Statin Use and Risk of Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders

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Background—Use of statins has been associated with an amyotrophic lateral sclerosis-like syndrome in 2 analyses of overlapping surveillance databases that record adverse events potentially related to prescription drug use. We assessed whether statin use is associated with the occurrence of amyotrophic lateral sclerosis and other motor neuron disorders.

Methods and Results—We conducted a population-based case-control study in Northern Denmark, with a population of 1.8 million. From the Danish National Registry of Patients, we identified incident cases coded with amyotrophic lateral sclerosis or other motor neuron syndromes during the period from 1999 to 2008. We selected 10 population control subjects matched to cases on sex, birth year, and calendar time. Statin use was ascertained in the prescription database in the region—and so recorded before diagnosis—and associated with disease occurrence by conditional logistic regression adjusting for covariates. We identified 556 cases of amyotrophic lateral sclerosis or other motor neuron syndromes and 5560 population control subjects. The odds ratio associating disease occurrence with statin use was 0.96 (95% confidence interval, 0.73 to 1.28). Recent users of statins, former users, and users of short or long duration had similarly near-null associations.

Conclusions—Any risk of amyotrophic lateral sclerosis associated with statin use probably is small, so outweighed by the important clinical advantages of statin medications to prevent and treat cardiovascular diseases.

Key Words: drugs ■ epidemiology ■ nervous system

Statins were first approved in 1987 and have since been a widely used class of cholesterol lowering drugs. Large randomized clinical trials have shown that statins reduce the risk of cardiovascular mortality, acute myocardial infarction, stroke, and arterial revascularization. Statins may cause myopathy and rhabdomyolysis in standard doses, although these adverse events are rare. Statin use has also been associated with peripheral neuropathy, but the mechanism is not well understood.

Two recent analyses of overlapping surveillance databases have suggested that statin use might be associated with the occurrence of an amyotrophic lateral sclerosis-like syndrome. These surveillance data bases record adverse events potentially related to prescription drug use but are not population-based and reporting is not mandatory. In the first study, the WHO Foundation Collaborating Centre for International Drug Monitoring reported that upper neuron lesions appeared more often than expected in combination with statin medications, but such a disproportionality was not seen associating statins with Parkinson disease. A similar signal was reported in the second study, which used the US Food and Drug Administration’s Spontaneous Event Reporting System. The authors of the second study also conducted a retrospective analysis of 41 statin trials, which did not reveal any increase in incidence of amyotrophic lateral sclerosis (ALS) in patients treated with statins compared with placebo. This pooled analysis identified only 19 ALS cases, which were evenly divided between statin (9 cases) and placebo (10 cases) arms. With so few cases and short follow-up, this null result was imprecisely measured and may result from too short an induction period.

Thus, it remains to be clarified whether use of statins increases the risk of ALS occurrence. Because ALS is a serious disease with a very poor prognosis, and has no known preventable causes, any association between statins and ALS would have important public health implications. Using a population-based case-control design, we examined the hypothesis that statin use increases the risk of ALS and other motor neuron syndromes. By design, we used prospectively recorded information on statin use to avoid recall bias and had complete participation to avoid selection bias.
WHAT IS KNOWN
- The use of HMG-CoA reductase inhibitors (statins) to prevent and treat heart disease has increased substantially in the past 2 decades.
- Two analyses of overlapping surveillance databases suggest a possible association between statins and amyotrophic lateral sclerosis–like syndromes.

WHAT THE STUDY ADDS
- In a population-based case-control study in Northern Denmark, we identified 556 cases of amyotrophic lateral sclerosis or other motor neuron syndromes and 5560 population control subjects.
- The odds ratio associating disease occurrence with statin use was 0.96 (95% confidence interval [CI], 0.73 to 1.28).
- During the period 1994 to 2008, the prevalence of statin use among those 30 years old and older in the northern part of Denmark increased more than 30-fold, whereas the annual incidence of amyotrophic lateral sclerosis increased only 1.4-fold.

Methods
The study was approved by the Danish Registry Board and the Registry Board at Aarhus University.

Study Population
We performed this population-based case-control study in the northern part of Denmark, which has approximately 1.8 million inhabitants. The Danish population receives tax-supported health care from the National Health Service, allowing unfettered access to hospital care. Through the use of a unique 10-digit Civil Registration Number (CRN) assigned to all Danish citizens and residents, a person’s hospital discharge and prescription history can be obtained and linked to one another.

Identification of ALS Cases
The Danish National Registry of Patients has recorded information on all patients discharged from hospitals in Denmark since 1977. This registry includes the CRN of the patient and up to 20 discharge diagnoses assigned by the discharging physician coded according to the 10th edition of the International Classification of Diseases (ICD-10) since 1994 and the 8th edition before that. Outpatient and emergency room visits have been recorded in the registry since 1994.

Using the National Registry of Patients, we identified all patients with a first-time diagnosis of ALS or other motor neuron syndromes (together coded as 348 in ICD-8 and G12.2 in ICD-10) from here forward, we will abbreviate this outcome as “ALS.” We defined the index date of cases as the date of first ALS diagnosis.

Because the ICD-10 code used to identify cases (G12.2) corresponds to diagnoses of ALS or other motor neuron syndromes, we conducted a validation study. We selected a random sample of 25 persons from among all those who satisfied the case definition, and one of us (H.T.S.) reviewed their discharge summaries. We computed the proportion of these 25 who had ALS. For those who did not, we reported their actual diagnoses. We used these results to inform a quantitative bias analysis to model the impact of false-positive ALS overdiagnoses.

Ascertainment of Statin Use
To determine exposure to statins, we used the prescription data base in northern Denmark. The region is served by pharmacies equipped with a computerized accounting system from which data are sent to the Danish National Health Service, which refunds 50% to 95% of costs associated with the purchase of drugs prescribed by a physician.

Statistical Analysis
We computed the frequency and proportion of cases and control subjects within categories of age, sex, statin use, and history of the covariate diseases. We first examined the association between ALS occurrence and statin use by comparing “ever-users” of statins with the reference population of “never-users.” Then, to examine the effect of temporality of statin use on ALS risk, we subdivided ever-users into recent users and former users of the drug. We defined recent users as those whose last use of statins was less than 60 days before the index date and former users as those whose last use of statins was 60 or more days before the index date. Finally, we examined the duration of statin use on ALS risk, we subdivided ever-users into those who used statins for less than 3 years before the index date and those who used statins for 3 or more years before the index date.

For all association analyses, we used conditional logistic regression to compute case-control ORs and their 95% CIs. This model inherently adjusts for the matched factors and indications for statin prescription: history of acute myocardial infarction, stroke, hypertension, kidney disease, and diabetes. These diseases were ascertained from the primary discharge diagnoses recorded in the National Registry of Patients before the index date.
misclassification because ICD-compliant coding of ALS is not specific.\textsuperscript{11} This nonspecificity would give rise to false-positive cases (A out of 25 in our validation substudy). We therefore conducted a quantitative bias analysis\textsuperscript{12} to investigate the potential impact on our results. We modeled the observed relative risk (RR) as a function of (a) the true incidence of ALS in never-users of statins (I\textsubscript{0}), (b) the true relative risk associating statin use with ALS occurrence (RR), and (c) a false-positive rate of ALS occurrence, informed by the validation substudy, independent of statin use, and modeled as a function of the odds of the true incidence of ALS in never-users of statins [(A/(25-A))/I\textsubscript{0}]. That is:

\[
RR' = \frac{RR \times I_0}{A/(25-A)/I_0}
\]

This model assumes that all ALS cases are diagnosed and correctly coded by the ICD scheme, which is reasonable because ALS is a severe disease and unlikely to be incorrectly diagnosed over the entire course of its progression. Using this model, we estimated the relative risk we would expect to observe (RR'), assuming the 2 surveillance studies\textsuperscript{4,5} provided accurate estimates of the true relative risk (RR), and assuming a valid bias model.

All statistical analyses were completed using SAS software (version 9.2, SAS Institute, Cary, NC).

Results
During the period from 1994 to 2008, the prevalence of statin use among those 30 years old and older in the northern part of Denmark increased more than 30-fold, from 1.1% to 36%. In the same population over the same calendar period, the annual incidence of ALS increased 1.4-fold, from 2.9 per 100 000 to 3.9 per 100 000. These time trends were thus very different, as displayed in the Figure.

A total of 556 cases of ALS and 5560 population control subjects were identified during the period 1999 to 2008. The mean age of the case group was 66.2 years and 54% of the cases were men (Table 1). Cases and control subjects were similar with regard to the prevalence of diagnoses that are indications for statin use, except possibly stroke (10.8% of cases and 8.1% of control subjects). A similar proportion of cases and control subjects were ever-users of statins before the index date (14.2% of cases and 14.5% of control subjects).

We found no evidence of an increased risk of ALS associated with ever-use of statins, compared with never-use of statins (adjusted OR, 0.96; 95% CI, 0.73 to 1.28) (Table 2). No sex-based differences were present. Recent users (OR, 0.74; 95% CI, 0.50 to 1.10) and former users (OR, 1.21; 95% CI, 0.86 to 1.72) also had estimates of association near the null and CIs that overlapped the null. The association also did not depend strongly on duration of statin use. Those with statin use for \(<3\) years (OR, 1.08; 95% CI, 0.78 to 1.51) and those with statins use for 3 or more years (OR, 0.79; 95% CI, 0.52 to 1.20) had near null estimates of association.

On review of the discharge summaries of a random selection of 25 cases, 17 patients (68%) had ALS, 5 (20%) had other motor neuron diseases, 1 (4%) was without final diagnosis, and 2 (8%) had Parkinson disease. Only 17 of the 25 are thus true ALS cases, and the latter 3 cases appear to have been improperly coded in the NPR. On the basis of these validation results, A=8 in the bias model described above. The ratio of the observed number of adverse events to the number expected in the first surveillance study\textsuperscript{6} was 3.28, and in the second surveillance study\textsuperscript{6} ranged from 1.6 to 8.5. If the true relative risk associating statin use with ALS occurrence

[Table 1. Characteristics of the 556 ALS Cases and 5560 Control Subjects, 1999 to 2008]

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cases, n (%)</th>
<th>Control Subjects, n (%)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, mean (SD)*</td>
<td>66.2 (12.0)</td>
<td>66.2 (12.0)</td>
<td></td>
</tr>
<tr>
<td>Male sex, n (%)*</td>
<td>302 (54.3)</td>
<td>3020 (54.3)</td>
<td></td>
</tr>
<tr>
<td>Use of statins, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>477 (85.8)</td>
<td>4754 (85.5)</td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>79 (14.2)</td>
<td>806 (14.5)</td>
<td></td>
</tr>
<tr>
<td>Acute myocardial infarction, n (%)</td>
<td>44 (7.9)</td>
<td>422 (7.6)</td>
<td></td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>60 (10.8)</td>
<td>450 (8.1)</td>
<td></td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>16 (2.9)</td>
<td>255 (4.6)</td>
<td></td>
</tr>
<tr>
<td>Renal disease, n (%)</td>
<td>3 (0.5)</td>
<td>61 (1.1)</td>
<td></td>
</tr>
</tbody>
</table>

*Control subjects matched to cases on this factor.

[Table 2. Frequency of Statin Use and ORs Associating Statin Use With ALS Occurrence, 1999 to 2008]

<table>
<thead>
<tr>
<th>Statin Use</th>
<th>Cases, n (%)</th>
<th>Control Subjects, n (%)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>477 (85.6)</td>
<td>4754 (85.5)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Ever</td>
<td>79 (14.2)</td>
<td>806 (14.5)</td>
<td>0.96 (0.73, 1.28)</td>
</tr>
<tr>
<td>Last statin use before index date</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 to 59 d</td>
<td>32 (5.8)</td>
<td>429 (7.7)</td>
<td>0.74 (0.50, 1.10)</td>
</tr>
<tr>
<td>(\geq 60) d</td>
<td>47 (8.5)</td>
<td>377 (6.8)</td>
<td>1.21 (0.86, 1.72)</td>
</tr>
<tr>
<td>Duration of statin use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(&lt; 3) y</td>
<td>50 (9.0)</td>
<td>455 (8.1)</td>
<td>1.08 (0.78, 1.51)</td>
</tr>
<tr>
<td>(\geq 3) y</td>
<td>29 (5.2)</td>
<td>351 (6.3)</td>
<td>0.79 (0.52, 1.20)</td>
</tr>
</tbody>
</table>

Adjusted ORs were estimated by conditional logistic regression modeling. This model inherently adjusts for the matched factors (age and sex), and we included dichotomous variables to adjust for the indications for statin treatment (history of acute myocardial infarction, stroke, diabetes, and renal disease).
equaled one of these values, then our result should have equaled 2.55, 1.4, or 6.1, respectively, given our bias model. However, none of these estimates even fell within the 95% CI of our comparison of ever-users with never-users (OR, 0.96; 95% CI, 0.73 to 1.28). Conversely, our strongest association in the causal direction (1.21 for former users, with 95% CI, 0.86 to 1.72) implies a true relative risk associating statin use with ALS occurrence of only 1.31, given the bias model, which is lower than any relative risk estimated by the surveillance studies.

Discussion
In the present large population-based study, we assessed the association between statin use and ALS occurrence. Statin use was not associated with development of ALS. The near-null association persisted in those who used statins for 3 or more years and regardless of whether the statin use was near in time to the date of ALS diagnosis.

We started our study in 1998, and before 1998 there was only limited use of statins in Denmark (Reference 13 and Figure). During the years after statins were marketed, no epidemic of ALS has been observed, although they are among the most often used drugs worldwide. For example, in a population-based study of 1 county in Northern Denmark, the prevalence of statin use among men 60 to 69 years old increased from 5% in 1991 to nearly 50% by 1998. Among women 60 to 69 years old, the prevalence of statin use increased from 5% to 33% over the same time period. The prevalence of statin use also increased rapidly over this period in Sweden and other nations, but was not accompanied by any substantial increase in the incidence of ALS.

Our results extend earlier findings in several important ways. First, we specifically focused on the association between statins and ALS and drew conclusions from a much larger sample of ALS cases than available in any previous study. Second, we were able to examine the association over a long induction period, allowing the analysis of the association between both recent and former user. Finally, nesting our analyses in a uniformly organized healthcare system allowed a population-based case-control design. The study population was stable, with more than 98% of cases and control subjects living in the study area for at least 10 years, thus providing substantial exposure and outcome data to be recorded. The prospectively recorded prescription information was not susceptible to recall bias. Furthermore, the registries allowed us to include all eligible subjects; therefore, the results are not susceptible to selection bias.

The limitations of our approach include reliance on a registry of filled prescriptions as a surrogate for actual use. This reliance could lead to misclassification of some persons as users who were actually nonusers, biasing our results against the finding of harm. However, Danish patients are only partially reimbursed for statin prescriptions, and the indications for statins are severe, so we expect good correspondence between filled prescriptions and prescription adherence. Complete prescription data were only available beginning in 1998, so the longest duration of statin use that we could measure was 10 years. If ALS occurrence is associated only with statin use of longer duration (eg, in the primary prevention setting) or requires an induction period longer than 10 years, our design would not be well-suited to estimate the association. We note, however, that because statin prescriptions only became prevalent in about 1998, few opportunities to study induction periods of longer duration are likely to be available.

As described above, ALS registration by hospital codes is also subject to misclassification because ICD-compliant coding of ALS is not specific. This nonspecificity would give rise to false-positive cases (as many as 8 of 25 in our validation substudy), which would also bias our results against the finding of harm. Because this bias had the potential to substantially influence our results, we conducted a quantitative bias analysis. The bias modeling results presented above provide assurance that false-positive disease misclassification does not fully explain our null results.

In conclusion, our near-null results are inconsistent with 2 recent analyses of overlapping surveillance databases. These analyses found that statins and ALS appeared together more often than expected among reports of potential adverse events associated with prescription drug use. Our results are consistent with the retrospective analysis of the pooled clinical trial data and with the lack of any substantial increase in ALS incidence in the time period when the prevalence of statin use has increased more than 30-fold. If there is any association between statin use and ALS occurrence, it is likely to be small and to pertain only to statin use of long duration or in the distant past. Such an association would differ in strength and exposure characteristics from those reported in analyses of the drug surveillance databases.

Disclosures
The authors declare no potential conflicts of interest. The Department of Clinical Epidemiology is, however, involved in studies with funding from various pharmaceutical companies as research grants to (and administered by) Aarhus University. None of these studies have relation to the present study.

References


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