

CME

Statins and risk of polyneuropathy

A case-control study

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Abstract—Background: Several case reports and a single epidemiologic study indicate that use of statins occasionally may have a deleterious effect on the peripheral nervous system. The authors therefore performed a population-based study to estimate the relative risk of idiopathic polyneuropathy in users of statins. **Method:** The authors used a population-based patient registry to identify first-time-ever cases of idiopathic polyneuropathy registered in the 5-year period 1994 to 1998. For each case, validated according to predefined criteria, 25 control subjects were randomly selected among subjects from the background population matched for age, sex, and calendar time. The authors used a prescription register to assess exposure to drugs and estimated the odds ratio of use of statins (ever and current use) in cases of idiopathic polyneuropathy compared with control subjects. **Results:** The authors verified a diagnosis of idiopathic polyneuropathy in 166 cases. The cases were classified as definite (35), probable (54), or possible (77). The odds ratio linking idiopathic polyneuropathy with statin use was 3.7 (95% CI 1.8 to 7.6) for all cases and 14.2 (5.3 to 38.0) for definite cases. The corresponding odds ratios in current users were 4.6 (2.1 to 10.0) for all cases and 16.1 (5.7 to 45.4) for definite cases. For patients treated with statins for 2 or more years the odds ratio of definite idiopathic polyneuropathy was 26.4 (7.8 to 45.4). **Conclusions:** Long-term exposure to statins may substantially increase the risk of polyneuropathy.

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Hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors or statins are lipid-lowering drugs. In Denmark statins are used in the primary and secondary prevention of coronary artery disease if satisfactory lowering of blood lipids is not achieved through life-style changes. An ever-growing number of patients are receiving long-term treatment with statins. According to a national prescription register with patient-specific data and complete coverage of Denmark (5.2 million inhabitants), the number of statin users in Denmark increased from 11,547 in 1994 to 50,318 in 1998.¹ Similar trends have been observed in the United Kingdom.² Although the efficacy and relative safety of statins have been well documented in large clinical trials,^{3,4} long-term use of these drugs in unselected populations of patients may still reveal previously unrecognized untoward effects. This may be the case in a small number of patients with polyneuropathy reportedly caused by statins.^{5–9} We conducted the only published epidemiologic study to date on this issue, a cohort study based on data from British general practitioners, and

found that use of statins increased the risk of idiopathic polyneuropathy, but the interpretation of our data were hampered by the small number of cases.¹⁰

We performed the current population-based, case-control study in a setting where we believed we could obtain a larger number of polyneuropathy cases and more detailed clinical data.

Methods. We performed a nested case control study in the county of Funen (465,000 inhabitants; 9% of the Danish population) based on information from local registries: The Funen County Hospital Registry, a patient registry, and the Odense University Pharmacoepidemiological Database¹¹ (OPED), a prescription registry. Simple and correct linkage across the registries was ensured by the civil registration number, a 10-digit code unique to each Danish citizen.

Case ascertainment and validation. The patient registry contains information on all outpatient visits and discharges from nonpsychiatric hospitals in the county. Recorded data include county of residence and discharge and outpatient diagnoses coded according to the International Classification of Diseases, 10th revision (ICD-10).

See also page 1321

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We retrieved data from outpatient visits or discharges registered between January 1, 1994 and December 31, 1998, listed with one or more of the following diagnoses: progressive idiopathic neuropathy (ICD-10 code G60.3), other hereditary and idiopathic neuropathies (G60.8), unspecified hereditary and idiopathic neuropathies (G60.9), drug-induced polyneuropathy (G62.0), or unspecified polyneuropathy (G62.9).

In all, 1,084 patients were registered under codes for polyneuropathy. We went through the lists manually and excluded 492 patients either because they also were registered with a polyneuropathy code before 1994, or owing to concurrent diagnoses of diseases that dispose to polyneuropathy, e.g., diabetes, severe renal failure, or alcohol abuse. This procedure left 592 patients for further validation. The medical records of 585 patients (98.8%) could be traced and were reviewed by a trainee in neurology (U.J.). Patients with a diagnosis of polyneuropathy in their medical records established before January 1, 1994 (n = 54) and potential cases, in whom the nerve conduction test did not support the diagnosis or had not been performed, were excluded (n = 75). Patients were also excluded if any of the following diseases and conditions were stated as diagnoses in the medical records, or appropriate tests indicated their presence (n = 287): diabetes, renal insufficiency, overuse of alcohol, hypothyroidism, cancer, monoclonal gammopathy of undetermined significance, AIDS, Lyme disease, connective tissue disease, heavy metal intoxication, cobalamin or folic acid deficiency, familial polyneuropathy, or chronic inflammatory idiopathic polyneuropathy. An erroneous code had been applied in two cases and one patient was excluded because she was not a resident of Funen.

Information on drug use and personal identifiers were suppressed in the medical records, after which the cases were evaluated by a neurologist with a special interest in polyneuropathy (S.H.S.). The clinical criteria for a diagnosis of polyneuropathy were distal symmetric sensory symptoms or symmetric motor symptoms and no upper motor neuron signs, or both. The neurophysiologic criteria were abnormal conduction (velocity or compound action potential) in two or more peripheral nerves, with at least one being a leg nerve. In cases where the nerve conduction study could not be retrieved, the conclusion of the study had to be reported in the medical record as being compatible with peripheral neuropathy. A diagnosis of peripheral neuropathy was only accepted if both the clinical data and the nerve conduction study were compatible with the diagnosis. Verified cases of peripheral neuropathy that had been adequately worked up, i.e., tested for all previously listed exclusion diagnoses and conditions, and where no apparent cause for the neuropathy had been established were classified as *definite idiopathic cases*. Cases where only sufficient information existed to rule out alcohol overuse, diabetes, and renal insufficiency were termed *probable idiopathic cases*. Finally, patients were classified as *possible idiopathic cases* if the information available was not sufficient to ascertain the presence or absence of any of the above-mentioned exclusion criteria.

All cases were assigned an index date that corresponded to the earliest of the following events: date of first contact with the hospital, or the date on which the patient's physician reached a polyneuropathy diagnosis.

Table 1 Characteristics of 166 cases of idiopathic polyneuropathy identified in Funen county, Denmark in 1994 to 1998

Characteristics	Statin users (n = 9)	Nonusers (n = 157)
Median age (interquartile range)	59.2 (51.1–59.5)	66.0 (55.7–74.2)
Male sex	5 (55.6)	105 (66.9)
Pain or paresthesia*	8 (88.9)	127 (80.9)
Numbness†	8 (88.9)	110 (70.6)
Absent tendon reflexes‡	4 (44.4)	72 (45.9)
Clinical classification		
Motor	1 (11.1)	9 (5.7)
Sensory	7 (77.8)	93 (59.2)
Sensorimotor	1 (11.1)	45 (28.7)
Unclassifiable	—	10 (6.4)
Neurophysiology		
Mainly axonal	8 (88.9)	137 (87.3)
Axonal and demyelinating	1 (11.1)	17 (10.8)
Unclassifiable§	0	3 (1.9)

Numbers in parentheses are percentages unless otherwise indicated.

Data missing in 7,* 15,† and 17‡ nondefinite cases, all of whom were nonusers of statins.

§ The conclusion of the nerve conduction studies was cited in the medical records but the neurophysiology test results could not be traced.

Controls. The residence history of all inhabitants of Funen county, regardless of medication status, is maintained and continuously updated as part of OPED, the prescription registry.¹¹ This feature enabled the selection of population control subjects in a nested design. For each case we identified all inhabitants of Funen of the same sex and age (year of birth) and assigned them the index date of the case. We randomly chose 25 control subjects per case among persons who were alive and residing in Funen at the time of the index date, and had no diagnosis of peripheral neuropathy before the index date. Control subjects were in effect matched for age, sex, and calendar time (index date).

Drug exposure. The prescription registry has provided complete coverage of all reimbursed prescriptions presented in Funen county since November 1992. For each prescription, the registry includes information on the civil registration number, the date the prescription was presented, and the brand, quantity, and form of the drug. The total package content of the drug is recorded as the number of Defined Daily Doses (DDD).¹² The DDD is established by an expert panel as the typical adult daily maintenance dose (15 mg simvastatin, 30 mg lovastatin, 20 mg pravastatin, 40 mg fluvastatin, 10 mg atorvastatin, or 0.2 mg cerivastatin). All drugs are classified according to the anatomic therapeutic chemical (ATC) system.¹² Information on the prescribed dosing and indication is not registered.

For both cases and controls we retrieved all available information from the prescription registry on the use of

statins and other drugs before the index date. Subjects were classified as ever (one or more prescriptions) or never users (no registered prescriptions) of statins. We also defined two time windows of exposure for statins: current and past use. A person was a "current user" if he or she presented a statin prescription at any time in the 3-month period before the index date. Persons whose last registered prescription was presented before this 3-month period were termed "past users." Never users were the reference group. Duration of use was estimated as the number of years between the first and the last registered prescription of statins, and the cumulative dose corresponded to the total amount of prescribed DDD in this period. Average daily dose was estimated as the cumulative dose divided by duration of use. Analyses on nonstatin lipid-lowering drugs were not performed owing to small numbers.

Cases and controls were also classified as ever or never users of antidiabetic agents, thyroid hormone supplements, or disulfiram. We also screened the prescription register data for ever use of various drugs previously associated with peripheral neuropathy^{13,14}: chemotherapy, gold, phenytoin, amiodarone, isoniazid, ethambutol, metronidazole, nitrofurantoin, chloramphenicol, griseofulvin, cloroquin, disulfiram, dapson, cimetidine, colchicine, hydralazine, pyridoxine, and thalidomide.

Analyses. We used conditional logistic regression to calculate the odds ratios (OR) and 95% CI of exposure to statins in cases of peripheral neuropathy compared with control subjects. Analyses were performed for ever use and current/past use, with never use as the reference group. Separate analyses were performed for all cases of idiopathic neuropathy, probable and definite cases, and definite cases only.

To minimize information bias we repeated all analyses after restricting the material to persons who had resided in Funen county for at least 3 years before the index date. We also repeated the above analyses after excluding patients with ever use of certain medications previously linked to polyneuropathy (listed in the Exposure to other drugs section). It is frequently difficult to establish the exact date of occurrence of polyneuropathy, owing to its insidious onset. This potential bias could be further accentuated by delayed referral. Therefore, we moved back the index date (1 and 2 years) for cases and control subjects, reclassified them with respect to statin exposure, and repeated the above analyses.

We calculated the number needed to harm, i.e., the number of patients needed to be treated for one additional patient to be harmed, by the method described by Bjerre and LeLorier.¹⁵ Data were analyzed using Stata version 6.0.¹⁶ The study was approved by the regional ethics committee and the Danish registry board.

Results. We identified 166 cases with a first-time diagnosis of idiopathic polyneuropathy: 35 definite, 54 probable, and 77 possible cases. The characteristics of the cases are presented in table 1.

Nine cases had been exposed to statins (simvastatin [5], pravastatin [2], lovastatin [1], fluvastatin [1], previous user of lovastatin), eight of whom were current users. One patient was switched from gemfibrozil to simvastatin 37 months before the index date. The median duration of statin use in the cases was 2.8 years (interquartile range [IQR] 1.9 to 3.0), and only two cases had taken statins for

Table 2 Relative risk estimate of peripheral neuropathy in statin users

Exposure to statins	Cases	Controls	Odds ratio (95% CI)
All cases			
Never use	157	4,084	1 (Reference)
Current use	8	49	4.6 (2.1–10.0)
Past use	1	17	1.4 (0.2–10.8)
Definite cases only			
Never use	27	854	1 (Reference)
Current use	7	17	16.1 (5.7–45.4)
Past use	1	4	6.5 (0.7–64.0)

Cases and controls were matched for age, sex, and calendar time.

less than 20 months. Cases had consumed a median cumulative statin dose of 803 DDD (IQR 506 to 1,181), which corresponded to a median daily consumption of 1.0 DDD (IQR 0.6 to 1.4). Of the 66 control subjects exposed to statins, 49 were current users (simvastatin [31], pravastatin [9], lovastatin [7], fluvastatin [2]).

The relative risk estimates (OR) of polyneuropathy in current users of statins were 4.6 (2.1 to 10.0) if all cases were included, 8.0 (3.4 to 18.2) in probable and definite cases, and 16.1 (5.7 to 45.4) in definite cases only (table 2). Analyses of ever use vs never use provided similar estimates (see table 3). The relative risk of polyneuropathy

Table 3 Influence of duration, cumulative dose, and average daily dose on the risk of peripheral neuropathy in ever users of statins

Variable	All cases (n = 166)	Definite cases only (n = 35)
Never use of statins	1.0 (Reference)	1.0 (Reference)
Ever use	3.7 (1.8–7.6)	14.2 (5.3–38.0)
Duration of statin use, y*		
<2	2.0 (0.6–6.5)	6.1 (1.2–29.8)
≥2	6.6 (2.6–16.5)	26.4 (7.8–89.4)
Cumulative dose, DDD†		
<560	1.5 (0.4–6.3)	3.4 (0.4–28.3)
≥560	6.3 (2.7–14.9)	27.2 (8.4–88.4)
Average daily dose, DDD‡		
<1	3.1 (1.1–8.8)	13.4 (3.8–47.4)
≥1	4.4 (1.7–11.4)	15.1 (4.2–54.2)

Values are expressed as odds ratio (95% CI).

Cases and controls were matched for age, sex, and calendar time.

* No. of years between date of first and last recorded statin prescription in register.

† Total registered dose in the prescription register in DDD. Cut off value corresponds to the median cumulative dose of all exposed subjects (cases and controls).

‡ Total registered dose in the prescription register in DDD divided by duration of statin use as defined above.

DDD = defined daily dose (2 DDD = 15 mg simvastatin, 30 mg lovastatin, 20 mg pravastatin, 40 mg fluvastatin, 10 mg atorvastatin, or 0.2 mg cerivastatin).

increased by duration of statin use and by cumulative dose, a relationship that was not reflected in the average daily dose. The data should, however, be interpreted with caution owing to the wide CI (see table 3).

In the remaining subanalyses, for simplicity, we compared changes in the relative risk of ever use of statins in definite cases of polyneuropathy (14.2 [5.3 to 38.0]). Neither excluding cases and control subjects with registered ever use of drugs previously associated with polyneuropathy (12.8 [3.1 to 53.1]) nor reducing the sample to subjects observed for more than 3 years had any major impact on the relative risk (15.2 [5.3 to 43.1]). Our attempt to partially adjust for confounding through exclusion of persons with registered prescriptions for thyroid replacement drugs, antidiabetic agents, or disulfiram primarily affected the control group, as users of these drugs had already been excluded among definite cases and predictably resulted in an increase of the relative risk estimate (17.6 [6.2 to 50.2]).

Moving the index date back by 1 year (16.0 [5.4 to 46.9]) and 2 years (20.2 [6.4 to 63.9]) also increased the relative risk. These results indicate that our choice of index date did not result in an overestimate of the relative risk.

The number needed to harm based on all age groups was 5,500 (2,200 to 18,500). Among those aged 50 years or older in our background population, we found an incidence of idiopathic polyneuropathy of 1.72 per 10,000 person-years among the unexposed to statins. With an OR of 3.7, it yields an excess rate of 4.5 per 10,000 person-years among the exposed, corresponding to one excess case of idiopathic peripheral neuropathy for every 2,200 (880 to 7,300) person-years of statin use.¹⁵

Discussion. We found that users of statins were at a 4- to 14-fold increased risk of developing idiopathic polyneuropathy compared with the background population, and that this adverse effect may primarily occur after long-term treatment with statins.

The current study has several strengths. We used population-based registries to screen for potential cases that were subsequently assessed according to predefined criteria by an expert in the field, who was blinded with regard to drug exposure. Only cases with electrophysiologic tests confirming the diagnosis were accepted. This approach minimized selection and information bias. Exposure to drugs was assessed through a prescription register, a data source not vulnerable to recall bias. Furthermore, the register information enabled us to choose an unbiased control group, i.e., a sample from the general population-at-risk that gave rise to the cases.

Our results are in line with several studies that indicate an association between statin use and polyneuropathy. In a study of 745 patients taking lovastatin with a median follow-up of 5.2 years, one case of peripheral neuropathy was reported.¹⁷ Several case reports and case series have linked statin use with peripheral neuropathy.⁵⁻⁹ In a cohort study based on data from general practitioners in the United Kingdom, we estimated the relative risk of polyneuropathy in current users of statins to be 2.5 (0.3 to 14.2) compared with the background population.¹⁰ The clinical data available for the evaluation

of the potential cases were less detailed and the absolute number of cases was small, which may explain in part the lower estimate of the relative risk compared with the current study.

A main concern is whether the neuropathy is caused not by the treatment but by the underlying disorder, i.e., hyperlipidemia. Although this possibility cannot be overruled in the current study, this explanation seems unlikely for several reasons. Hyperlipidemia-induced polyneuropathy has been suggested in a series with six patients with hypercholesterolemia and extremely high levels of serum triglyceride.¹⁸ However, the cases described in that series had only pain symptoms and a clinical picture compatible with a small-fiber peripheral neuropathy. In case series associated with statin use, a predominance of axonal sensorimotor neuropathy also involving large fibers has been reported, as in the current study. In our previous cohort study, the risk of polyneuropathy in subjects with untreated hyperlipidemia was comparable with that of the background population.¹⁰ Furthermore, several cases have been reported with reappearance or aggravation of peripheral neuropathy symptoms after reexposure to statins.⁶⁻⁸ These rechallenge cases along with the previously described neurophysiology findings strongly suggest a toxic effect of statins on peripheral nerves.

The mechanism underlying statin-induced peripheral neuropathy is unknown. It appears to be a drug class effect, as it has been observed with several of the statins. Interference with cholesterol synthesis through statin-induced inhibition of HMG-CoA reductase may alter nerve membrane function because cholesterol is a ubiquitous component of human cell membranes. Statins also co-inhibit the synthesis of the key mitochondrial respiratory chain enzyme, ubiquinone, which may disturb neuron energy utilization and thereby induce neuropathy, as has been suggested previously.⁷ Structural and functional changes of the neurons by long-term exposure to statins could be explained by both mechanisms.

A number of potential limitations of the study must be considered. Our hospital register probably did not provide complete coverage of all idiopathic peripheral neuropathy cases in Funen county. Not all patients with peripheral neuropathy are referred for further workup, and some patients are referred to private neurologists. In Funen county, however, neurophysiology tests are mainly performed at Odense University Hospital, which is covered by the hospital register. Based on the 166 cases identified in the current study, we estimated the incidence of idiopathic polyneuropathy to be 0.71 per 10,000 person-years, which, considering we applied strict neurophysiology criteria, seems reasonable compared with an incidence rate of 1.5 per 10,000 person-years reported in a recent British population-based study.¹⁹

Access to medical care is free in Denmark and expenses for statin use are reimbursed in docu-

mented cases of hyperlipidemia. Polyneuropathy as a side effect to statin use is not mentioned in the Danish physicians drug reference book, and this potential side effect received little attention in the international medical literature during the study period. We therefore believe that the current study is not subject to diagnostic bias, i.e., case ascertainment was not linked to use of statins.

Diabetes, renal insufficiency, hypothyroidism, and overuse of alcohol predispose to polyneuropathy and are also associated with hyperlipidemia. The presence of such conditions in the cases could severely confound our results. We therefore classified cases into three classes according to the degree of certainty with which a diagnosis of idiopathic polyneuropathy had been established. Stepwise restriction of the material according to diagnostic certainty increased the estimates dramatically, and definite cases produced the highest relative risk. The information we had on potential confounders in the control group was more limited. However, failure to adjust for these potential confounders in the control group only, as is the case here, would lead to an underestimate of the relative risk of polyneuropathy. The direction of this bias was confirmed in our subanalysis restricted to cases and control subjects with no recorded use of antidiabetic agents, thyroid hormones, or disulfiram in the prescription register. A number of other drugs have been linked to peripheral neuropathy, but the exclusion of ever users of these drugs, although predictably resulting in wider CI, only had a marginal effect on the risk estimate and therefore cannot explain our findings.

We initially published a case series including seven patients in whom statin-induced polyneuropathy was suspected.⁹ After completing our analyses we broke the scrambling code of the personal identifiers and found that all seven previously reported patients were included in the current study. Six patients were classified as current users of statins according to the prescription register. One patient was misclassified as a never user of the drug, probably due to short-term residency in Funen county at the time of case ascertainment. We consider the inclusion of these patients to be unbiased because they were diagnosed during the study period and subject to the same identification and blinded validation procedures as other potential cases.

The substantial protective effect of statins, particularly on coronary artery disease, is well documented and by far outweighs the potential risk of statin-induced polyneuropathy. We therefore believe

that the results of the current study should not influence the decision to initiate statin treatment. Complaints compatible with peripheral neuropathy in statin users should, however, prompt a thorough workup by the physician who should also reconsider the indication for continuous treatment.

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