Use of Lipid-Lowering Drugs in Older Adults With and Without Dementia: A Community-Based Epidemiological Study

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OBJECTIVES: To compare the use of lipid-lowering drugs in community-dwelling older adults with and without dementia.

DESIGN: Comparison of lipid-lowering drug use by demented cases and nondemented controls based on secondary analysis of data from a longitudinal epidemiologic study.

SETTING: Longitudinal study of a largely rural, low-socioeconomic-status, community-based cohort of older persons residing in the mid-Monongahela Valley of Southwest Pennsylvania (the Monongahela Valley Independent Elders Survey).

PARTICIPANTS: Eight hundred forty-five individuals of mean ± standard deviation (SD) age of 80.5 ± 4.6, participating in the fifth biennial wave of data collection.

MEASUREMENTS: Demographics; medical history; medication regimen (including examination of prescription bottle labels); self-report of most recent visit to primary care physician (PCP); and standardized clinical assessment to determine presence of dementia, including Clinical Dementia Rating (CDR).

RESULTS: One hundred seventy participants (20.1% of total subject cohort) had dementia, with a CDR of 0.5 or greater. Mean ages of demented and nondemented individuals were 83.5 ± 5.1 and 79.8 ± 4.2, respectively. Similar proportions, 87.7% and 89.5%, of these groups reported PCP visits in the previous year. Of the total sample, 9.4% (3.5% of the demented and 10.8% of the nondemented) were taking lipid-lowering drugs. After adjustment for age, sex, education, visit with PCP within the past year, and potential confounding clinical and lifestyle variables (self-reported heart disease, stroke or transient ischemic attacks, hypertension, smoking, and alcohol consumption), dementia was associated with a lower likelihood of taking a lipid-lowering drug (odds ratio = 0.39, 95% confidence interval = 0.16–0.95). In post hoc subgroup analyses, similar results were found when restricting lipid-lowering drugs to statins alone but were not statistically significant. Drug use was not associated with severity of dementia (CDR = 0.5 vs CDR ≥ 1).

CONCLUSIONS: Demented individuals were less likely than their nondemented counterparts to be taking lipid-lowering drugs. This finding could reflect different prescribing patterns by physicians for demented and nondemented patients or a possible protective effect of these drugs against dementia.

It has recently been reported that the presence of dementia is inversely associated with the use of lipid-lowering hydroxymethylglutaryl-coenzyme A reductase inhibitors (statins).1,2 This finding may have major importance regarding the role of lipid metabolism in dementia pathogenesis and in developing strategies for dementia pharmacotherapy. Given its potential implications, the plausibility of the association would be increased by its replication in demographically diverse populations recruited from a variety of sources. The cited studies were based on patients from clinical populations with clinical chart diagnoses of dementia. An association between dementia and relative underuse of lipid-lowering agents was examined by the authors, including statins, in a population-based epidemiological study involving subjects in whom the research diagnosis of dementia was based on standard methods and
METHODS
Study Site and Population
Originally designed as a population-based dementia registry, the Monongahela Valley Independent Elders Survey (MoVIES) is being conducted within the mid-Monongahela Valley area in southwestern Pennsylvania. Subjects provided informed consent according to procedures approved annually by the University of Pittsburgh Institutional Review Board. Eligibility criteria for entry into the study cohort, between 1987 and 1989, included community residence (not already in long-term care at study entry), aged 65 and older, fluency in English, and at least sixth grade education. One thousand four hundred twenty-two randomly selected participants met eligibility criteria and consented to participate. An additional 259 volunteer participants met the same entry criteria, bringing the cohort size to 1,681 at study entry (1987–89). Further details of sampling and recruitment of the study cohort have been described previously. All participants underwent a screening interview at study entry, and a subset of them underwent a clinical assessment (see below). All surviving participants were subsequently contacted for follow-up screening interviews at approximately 2-year intervals in a series of data collection “waves.” Data reported in this article were collected from 845 participants who survived and consented to participate in Wave 5 (1996–99).

Screening
Each subject underwent an in-home screening and risk factor assessment interview, which included a medication use history, with additional drug information obtained from medication bottle labels. Data were gathered about use of prescription and nonprescription (over-the-counter) drugs. Participants were asked about their medical history, including self-reports of high blood pressure/hypertension, heart attacks or angina pectoris, stroke or mini-stroke/transient ischemic attacks (TIA); lifestyle variables including smoking and alcohol consumption; and use of health services, including visits to their primary care physicians (PCPs). Whenever possible, corroborative information was obtained from an additional informant. In 11% of Wave 5 participants, part or all of the information was obtained from an informant other than the subject; most often this was the spouse, but in some cases was other family, friends, or paid caregivers.

The interview also included approximately 25 minutes of cognitive testing with a test battery designed to briefly assess general mental status and several specific cognitive domains known to be affected by dementia, including (but not limited to) the neuropsychological battery of the Consortium to Establish a Registry for Alzheimer’s disease (CERAD). Based on their screening cognitive test scores at study entry, subjects were classified as cognitively intact or impaired based on scores at or below the 10th percentile of the sample on the Mini-Mental State Examination or on at least one memory test and one other cognitive test. During subsequent biennial follow-up “waves” of cognitive screening with identical measures, subjects whose decline in scores from any previous wave placed them at the 95th percentile of the cohort’s decline and those whose scores had newly fallen to below impaired levels as defined above were classified as cognitively declined. Subjects classified as cognitively impaired or declined were asked to undergo a clinical (diagnostic) evaluation for dementia, described below. In addition, a sample of cognitively intact subjects, matched on age, sex, and education to subjects diagnosed as demented (see below) at the first wave, was also selected as a control group for clinical evaluation at all subsequent waves.

Diagnosis of Dementia and Subtypes of Dementia
The MoVIES clinical evaluation protocol followed the diagnostic protocols established by CERAD and the University of Pittsburgh Alzheimer’s Disease Research Center. It included general medical and neurological history, general physical and detailed neurological examinations, mental status examinations, an informant interview, and a standard laboratory panel. Clinical evaluations were performed blind to subjects’ screening cognitive scores. Diagnostically evaluated subjects received a Clinical Dementia Rating (CDR) according to CERAD protocol. On the CDR scale, scores (stages) of 0, 0.5, 1, 2, and 3 indicate no, possible/incipient, mild, moderate, and severe dementia, respectively, and are based on functional impairment rather than on cognitive test scores. For the current analyses, we categorized as demented all those with CDR scores of 0.5 or greater.

Therapeutic Categories of Drugs
Medication data were initially classified within American Hospital Formulary System categories. The subcategory of interest for the current analyses was antilipemic agents.

Statistical Methods
Frequencies of use for statins alone and for all lipid-lowering drugs were examined in the total sample and in those with dementia at different severity (CDR) levels. Chi-square statistics were used to assess unadjusted differences in odds of taking lipid-lowering drugs between the demented (CDR ≥ 0.5) and nondemented subjects. Subsequently, multiple logistic regression was used to assess the odds ratios (ORs) and the associated 95% confidence intervals (CIs) for taking the medications in demented and nondemented participants. In this model, we adjusted for age (continuous variable); sex; education (at least high school vs less than high school education); visit with PCP at least once during the preceding year; and self-reported history of heart attack/angina pectoris, stroke/TIA, hypertension, alcohol consumption (at least one drink per week), and current cigarette smoking. To determine whether severity of dementia was associated with the likelihood of use of the drugs, we also performed logistic regression analysis limited to demented subjects (CDR ≥ 0.5), comparing those with CDR scores of 0.5 to those with CDR scores of 1 or greater. In post hoc analyses, to determine whether the same relationship found between dementia and all lipid-lowering agents would be found between dementia and statins alone, we repeated the logistic regres-
sion analysis, first classifying those taking nonstatin antilipemics as nonusers, and then excluding them altogether. We lacked sufficient power to determine whether the same associations would be found with Alzheimer’s disease (AD) alone, rather than overall dementia. Goodness of fit of the logistic regression models was assessed using Hosmer-Lemeshow statistics.10

RESULTS

Demographics and Drug Use

Sixty-five percent of the 845 participants in the Wave 5 cohort were women. The mean ± standard deviation age of the cohort was 80.5 ± 4.6; 63.7% had at least a high school education; and 79 (9.4%) were taking lipid-lowering drugs, of whom 18 (22.8%) were taking nonstatins. The frequencies of individual drug use were simvastatin in 30 subjects (3.55%); gemfibrozil in 11 subjects (1.3%); lovastatin in nine subjects (1.07%); less than 1% taking each of the remaining drugs: pravastatin (n = 8), atorvastatin (n = 6), fluvastatin (n = 5), niacin (n = 3), and colestipol (n = 2); and one each taking probucol, cerivastatin, colestipol plus gemfibrozil, cholestyramine plus simvastatin, and cholestyramine plus pravastatin.

Demented Versus Nondemented Participants

Of the cohort, 170 (20.1%) at Wave 5 were diagnosed as demented with a CDR score of 0.5 or higher, of whom 147 (86.5%) were diagnosed as having probable or possible AD; 76 and 94 of them had a CDR score of 0.5 and CDR score of 1 or greater, respectively. The demented individuals had a mean age of 83.5 ± 5.1, and 45.9% of them had a high school or greater education. Nondemented persons had a mean age of 79.8 ± 4.2, and 68.2% had a high school or greater education. Participants with dementia were significantly older (P < .001 by Wilcoxon rank sum test) and less likely to have completed high school (P < .001 by chi-square test) than those without dementia. There was no significant difference between demented and nondemented persons with respect to sex (62.4% vs 65.6% female) or PCP visit during the previous year (87.7% vs 89.5%).

Likelihood of Taking Lipid-Lowering Drugs, in Different Subgroups

All Lipid-Lowering Drugs, Any Dementia Versus No Dementia

Of those with dementia, 3.5% were taking lipid-lowering drugs, compared with 10.8% of those without dementia; these proportions were significantly different (P = .004 by \( \chi^2 \) test). After adjustment for age, sex, education, visit with physician in the past year, reported heart attack or angina pectoris, stroke or TIA, hypertension, alcohol consumption, and smoking, demented participants were significantly less likely than nondemented to be taking lipid-lowering drugs (OR = 0.39, 95% CI = 0.16–0.95) (Table 1).

When frequencies were examined for post hoc analyses separating statins from other lipid-lowering drugs, and separating AD from other dementias, two unexpected findings were noted; none of the subjects with any dementia were taking nonstatin lipid-lowering agents (i.e., they were using statins or no lipid-lowering agents at all), and none of the subjects with non-AD dementias were taking any lipid-lowering agents.

Statins Alone, Any Dementia Versus No Dementia

To determine whether there was a similar negative association when the outcome variable in the model was restricted to statin drugs alone, two models were tested. In the first, excluding those using other lipid-lowering agents, subjects with dementia were less likely to be taking statins, but this association was not statistically significant (OR = 0.54, 95% CI = 0.22–1.33, P = .179). In a second model also restricted to statins, when users of nonstatin agents were included but classified as nonusers, results were almost identical.

### Table 1. Variables Associated with the Use of Lipid-Lowering Agents (LLAs)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted Analyses</th>
<th>Adjusted Analyses*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LLA Users</td>
<td>LLA Nonusers</td>
</tr>
<tr>
<td>Age, mean ± standard deviation</td>
<td>79.4 ± 3.8</td>
<td>80.6 ± 4.7</td>
</tr>
<tr>
<td>Women, %</td>
<td>67.1</td>
<td>64.6</td>
</tr>
<tr>
<td>Education less than high school graduate, %</td>
<td>29.1</td>
<td>37.1</td>
</tr>
<tr>
<td>Saw primary care physician in the last year, %</td>
<td>97.5</td>
<td>88.3</td>
</tr>
<tr>
<td>With dementia (Clinical Dementia Rating ≥0.5), %</td>
<td>7.6</td>
<td>21.4</td>
</tr>
<tr>
<td>Reporting heart attack/angina pectoris, %</td>
<td>22.8</td>
<td>11.8</td>
</tr>
<tr>
<td>Reporting stroke/transient ischemic attack, %</td>
<td>3.8</td>
<td>6.9</td>
</tr>
<tr>
<td>Reporting high blood pressure, %</td>
<td>48.1</td>
<td>47.1</td>
</tr>
<tr>
<td>Reporting at least weekly alcohol use, %</td>
<td>16.5</td>
<td>13.1</td>
</tr>
<tr>
<td>Currently smoking cigarettes, %</td>
<td>5.1</td>
<td>6.7</td>
</tr>
</tbody>
</table>

Note: ‡ log-likelihood ratio = 29.34; df = 10; P-value = .001.

*Multiple regression.

†Significance testing based on chi-square test except where otherwise indicated.

‡Based on Wilcoxon rank sum test.
Lipid-Lowering Drugs and Severity of Dementia
We found no difference in the use of lipid-lowering drugs between those more and less severely demented; 3.9% of demented participants with a CDR score of 0.5 \((n = 76)\) were taking lipid-lowering drugs, compared with 3.2% of more severely demented participants with a CDR score of 1 or greater \((n = 94)\). A logistic regression model restricted to subjects with dementia \((CDR \geq 0.5)\), comparing those with a CDR score of 1.0 or greater with those with a CDR score of 0.5, adjusting for age, sex, education and PCP visit, revealed no significant association between the severity of dementia and odds of taking lipid-lowering drugs (data not shown).

DISCUSSION
In analyses adjusted for age, sex, education, recent contact with PCP, and several potentially confounding clinical factors, we found that older adults with dementia were significantly less likely than their nondemented peers to be taking lipid-lowering agents. Similar relationships were seen with statins alone, but these associations were not statistically significant, probably because of insufficient power.

In interpreting these findings, we assumed that hyperlipidemia had similar prevalence in demented and nondemented individuals. Unfortunately, we did not have objective measures of serum cholesterol in all participants. We are aware of no literature to support the potential explanation that hyperlipidemia could be less prevalent in demented than nondemented participants. There is in fact some evidence to the contrary, that at least in the preclinical or early stages of AD, affected persons have higher total cholesterol levels than persons without AD.\(^1\)\(^{11}\) In addition, persons with vascular dementia may have increased likelihood of hyperlipidemia, which has been found to be a risk factor for decline in cerebral perfusion\(^1\)\(^{12}\) and was also associated with vascular dementia in one cohort study.\(^1\)\(^{13}\) Although the contribution of hyperlipidemia to the risk of stroke, a cause of vascular dementia, has been difficult to demonstrate,\(^1\)\(^{14}\) use of statins has been shown to reduce stroke incidence.\(^1\)\(^{15}\)

The mix of various subtypes of dementia in this study population might have influenced the use of lipid-lowering agents. One study found less-frequent use of cardiovascular and other classes of drugs in persons with AD than in those with vascular dementia; the authors’ interpretation was that patients with AD were less likely to have comorbid conditions than were those with vascular dementia.\(^1\)\(^{16}\) In our cohort, approximately 47% and 40% of demented individuals were diagnosed as probable and possible AD, respectively, according to National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer’s Disease and Related Disorders Association criteria;\(^1\)\(^{17}\) the remaining 13% were diagnosed as other dementia. Of these three groups, approximately 34%, 60%, and 63% had histories of stroke and/or TIA. These stroke/TIA frequencies reflect at least partly the relationship between the comorbid condition and diagnostic criteria for the different dementia subtypes. Differences in the use of lipid-lowering drugs probably depend less on accurate subtyping of the dementia by the treating physician and more on the relative prevalence of comorbid vascular disease in each of the types. A history of myocardial infarction or angina pectoris was strongly associated with the use of lipid-lowering agents suggests that hyperlipidemia was likely to be detected and treated after the occurrence of a recognizable cardiac event.

Preliminary evidence for an association between use of lipid-lowering agents and reduced risk of AD comes from laboratory-based studies and clinical epidemiological studies. Early findings in cell culture and animal research provide underpinnings for a causal relationship between the use of statins and a reduction in the risk of AD, for example by an effect of cholesterol-lowering agents on beta-amyloid production.\(^1\)\(^{18}\) Two recent cross-sectional studies of patient populations document an association between statins and reduced risk of AD.\(^1\)\(^{12}\) These two studies were based on drug and diagnostic information from clinical databases. In this study, subjects were recruited from the community at large; drug data were obtained by examination of medication bottle labels present in the subjects’ homes and reported by the patients as reflecting their daily use. In addition, dementia was diagnosed by direct clinical examination of the subjects. Thus, epidemiological data supplement and help confirm the evidence from earlier clinical database studies\(^1\)\(^{12}\).

Nevertheless, the interpretation of this finding in these recent studies and our own is open to question. Because all the data are cross-sectional, neither the temporal relationship between the recognition of the dementia and the prescribing of lipid-lowering agents nor the direction of the association between the use of lipid-lowering agents and the presence of dementia can be determined. Despite the prospective nature of this study, it was not feasible to test our hypothesis longitudinally because of insufficient numbers of participants taking lipid-lowering drugs before Wave 5 (1996–99). Therefore it could not be concluded whether the use of lipid-lowering drugs resulted in a lower prevalence of dementia, whether the presence of dementia resulted in a lower frequency of drug use, or whether a third factor was responsible for both.

How might the presence of dementia result in the reduced use of lipid-lowering drugs? Persons with significant competing comorbidities are known to be at risk for undertreatment of at least some index conditions.\(^1\)\(^{19}\) The presence of dementia may incline physicians to be less aggressive in treating comorbid conditions.\(^2\)\(^{20}\) Arguments for limiting treatment of associated conditions in persons with dementia include an increased risk of treatment complications, reduced ability to adhere to treatment, reduced capacity to experience benefit, and lack of data on risks and benefits of specific treatments in persons with dementia.\(^2\)\(^{21}\) Treatment with the goal of extending life in dementia arguably confers harm, because it may obligate patients to suffer more of the inevitable losses associated with dementia.\(^2\)\(^{22}\) In addition, the shortened life expectancy of persons with end-stage dementia may reduce the potential benefit of burdensome preventive interventions.\(^2\)\(^{23}\)

Understandably, when confronted with the need to decide how to allocate healthcare resources, clinicians may assign a relatively lower priority to treating patients with dementia.\(^2\)\(^{24}\) Given the above considerations, it is not surprising that community-dwelling persons with dementia use fewer medications than do nondemented peers.\(^2\)\(^{25}\)\(^\text{a}\)\(^{26}\) If there is a disinclination to treat persons with dementia for
To argue that the lower use of lipid-lowering drugs in demented participants is the result of decisions to limit risk-reducing therapies in demented patients is to imply that physicians recognize dementia with reasonable sensitivity. When physicians are specifically asked to assess their patients for the presence and severity of dementia, they demonstrate good ability to do so, but documented recognition rates tend to be low in observational studies; the diagnosis of dementia was documented in fewer than 25% of patients with moderate to severe cognitive impairment in a university-affiliated primary care practice. In our study, participants with more severe dementia, whose physicians would presumably more readily recognize them as demented than would milder cases, did not use lipid-lowering agents less often.

A potential limitation of this study is its reliance on self-report, including report by persons with dementia, but efforts were made to corroborate subjects’ self-report using family and paid caregivers as informants. Drug information was also obtained from the medication bottles available in the homes.

In summary, this epidemiological study adds further evidence regarding the observed association between reduced use of lipid-lowering agents and the presence of dementia. In contrast to earlier reports, significantly lower use specifically of statin drugs in demented persons was not found. The available evidence cannot determine the direction of the observed association; prospective observational studies and clinical trials are required to determine whether lipid-lowering agents, and the statin class in particular, can reduce the risk of dementia, including AD.

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REFERENCES