradual manner. Therefore, from a biological perspective, exposures that provide a protective effect would typically be present months or years before clinical de-

Table 2. Relative Risks of Incident All-Cause and Type-Specific Dementia According to Use of Lipid-Lowering Agents*

	All-Cause Dementia					Alzheimer Disease Alone			Mixed Alzheimer Disease and Vascular Dementia			Vascular Dementia Alone		
Use of Lipid-Lowering Agents	Events	Person-years	Rate†	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Events	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Events	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Events	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Never use‡ statin therapy	428	13 209	32.4	1	1	216	1	1	137	1	1	55	1	1
Ever use	**38**	**1284**	29.6	1.15 (0.82-1.60)	1.08 (0.77-1.52)	**21**	1.20 (0.76-1.89)	1.21 (0.76-1.91)	**9**	0.95 (0.48-1.87)	0.87 (0.44-1.72)	**7**	1.64 (0.74-3.65)	1.36 (0.61-3.06)
Current use	26	1069	24.3	0.95 (0.64-1.42)	0.90 (0.61-1.35)	13	0.91 (0.52-1.60)	0.92 (0.52-1.62)	6	0.77 (0.34-1.75)	0.71 (0.31-1.61)	6	1.70 (0.72-3.99)	1.39 (0.59-3.31)
Former use	12	215	55.8	2.04 (1.14-3.63)	1.88 (1.05-3.36)	8	2.56 (1.25-5.22)	2.54 (1.24-5.20)	3	1.82 (0.57-5.75)	1.61 (0.51-5.12)	1	1.35 (0.18-9.88)	. . .
Other lipid-lowering therapy														
Ever use	**14**	**537**	26.1	0.86 (0.50-1.46)	0.86 (0.50-1.46)	**8**	1.00 (0.49-2.02)	1.05 (0.51-2.13)	**5**	0.93 (0.38-2.28)	0.95 (0.39-2.34)	0	. . .	. . .
Current use	10	348	28.7	1.01 (0.54-1.89)	0.98 (0.52-1.85)	6	1.24 (0.55-2.80)	1.28 (0.57-2.90)	3	0.92 (0.29-2.88)	0.90 (0.29-2.86)	0	. . .	. . .
Former use	4	189	21.2	0.62 (0.23-1.66)	0.65 (0.24-1.74)	2	0.62 (0.15-2.52)	0.67 (0.17-2.71)	2	0.96 (0.24-3.89)	1.03 (0.25-4.21)	0	. . .	. . .

Abbreviations: CI, confidence interval; HR, hazard ratio.

*Model 1 adjusts for age and sex. Model 2 adjusts for age, sex, educational level, baseline alcohol consumption, baseline Modified Mini-Mental State Examination score, baseline coronary heart disease status, and baseline stroke status. Only the estimate for the age- and sex-adjusted model is presented when a single event occurs for a particular exposure.

†Rate is events per 1000 person-years.

‡"1" indicates the referent group.

mentia. A secondary set of models included the final year of exposure status and modeled LLA use as current use vs nonuse because this model best approximates the case-control approach.[9-12]

Additional analyses were restricted to persons with a diagnosis of coronary heart disease or a baseline total cholesterol level of 200 mg/dL or higher (≥5.18 mmol/L), which are indications for LLA therapy. Differences between subgroups defined by sex, age (≤75 vs >75 years), race, smoking status, hypertension, diabetes mellitus, clinical cerebrovascular disease, *APOE* ε4 genotype, or quartiles of C-reactive protein levels were assessed with the addition of a cross-product term between the covariate of interest and the categorical LLA variable. Analyses were done using Stata version 7.0 (StataCorp LP, College Station, Tex).

RESULTS

On average, person-years of LLA use were associated with alcohol abstinence, a higher score on the Mini-Mental State Examination, diabetes mellitus, clinical heart disease, and elevated total cholesterol and C-reactive protein levels (**Table 1**). In addition, person-years of statin use were associated with female sex and the presence of an *APOE* ε4 allele.

During 15 030 person-years of follow-up, there were 480 incident cases of dementia, including 245 attributable to AD alone, 151 attributable to a combination of AD and VaD, 62 attributable to VaD alone, and 22 attributable to other causes. In the primary analyses with the 1-year lag in exposure classification (**Table 2**), ever use of statins was not associated with the risk of all-cause dementia (HR, 1.08; 95% CI, 0.77-1.52), AD alone (HR, 1.21; 95% CI, 0.76-1.91), mixed AD and VaD (HR, 0.87; 95% CI, 0.44-1.72), or VaD alone (HR, 1.36; 95% CI, 0.61-3.06) compared with never users. In analyses that recoded ever use of statin therapy into current or former use, current use was not associated with the risk of dementia. However, former use of statins was associated with an elevated risk of all-cause dementia (HR, 1.88; 95% CI, 1.05-3.36) and AD alone (HR, 2.54; 95% CI, 1.24-5.20) compared with never users. Ever use of nonstatin LLAs was not associated with the risk of all-cause dementia (HR, 0.86; 95% CI, 0.50-1.46) or AD alone (HR, 1.05; 95% CI, 0.51-2.13) compared with never use of LLAs. Further adjustment for race, smoking status, hypertension, diabetes mellitus, atrial fibrillation, low-density lipoprotein and total cholesterol levels, *APOE* ε4 genotype, C-reactive protein level, carotid intima-media thickness, aspirin use, benzodiazepine use, or total number of medications used did not appreciably change the estimates.

No dose response was detected with regard to risk and duration of statin use. Compared with never use of LLAs, the HRs of all-cause dementia were 0.98 (95% CI, 0.55-1.74) for ever use of statins for less than 1 year, 1.41 (95% CI, 0.89-2.25) for 1 to 3 years, and 0.74 (95% CI, 0.35-1.57) for greater than 3 years. For AD alone, the HRs were 1.52 (95% CI, 0.78-2.98) for ever use of statins for less than 1 year, 1.05 (95% CI, 0.49-2.24) for 1 to 3 years, and 1.04 (95% CI, 0.42-2.56) for greater than 3 years. Similarly, no difference was detected between use of statins that were more or less lipophilic. Compared with never use of LLAs, ever use of more lipophilic statins was associated with HRs of 0.94 (95% CI, 0.61-1.44) for all-

cause dementia and 1.03 (95% CI, 0.57-1.86) for AD alone, and ever use of less lipophilic statins was associated with HRs of 1.38 (95% CI, 0.83-2.29) for all-cause dementia and 1.58 (95% CI, 0.80-3.11) for AD alone. When analyses were restricted to subjects with clinical coronary heart disease or a total cholesterol level of 200 mg/dL or higher (≥5.18 mmol/L), the HRs associated with ever use of statins were 0.97 (95% CI, 0.67-1.42) for all-cause dementia and 1.01 (95% CI, 0.61-1.69) for AD alone compared with never use. Similarly, no association differences were detected across the specific subgroups detailed in the "Methods" section.

In secondary analyses that included the final year of exposure, current use of statins compared with nonuse of LLAs was associated with HRs of 0.69 (95% CI, 0.46-1.02) for all-cause dementia and 0.59 (95% CI, 0.32-1.10) for AD alone. The HR for the association between current statin use and any AD, combining the AD alone and mixed AD and VaD events (n=396), was 0.56 (95% CI, 0.35-0.92).

COMMENT

Given the prevalence of dementia and its associated morbidity and mortality, an effective preventive pharmacological treatment would have important public health implications. In this prospective cohort of older adults, antecedent statin use was not associated with a lower risk of all-cause dementia or AD compared with never use of LLAs after considering other known or suspected risk factors. In contrast, the results suggested a protective statin association in models that simulated the typical case-control design of a cross-sectional statin exposure and dementia outcome.

Several factors may explain why statin use was not associated with a lower risk of dementia. Participants were on average 75 years of age, and statin use was assessed for a median of 5 years. Statin exposure may need to occur earlier in adulthood or for longer periods to prevent dementia, although analyses that stratified the duration of statin use did not suggest a duration-dependent association. The potential benefit may depend on the particular type of statin used or the characteristics of the patient, although analyses that assessed the association by statin lipophilicity or by clinical subgroup did not detect differences.

Alternatively, statin use may not affect the development of dementia. Case-control studies[9-12] have reported a protective association typically based on cross-sectional statin exposures and dementia outcomes and have not considered former use or incorporated a lag period into the analysis. A protective statin association was observed in the present investigation when analyses modeled the statin exposure as current use vs nonuse and did not incorporate a lag period, thereby simulating a case-control approach. In contrast, no association was evident in the primary analyses. Indeed, former use of statins was associated with an elevated risk of dementia. Although starting and stopping statin therapy may somehow trigger the dementia process, the most likely explanation is that former statin use (discontinuation of statin therapy) is a surrogate marker for declining health. Patients and physicians may be less inclined to maintain preventive treatments such as statin use as overall health deteriorates.[21] Conversely, current statin use may be a surrogate marker for good health, which may be associated with a lower risk of dementia.

This study has limitations. Despite efforts to minimize confounding, we cannot exclude the possibility of uncontrolled confounding in this prospective cohort study. For example, the primary indication for statin therapy was elevated cholesterol in the setting of coronary heart disease or its risk factors. Some authors have reported that heart disease is a risk factor for dementia.[3] However, analyses that adjusted for heart disease or restricted the assessment to persons with a clinical indication for statin therapy did not reveal an association. The primary analyses had greater than 80% power to detect a 50% decrease in risk of all-cause dementia or AD (a risk difference comparable to previous reports from epidemiological studies[9-12]); however, the study had modest power to detect associations among subgroups of interest.

In this investigation, statin therapy was not associated with a lower risk of dementia. Although statin use is an important treatment for cardiovascular disease, additional investigation is needed to determine whether and for whom statin use may affect dementia risk.

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