Decreased Prevalence of Alzheimer Disease Associated With 3-Hydroxy-3-Methyglutaryl Coenzyme A Reductase Inhibitors

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Context: Increasing evidence suggests that cholesterol plays a role in the pathophysiology of Alzheimer disease (AD). For instance, an elevated serum cholesterol level has been shown to be a risk factor for AD.

Objective: To determine whether patients taking 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), which are a group of medicines that inhibit the synthesis of cholesterol, have a lower prevalence of probable AD.

Design: The experiment uses a cross-sectional analysis comparing the prevalence of probable AD in 3 groups of patients from hospital records: the entire population, patients receiving 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (hereafter referred to as the statins), and patients receiving medications used to treat hypertension or cardiovascular disease.

Patients: The subjects studied were those included in the computer databases of 3 different hospitals for the years October 1, 1996, through August 31, 1998.

Main Outcome Measures: Diagnosis of probable AD.

Results: We find that the prevalence of probable AD in the cohort taking statins during the study interval is 60% to 73% (P<.001) lower than the total patient population or compared with patients taking other medications typically used in the treatment of hypertension or cardiovascular disease.

Conclusions: There is a lower prevalence of diagnosed probable AD in patients taking 2 different 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors—lovastatin and pravastatin. While one cannot infer causative mechanisms based on these data, this study reveals an interesting association in the data, which warrants further study.

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The pathophysiology of Alzheimer disease (AD) has many connections with cholesterol metabolism. Epidemiological studies show that patients with elevated cholesterol levels have an increased risk of AD. One of the major risk factors for AD, is apolipoprotein E type 4 (APOE4), which is a cholesterol transport protein. Patients carrying the APOE4 polymorphism have elevated cholesterol levels, although at least part of the risk for AD seems to derive from factors unrelated to cholesterol level. Patients with the APOE4 polymorphism also have increased risk of cardiovascular disease, and epidemiological studies show that patients with cardiovascular disease have an increased risk of AD. A second putative risk factor for AD, α2-macroglobulin, binds to the same receptor as does APOE4. This receptor, the lipoprotein receptor–related protein, is important for cellular uptake of cholesterol. Cholesterol also effects the biology of β-amyloid (Aβ). β-Amyloid is a protein that accumulates in the affected brains of patients with AD and is thought to cause the neurodegeneration underlying AD. Production of the Aβ peptide is increased by cholesterol in some cells. These multiple links suggest a potentially important relation between cholesterol and AD.

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PATIENTS, MATERIALS, AND METHODS

This is a cross-sectional analysis comparing the prevalence of AD in patients 60 years or older in the following 3 groups (which are each subdivided by the particular medication): (1) the entire population, (2) patients receiving statins, and (3) patients receiving medications used to treat hypertension or cardiovascular disease. The term "AD," as used for data in this article, refers to probable AD. To perform the study, we searched relational databases at 3 different hospitals (Loyola University Medical Center, Maywood, Ill, 22143 medical records; Edward Hines Jr Veterans Affairs Hospital, Hines, Ill, 23028 medical records; and Carl T. Hayden Veterans Affairs Medical Center, Phoenix, Ariz, 15178 medical records) to obtain aggregate data about the frequency of AD. The relational databases allow correlational analysis of fields (such as diagnosis and medication) within a patient medical record from an aggregate patient database. The 3 databases are independent and do not overlap. The databases contain patient medical records, including information relevant to this study: age, sex, International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnoses, and medications history. Severity of disease was not present in the databases. For Edward Hines Jr Veterans Affairs Hospital and Carl T. Hayden Veterans Affairs Medical Center, the medical records describe patients who used the hospitals in the last 2 years (October 1, 1996, through August 31, 1998). Entries in the databases that contained patients' names but no medical information were excluded. Patients younger than 60 years were also excluded. Next we identified all patients who were taking 8 different medications (Table). Some of the patients may have received more than 1 medication or had more than 1 diagnosis. We then determined the prevalence of AD or transient ischemic attacks (TIAs) for patients taking each medication. The patient searches were carried out using ICD-9-CM codes. Alzheimer disease was specifically identified under the code 331.0. However, as other codes also apply to AD, we included the following: 331.2 and 290.0, 290.10 to 290.13, 290.20, 290.21, and 290.3. Patients with TIAs were identified with ICD-9-CM codes: 434.00, 433.00, 433.10, 433.20, 435.0, and 435.2. Patients at each site who were being assessed for dementia were all seen or their medical records reviewed by the same attending neurologist or geriatrictian (Loyola University Medical Center [G.G.C.]; Edward Hines Jr Veterans Affairs Hospital [G.S.]; and Carl T. Hayden Veterans Affairs Medical Center [P.R.]). The diagnosis of AD was made according to the criteria of the National Institute of Neurology, Communicative Disorders, and Stroke—Alzheimer's Disease and Related Disorders Association:11 clinical evidence of progressive dementia in more than 1 area of cognition in patients aged between 40 and 90 years, documentation of cognitive impairment by the Mini-Mental State Examination (MMSE), neuropsychological examination, and exclusion of other diagnoses by computed tomography or magnetic resonance imaging of the brain. The patients with the diagnosis of AD were all screened for other causes of their dementia. Each patient was screened for other metabolic, toxic, or affective disorders that may produce dementia. To screen for toxic or metabolic disorders, every patient with a putative diagnosis of AD underwent blood workup that included tests for VDRL findings and for thyrotropin, electrolytes, vitamin B12, folic acid, hepatic enzymes, serum creatinine, and serum urea nitrogen levels. Patients were screened for drug abuse, alcohol abuse, or affective disorder by clinical assessment. However, it is recognized that there may be considerable overlap of probable AD with ischemic white matter and subcortical nuclear lesions and leukoaroitis as shown in prospective clinical longitudinal studies,12 as well as overlap of definite AD with infarction on postmortem analyses. Thus, the diagnosis of probable AD by the usual conventional criteria does not exclude confounding vascular disease factors. In this study, the diagnosis of AD refers to probable AD and does not exclude the possibility of overlapping leukoaroitis or ischemic white matter or subcortical nuclear lesions. At the Carl T. Hayden Veterans Affairs Medical Center, all patients with a diagnosis of AD had MMSE scores of 24 or less. At Loyola University Medical Center all patients either had a MMSE score of 24 or less or had taken a full battery of neuropsychological testing. At the Edward Hines Jr Veterans Affairs Hospital, all patients for whom a MMSE test result was available had scores of 24 or less.

Statistics were determined by comparisons of proportions using χ² analyses. All statistics list P values.

RESULTS

The mean age of patients (>60 years) taking each medication did not differ significantly among the 8 samples (Table). In all 3 databases the overall prevalence of diagnosis of AD (1.28%) was found to be below the estimated population prevalence of AD in the elderly subjects (2%-10%).14 This could be owing to the use of register-based case finding vs population-based active screening.

The trends seen at each hospital were similar. At each of the 3 sites, the prevalence of diagnosed AD in patients taking lovastatin or pravastatin was 60% to 73% lower than the entire patient population aged 60 years or older (Table, P<.001 for each site). At each site, patients taking lovastatin or pravastatin also had a lower prevalence of diagnosed AD than patients taking β-blockers, furosemide, or captopril (Table). However, although the trends for each medication were clear, the number of patients receiving each medication at each site was not sufficiently large to allow meaningful statistical analysis. To maximize the statistical power of the analysis, we combined the data from the 3 sites. This was justified because of the similar diagnostic trends and simi-
The total patient sample size used for this study was 26,171 patients. Statistical significance was set at P < .001. Results were seen at the other 2 sites (Edward Hines Jr Veterans Affairs Hospital, Maywood, and Carl T. Hayden Veterans Affairs Medical Center, Phoenix, Ariz).

The prevalence of diagnosed Alzheimer disease (AD) in patients taking the statins on the prevalence of another syndrome (TIAs). The sex distribution did differ between the 3 sites, but the differences did not seem to effect the outcome. The patients at both veterans affairs medical centers were more than 95% male, while the patients at Loyola University Medical Center were 46.5% male and 54.5% female. The presence of a larger population of female subjects in the Loyola University Medical Center database does not seem likely to account for the smaller apparent efficacy of lovastatin or pravastatin in reducing the prevalence of diagnosed AD, such as those with hypertension or cardiovascular disease. Patients taking either lovastatin or pravastatin had a prevalence of diagnosed AD that was 73% lower than those taking β-blockers, 64.2% less than those taking captopril, and 57.3% lower than those taking furosemide (Figure 1, left, and Table). The comparisons to other medications are particularly informative because they control for potential biases that could occur if clinicians were reticent to refer patients being treated for cardiovascular disorders for a neurologic workup of AD.

The prevalence of diagnosed AD in the combined set was 69.6% less than in the total patient population (Figure 1, left, and Table). The prevalence of diagnosed AD for patients taking lovastatin or pravastatin was lower than the prevalence of diagnosed AD for patients taking each of the individual medications examined as well. Our study contained 2 different controls for potential selection biases: the effects of other medications on the prevalence of diagnosed AD, and the effects of the statins on the prevalence of another syndrome (TIAs). The prevalence of diagnosed AD in patients taking the statins to patients taking other medications related to hypertension and cardiovascular disease was examined to compensate for potential errors in assessment of the total number of patients in the database. This analysis permits comparison of the patients receiving the statins with patients who one expects to have a similar age-related

### Table: Prevalence of AD

<table>
<thead>
<tr>
<th>Medication</th>
<th>No. of Patients</th>
<th>Age, Mean ± SD, y</th>
<th>3 Sites Combined</th>
<th>Hines, Ill</th>
<th>Maywood, Ill</th>
<th>Phoenix, Ariz</th>
<th>SE</th>
<th>P vs Lovastatin + Pravastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovastatin</td>
<td>4180</td>
<td>71 ± 1</td>
<td>3.6</td>
<td>2.5</td>
<td>6.4</td>
<td>8.2</td>
<td>2</td>
<td>.998</td>
</tr>
<tr>
<td>Pravastatin sodium</td>
<td>2326</td>
<td>72 ± 1</td>
<td>4.3</td>
<td>1.1</td>
<td>0</td>
<td>8.3</td>
<td>2</td>
<td>.890</td>
</tr>
<tr>
<td>Lovastatin + pravastatin</td>
<td>6596</td>
<td>72 ± 1</td>
<td>3.8</td>
<td>2.2</td>
<td>4.7</td>
<td>8.2</td>
<td>2</td>
<td>1.00</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>3580</td>
<td>71 ± 3</td>
<td>11.2</td>
<td>N/A</td>
<td>8.1</td>
<td>11.2</td>
<td>2</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>Captopril</td>
<td>4616</td>
<td>74 ± 2</td>
<td>10.6</td>
<td>8.4</td>
<td>13.6</td>
<td>10.6</td>
<td>2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Furosemide</td>
<td>15 106</td>
<td>74 ± 1</td>
<td>8.9</td>
<td>9.0</td>
<td>16.7</td>
<td>14.1</td>
<td>1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Atenolol</td>
<td>5340</td>
<td>72 ± 2</td>
<td>14.8</td>
<td>7.1</td>
<td>19.2</td>
<td>19.0</td>
<td>2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Metoprolol tartrate</td>
<td>3799</td>
<td>72 ± 2</td>
<td>12.1</td>
<td>4.4</td>
<td>15.3</td>
<td>12.4</td>
<td>2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Propranolol hydrochloride</td>
<td>1256</td>
<td>72 ± 2</td>
<td>17.5</td>
<td>3.9</td>
<td>42.4</td>
<td>20.7</td>
<td>2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>β-Blocker combination</td>
<td>10 395</td>
<td>72 ± 2</td>
<td>14.1</td>
<td>5.9</td>
<td>22.8</td>
<td>16.6</td>
<td>2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Total No. of Patients</td>
<td>57 184</td>
<td>74 ± 1</td>
<td>12.8</td>
<td>8.1</td>
<td>11.7</td>
<td>24.4</td>
<td>1</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Hines, Ill, represents the Edward Hines Jr Veterans Affairs Hospital; Maywood, Ill, Loyola University Medical Center; and Phoenix, Ariz, Carl T. Hayden Veterans Affairs Medical Center.

†The total number of patients included in the study was 60,349. Some patients were not taking any of the medications listed; therefore, they are not included in the subcategories.

Left, Prevalence of diagnosed Alzheimer disease (AD) for patients receiving statins and related medications. The total patient sample size used for this study was 56,790 patients. The total number of patients with a diagnosis of AD, both taking and not taking medications, is 753. Right, Prevalence of transient ischemic attack (TIA) for patients receiving statins and related medications. Data are shown from the database at Loyola University Medical Center, Maywood, Ill, but similar results were seen at the other 2 sites (Edward Hines Jr Veterans Affairs Hospital, Maywood, and Carl T. Hayden Veterans Affairs Medical Center, Phoenix, Ariz). The total patient sample size used for this study was 26,171 patients. Statistical significance was set at P < .001.
lence of diagnosed AD there because the females in the Loyola University Medical Center database showed a greater reduction in the prevalence of diagnosed AD than the males (96.3% vs 58%, respectively).

Another possible source of bias could have originated from physicians terminating statin treatment for a patient receiving the diagnosis of AD. To examine this issue, we examined the medical records of patients from the Edward Hines Jr Veterans Affairs Medical Center to determine whether patients with diagnoses of AD had their statin treatment terminated. We did not observe any cases in which treatment for hypercholesterolemia was terminated among patients already diagnosed with AD. Among the patient medical records examined, the duration of statin use varied from 1 to 5 years, with the exception of 1 case in which a patient briefly started a trial of lovastatin therapy, then stopped treatment after 1 month because of side effects and subsequently progressed to AD. This suggests that termination of statin treatment in patients with AD did not account for the lower prevalence of diagnosed AD in patients receiving statins.

To control for other selection biases, such as the possibility that internists might not refer patients for neurologic workups, we also examined the prevalence of TIAs in patients receiving the 8 medications. None of the HMG-CoA reductase inhibitors (nor any of the other medications) had any effect on reducing the rate of TIAs in the patient populations examined (Figure, right). In fact, the prevalence of TIAs was increased for all of the medications examined compared with the total patient database. This likely reflects the fact that a TIA is the result of vascular disease, which is expected to be increased in all of the patients receiving all of the medications studied. A significant variable that could not be determined in this study is the prevalence of coexisting cerebral ischemic disease in the populations receiving and not receiving statin therapy.

Despite being an HMG-CoA reductase inhibitor, simvastatin was not associated with a lower prevalence of diagnosed AD. Patients receiving simvastatin had a prevalence of diagnosed AD that did not differ significantly from that of the total patient population or that of patients receiving captopril or furosemide.

This study examines the relation between use of HMG-CoA reductase inhibitors, collectively termed statins, and the prevalence of diagnosed AD. We chose to examine the statins because of increasing evidence linking cholesterol metabolism to AD. The results present evidence that there is a lower prevalence of diagnosed AD in patients taking 2 different HMG-CoA reductase inhibitors—lovastatin and pravastatin. While one cannot infer causative mechanisms based on these data, data do suggest an interesting association, which warrants further study.

In this study we performed a cross-sectional analysis of 3 independent hospital patient databases and observed that patients taking the HMG-CoA reductase inhibitors lovastatin or pravastatin exhibited a 69.6% reduction in the prevalence of diagnosed AD. A number of controls present in our study lead us to conclude that the lower prevalence in diagnosed AD associated with the statins represents a protective effect of these medications rather than a spurious bias in the databases. To control for the possibility that physicians might not prescribe statins to patients with dementias, we compared the prevalence of diagnosed AD for patients taking statins with patients taking other medications that are used to treat cardiovascular disease but that do not influence cholesterol metabolism. Compared with other cardiovascular medications, patients taking the statins also exhibited a significant reduction in the prevalence of diagnosed AD. To control for the possibility that physicians might not diagnose neurologic diseases in patients receiving the statins, we compared the prevalence of diagnosed AD to the prevalence of TIAs for patients receiving the statins, as well as other cardiovascular medications. Only patients taking the statins had a lower prevalence of AD compared with patients taking other cardiovascular medications. Finally, we also examined the medical records of some of the patients and observed no evidence suggesting that physicians were discontinuing statin treatment in patients with AD.

The particular relational databases used in this study are best at determining associations. While data were not analyzed using a case-control paradigm, in which identified patients are matched for age, sex, and ethnicity to determine an odds ratio, the aggregate nature of the data does benefit from the ability to analyze a large population cohort. Future studies will allow us to determine the relation between the length of time taking medication, the dose of medication, cholesterol levels, and the degree of risk reduction for AD.

Two aspects of our study produced unexpected results. First, the prevalence of patients with a diagnosis of AD in these databases is less than has been reported in the literature. This difference in the observed rate of AD might be owing in part to our use of register-based hospital databases because the physicians generating such databases do not specifically focus on the diagnosis of AD and other dementias. In such hospitals, the threshold for considering a diagnosis of AD (and referring such patients to a neurologist for evaluation) is likely to be higher than in a study in which the physicians are specifically focusing on detecting and diagnosing dementia. It is possible that some subjects with MMSE scores higher than 24 who actually had mild or very mild AD would have been missed by this study. The low prevalence of diagnosed AD reported at the Edward Hines Jr Veterans Affairs Hospital suggests that the underreporting of AD may be particularly prevalent at this site. However, even at this site, no particular selection bias was evident because the prevalence in diagnosed AD was proportionately lower in all the groups examined.

A second surprising finding in our study is that the HMG-CoA reductase inhibitor simvastatin has only a weak effect, if any at all, in reducing the prevalence of diagnosed AD. Simvastatin and pravastatin are similar in structure, are equally effective at inhibiting liver HMG-CoA reductase, and share similar blood-brain barrier permeabilities. The differential effects of the statins on the prevalence of diagnosed AD contrasts with the similar efficacy at inhibiting liver HMG-CoA and, therefore, sug-
gests that the reason for the bias in these data relates to a factor other than the reduction in liver HMG-CoA activity. The reason might be due to biological considerations, such as the actions of HMG-CoA reductase inhibitors on the brain or cerebral vasculature. Alternately, the difference could be owing to clinical considerations. For instance, since simvastatin is slightly newer than lovastatin or pravastatin, a lower prevalence of AD among patients taking simvastatin could have resulted from differences in physician prescribing patterns among the statins. Finally, it is also possible that these heterogeneity of effects could be owing to chance.

A number of studies have noted a potential relation between cholesterol level and AD, although whether this relation is direct and causative or indirect remains to be determined. A number of studies suggest that elevated cholesterol levels might correlate with AD.1,2,5 Notkola et al1 observed that an elevated cholesterol level increases the risk of AD. Similarly, Sparks5 observed that patients with cardiovascular disease, which is a disease associated with an elevated cholesterol level, are at increased risk of AD. The ApoE4 isoform, a cholesterol transport protein associated with an elevated cholesterol level, is known to increase the risk of AD.5 In addition, cholesterol has also been shown to directly affect Aβ secretion.9 Recent studies have shown a direct connection between cholesterol level and neuritic plaque burden using the PDAPP transgenic mice, which are transgenic for the human amyloid precursor protein and develop neuritic plaques.10,17 Refolo et al17 have shown increased dietary cholesterol intake in PDAPP transgenic mice leads to an elevated serum cholesterol level, is known to increase the risk of AD. In addition, cholesterol has also been shown to directly affect Aβ secretion.9 Recent studies have shown a direct connection between cholesterol level and neuritic plaque burden using the PDAPP transgenic mice, which are transgenic for the human amyloid precursor protein and develop neuritic plaques.10,17 Refolo et al17 have shown increased dietary cholesterol intake in PDAPP transgenic mice leads to an elevated serum cholesterol level and an increased plaque load compared with mice fed normal diets.17 Our observations of decreased prevalence of diagnosed AD associated with treatment of hypercholesterolemia provides further evidence of a potential link between cholesterol level and AD.

The results of this article, while not showing any causal relations, establish a distinct association between use of the statins among a population of patients with the diagnosis of probable AD. The source of the association may be related to (1) the criteria for the diagnosis of AD and for exclusion of ischemic cerebral disease, (2) the criteria for selection of patients for statin treatment, or (3) some other unknown confounding variable in this population of patients with dementia. In any of these cases, the fact of an inverse relation of statin therapy to dementia of any form is of considerable potential importance and needs to be tested with a rigorous prospective clinical trial.

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REFERENCES