The Impact of the Use of Statins on the Prevalence of Dementia and the Progression of Cognitive Impairment

Ihab Hajjar, Jeannie Schumpert, Victor Hirth, Darryl Wieland, and G. Paul Eleazer

Background. Previous evidence suggests that treatment with 3-hydroxy-3-methylglutaryl-coenzyme-A reductase inhibitors (statins) has a positive impact on dementia. We decided to investigate the association between the use of statins and the prevalence of dementia and statins’ impact on the progression of cognitive impairment.

Methods. This is a case-control and a retrospective cohort study of a community-based ambulatory primary care geriatric practice. We included a convenience sample of all patients (N = 655, mean age 78.7 ± 3 years, 85% Caucasian, 74% women) with hypercholesterolemia or dementia, or using statins. We compared those using statins with those who do not with respect to the clinical diagnosis of dementia and its subtypes and the progression of cognitive impairment.

Results. At the initial visit, 35% had dementia, and 17% were using statins. After covariate adjustments, patients on statins were less likely to have dementia (odds ratio [OR] for dementia based on composite definition = 0.23; 95% confidence interval [CI] [0.1–0.56], p = .001, OR Alzheimer’s disease = 0.37; 95% CI [0.19–0.74], p = .005, OR vascular dementia = 0.25; 95% CI [0.08–0.85], p = .027). At follow-up, patients on statins showed an improvement on their Mini-Mental Status Examination score by 0.7 ± 0.4 compared to a decline by 0.5 ± 0.3 in controls, p = .025 (OR for no change or improvement on statins = 2.81; 95% CI [1.02–8.43], p = .045) and scored higher on the Clock Drawing Test (difference of 1.5 ± 0.1, p = .036).

Conclusions. The use of statins is associated with a lower prevalence of dementia and has a positive impact on the progression of cognitive impairment.
mentia, or Diffuse Lewy Body disease) were recorded. Cognitive and mood assessments were performed at baseline and follow-up. The Folstein Mini-Mental Status Examination (MMSE) (16), Clock Drawing Test (CDT) (17), and the Geriatric Depression Scale (GDS) (18,19) were administered by a trained geriatric social worker to all patients, using a uniform procedure. Two social workers performed all the testing, minimizing interoperator variability. We use the scale of 7 (with 7/7 as the perfect score) for CDT scoring.

Statin use at baseline and duration of use were also recorded. To confirm use of statins, prescriptions written and provided to patients during the period of follow-up were recovered from the charts. In addition, we extracted data on baseline and continuing use of aspirin, donepezil (Aricept), vitamin B12, and vitamin E.

Physical exam information included blood pressure readings and heart rate. We used the higher of the left or right arm while sitting. Laboratory information included total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglyceride (TG). We used only values obtained in our local laboratory to minimize variations. For follow-up examinations, we extracted information on blood pressure, heart rate, cholesterol level, LDL, HDL, and TG from charts as well as medications used, MMSE, CDT, and GDS.

To operationalize the diagnosis of dementia for this study, we developed a composite variable with a positive diagnosis when both a clinical diagnosis of dementia or one of its types were documented in the chart and the patient had a MMSE score less than 24. This cutoff has been shown to improve diagnostic accuracy (20). We performed the analysis using this composite variable, as well as each individual diagnostic criterion (clinical diagnosis and MMSE score). For the longitudinal analysis of cognitive change, we used the absolute change in MMSE score and CDT score between the follow-up cognitive testing and baseline testing at the initial visit.

Practice enrollment data were used for the analysis of dementia/cognitive impairment prevalence. The study of cognitive status change was conducted on patients for whom follow-up cognitive testing data were available. Patients were assigned to the “statin” group (those using statins at the initial visit) or the control group (not using statins). Review of the control charts indicated that none of the patients in this group had been exposed to statins. A chi-square test compared prevalence of dementia in the two groups. Bivariate and multivariate analyses were employed to explore the impact of other potential dementia risk factors. Multiple logistic, linear regression, and stepwise regression techniques were used to develop models, adjusting for multiple covariates. Goodness-of-fit tests were used to select the best-fitted models (21). Covariates included age, gender, race, education, smoking, alcohol, blood pressure, medical diagnoses (stroke or TIA, hypertension, depression), family history of dementia or AD, cholesterol level, LDL, HDL, and TG.

### Table 1. Baseline Characteristics at the Initial Visit of the Overall Sample, the Statin Group, and the Control Group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall</th>
<th>Control Group</th>
<th>Statin Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>655</td>
<td>542 (83%)</td>
<td>113 (17%)</td>
</tr>
<tr>
<td>Age* (in years)</td>
<td>78.7 ± 0.3</td>
<td>79.5 ± 0.3</td>
<td>75.1 ± 0.7</td>
</tr>
<tr>
<td>Gender (Male)</td>
<td>26%</td>
<td>26%</td>
<td>23%</td>
</tr>
<tr>
<td>Race</td>
<td>85% W</td>
<td>84% W</td>
<td>88% W</td>
</tr>
<tr>
<td>Family History of Dementia*</td>
<td>30%</td>
<td>32%</td>
<td>23%</td>
</tr>
<tr>
<td>Hypercholesterolemia*</td>
<td>36%</td>
<td>24%</td>
<td>96%</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>61%</td>
<td>24%</td>
<td>95%</td>
</tr>
<tr>
<td>Stroke</td>
<td>19%</td>
<td>19%</td>
<td>16%</td>
</tr>
<tr>
<td>Transient Ischemic Attacks</td>
<td>3%</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Depression</td>
<td>45%</td>
<td>45%</td>
<td>45%</td>
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<tr>
<td>Aricept*</td>
<td>15%</td>
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<td>7%</td>
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<td>Aspirin*</td>
<td>32%</td>
<td>30%</td>
<td>43%</td>
</tr>
<tr>
<td>Vitamin B12*</td>
<td>6%</td>
<td>5%</td>
<td>12%</td>
</tr>
<tr>
<td>Vitamin E*</td>
<td>17%</td>
<td>15%</td>
<td>25%</td>
</tr>
<tr>
<td>SBP* (mmHg)</td>
<td>141 ± 0.9</td>
<td>140.7 ± 1</td>
<td>146 ± 1</td>
</tr>
<tr>
<td>Cholesterol Level* (mg/dl)</td>
<td>218 ± 15</td>
<td>224 ± 3</td>
<td>204 ± 4</td>
</tr>
<tr>
<td>LDL*</td>
<td>133 ± 41</td>
<td>142 ± 3</td>
<td>116 ± 4</td>
</tr>
<tr>
<td>HDL</td>
<td>54 ± 19</td>
<td>54 ± 1</td>
<td>52 ± 2</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>185 ± 46</td>
<td>179 ± 8</td>
<td>200 ± 9</td>
</tr>
<tr>
<td>Geriatric Depression Scale</td>
<td>3.3 ± 0.0</td>
<td>3.3 ± 0.1</td>
<td>3.4 ± 0.3</td>
</tr>
<tr>
<td>Education (in years)</td>
<td>15 ± 2</td>
<td>15.5 ± 3</td>
<td>13.1 ± 0.3</td>
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<tr>
<td>Alcohol Use</td>
<td>30% C</td>
<td>28% C</td>
<td>38% C</td>
</tr>
<tr>
<td>Smoking</td>
<td>4% P</td>
<td>4% P</td>
<td>2% P</td>
</tr>
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<td>68% N</td>
<td>60% N</td>
</tr>
<tr>
<td>Smoking</td>
<td>37% P</td>
<td>37% P</td>
<td>37% P</td>
</tr>
<tr>
<td>Smoking</td>
<td>55% N</td>
<td>56% N</td>
<td>51% N</td>
</tr>
</tbody>
</table>

Note: B = Black; W = White; C = current users; P = past users; N = never users; SBP = systolic blood pressure; DBP = diastolic blood pressure; LDL = low-density lipoprotein; HDL = high-density lipoprotein.

*p < .05 for the difference between the statin and the control groups.
Models were tested for the composite variable, clinical diagnosis of dementia, AD, vascular dementia, mixed dementia, MMSE, and CDT. The institutional review board approved the study at the local institution.

**Results**

We identified 655 eligible patients (mean age 78.7 ± 0.3 years, range 52 to 98 years, 85% Caucasian, 15% African American, and 74% women) (Table 1). Sixty percent had dementia based on chart diagnosis, and 48% had an MMSE score less than 24 (concordance rate was 89%, p < .001). Of all patients selected, 233 (35.4%) were positive for dementia using the composite variable. Twenty-three percent had a clinical diagnosis of AD, 9% had vascular dementia, 4% had mixed-type dementia, 0.5% had Diffuse Lewy Body disease, and 63.5% had dementia not otherwise specified. One hundred and thirteen (17%) patients were using statins on the initial visit and 17% on follow-up.

Of the sample selected, 165 (25%) patients had follow-up MMSE, and 82 (12%) had follow-up CDT. The mean follow-up period was 10.6 ± 0.6 months (range 0 to 42.2 months). Apart from race and family history of dementia, there were no differences between the patients who had follow-up cognitive testing available in their records and those who did not (Table 2). Cognitive function was not different between the groups with and without follow-up cognitive testing (MMSE score of 22.0 ± 0.4 and CDT score of 4.3 ± 0.2 in the group with follow-up vs 22.4 ± 0.4 and 4.2 ± 0.1 in the group without follow-up, p = .47 and p = .59, respectively). There was no difference between the two groups in the percentage of patients on statin (14% in the group with vs 18% in the group without follow-up, p = .193). Data on the duration of dementia were not available in the records of the selected sample and could not be included in the analysis.

On the initial visit, the statin group was less likely to have dementia based on the chart diagnosis, MMSE criterion, and composite variable definition (22% of those on statins had dementia based on chart diagnosis vs 68% in the control group, p < .001). 15% of the statin group had dementia using the MMSE criterion vs 56% in the control group, p < .001, 24% of the statin group had dementia based on the composite variable definition vs 73% in the control group, p < .001). This was also true for AD (9% in the statin group vs 25% in the controls, p < .001) and vascular dementia (3% in the statin group vs 10%, p < .001). There was no difference in those diagnosed with mixed dementia or Diffuse Lewy Body disease.

All models developed to adjust for covariates showed a persistent association. After adjusting for age, gender, race, education, blood pressure, family history of dementia, cholesterol, LDL and triglyceride levels, clinical diagnosis of stroke, TIA, depression, and hypertension, GDS, use of alcohol and smoking, and medications used, current use of statin was associated with a lower risk of dementia based on all criteria and for both AD and vascular dementia (odds ratio [OR] for dementia based on composite definition = 0.23; 95% confidence interval [CI] [0.1–0.55], p = .001; OR for dementia based on chart diagnosis = 0.16; 95% CI [0.09–0.27], p < .001; OR based on MMSE cutpoint = 0.23; 95% CI [0.1–0.55], p = .001; OR for AD = 0.37; 95% CI [0.19–0.74], p = .005; OR for vascular dementia = 0.25; 95% CI [0.08–0.85], p = .027) (Figure 1).

Mean MMSE for the statin group was 26.5 ± 0.5 versus 21.4 ± 0.3 in the control group (p < .0001) and mean CDT was 5.45 ± 0.2 versus 3.9 ± 0.1 (p < .0001). Multiple regression models with the covariate adjustments showed that the statin group had a higher MMSE (statin group 2.4 [standard deviation ± 0.8] points higher than the control group, p = .001). This was also true for the CDT (statin group had 1.2 ± 0.5 points higher than the control group, p < .001).

When compared with the cognitive testing at the initial visit, the statin group showed an improvement in their MMSE scores by 0.7 ± 0.4 versus a decline of 0.5 ± 0.3 points in the control group at follow-up (p = .025) (Figure 2). After covariate adjustments including other medication use, patients on statins were more likely to show improvement or no change as compared to the control group (OR of having an improvement or no change on their MMSE = 2.81; 95% CI [1.02–8.43], p = .045). In addition, at follow-up, the statin group persistently had higher CDT scores as compared with the control group (p = .036) (Table 3).

**Discussion**

This study explores the impact of the use of cholesterol-lowering drugs in the statin class on both the prevalence of...
dementia and the progression of cognitive impairment. Our study confirms prior observations that have found a lower prevalence of dementia in patients using statins (15,22). These observations, as in the current study, have found this association to be true for both AD and vascular dementia (15,22). We have found that patients using statins have higher scores on cognitive testing compared to patients not using statins. In addition, we identified an association between statins and an arrest in the progression of cognitive impairment.

There is increasing evidence to suggest an important role of cholesterol in the pathophysiology of dementia and AD (7,8,11,12,23–25). For example, Jarvik and colleagues found an increased risk of AD in patients with hypercholesterolemia (8). In the Rotterdam study, hyperlipidemia was found to be associated with vascular dementia and AD (3). Statins lower cholesterol levels by inhibiting cholesterol synthesis, decreasing LDL circulation, and modulating the LDL receptor (26). In addition, statins have an effect on nitric oxide, decrease endothelin, and may have an antioxidant effect (27–30). The mechanism of the potential effect of statins on dementia and cognitive impairment is unknown. Our study showed an association between the use of statins and dementia, both vascular dementia and AD. This association was persistent even after adjusting for cholesterol, LDL levels, and stroke, suggesting that the effect of statins is independent of their effect on cholesterol and stroke prevention.

One limitation of this study is “bias by indication” (31, 32), which implies that statins are less likely to be prescribed to patients with dementia. Although we understand that this is a major problem of any cross-sectional or retrospective analysis that investigates the impact of an intervention, both the control and the statin groups were similar in many risk factors for dementia. Both groups were similar in education, alcohol consumption, tobacco use, stroke or TIA, and depression. We also performed multivariate analyses controlling for many covariates that could potentially affect the physicians’ prescribing of the statin drugs. The impact of statins on dementia prevalence remained after these adjustments, minimizing the impact of this bias. Also, the association was persistent in the longitudinal analysis at follow-up, suggesting that the effect of statins is more likely to be valid and not only due to the bias by indication.

Another limitation of this study is the accuracy of the diagnosis of dementia. We were not able to confirm the diagnosis of dementia or its subtypes in the patients selected. The diagnosis of dementia is mostly a clinical diagnosis that is relatively accurate (33). We used two cognitive measures and developed a composite variable based on the clinical diagnosis and cognitive testing, which should improve diagnostic accuracy. The high rate of concordance between the clinical diagnosis and the cognitive testing results suggests accuracy of the diagnosis of dementia. In our sample, the majority of patients with a clinical diagnosis of dementia had no documented subtype. The impact of statins was true for these patients as well as for the overall sample and for those with either vascular dementia or AD, making the impact of this limitation on our results relatively low.

In part due to the recent growth in patient enrollment, many patients did not have follow-up cognitive testing. This limited our ability to perform subgroup analysis. There were no differences, including in cognitive testing score at baseline or use of statins, between the patients who had documented cognitive testing on follow-up and those who did not. Therefore, missing data from our analysis most likely have little impact on our results.

We had little information on patients’ compliance with the use of statins. The finding that the mean cholesterol and LDL of the statin group was lower than the control group suggests that the patients were using the prescribed drugs. Our study was not designed to test the impact of other lipido-lowering agents or to compare the differences between the multiple statin drugs. We did not assess the incidence of adverse drug reaction from statins or the rate of drug withdrawal. A similar percentage of patients was using statins at baseline and at follow-up. We also could not assess the impact of statins on cognition beyond the follow-up period.

**Figure 1.** Odds ratio of having dementia in the statin group compared with the control group. *p* < .05 for all categories. Models adjusted for all covariates.

**Figure 2.** Change of Mini-Mental Status Examination (MMSE) score at follow-up after 10.6 ± 0.6 months in the statin versus control group. *p* value for the comparison of the two groups = .025. Delta is the score at follow-up — score at baseline on the initial visit.
Until a randomized trial is performed, evidence concerning the impact of statins on dementia and their potential benefit for cognitive function will depend largely on observational studies. Our study suggests that the use of statins is associated with a lower prevalence of vascular dementia and AD. In addition, we have found a potential benefit of the use of statins on the progression of cognitive impairment in a select group of older patients followed in a community-based primary care geriatric practice. Clinical trials are urgently needed to confirm the positive impact of these drugs on cognitive function and dementia.

Acknowledgment

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References


