NULL HYPOTHESIS CLASS OF EVIDENCE

# Statins do not increase risk of polyneuropathy

## A case-control study and literature review

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## Abstract

### Objective

To investigate whether there is an association between cholesterol-lowering medication use, specifically statins, and chronic polyneuropathy.

### Methods

A literature study was carried out to assess the current state of evidence on the association between chronic polyneuropathy and cholesterol-lowering medication use. We also conducted a prospective case-control study to compare exposure to cholesterol-lowering medication between patients with cryptogenic axonal polyneuropathy and controls prior to the index date (defined in patients as date of onset of polyneuropathy symptoms, in controls as date of first study survey). Outcomes were adjusted for potential confounders such as cardiovascular history and metabolic syndrome.

### Results

The 13 studies identified in our literature search showed conflicting results (odds ratios [ORs] ranging from 0.66 to 14.2), but most studies had methodologic limitations. There was insufficient evidence that statin use is a risk factor for polyneuropathy. Our prospective case-control study included 333 patients with cryptogenic axonal polyneuropathy and 283 controls. Patients with polyneuropathy were less likely to have been exposed to statins than controls (OR 0.56, 95% confidence interval 0.34–0.95, $p = 0.03$). The odds of polyneuropathy decreased as exposure duration to statins increased. Cholesterol-lowering medication consisted almost exclusively of statins; therefore we only draw conclusions on the effect of statin use.

### Conclusions

Statin use does not increase the risk of chronic polyneuropathy. Therefore, statins should not be routinely withheld from polyneuropathy patients.

### Classification of evidence

This study provides Class III evidence that statin use does not increase the risk of polyneuropathy.

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## Glossary

**ATP-III** = Adult Treatment Panel III; **BMI** = body mass index; **CI** = confidence interval; **DDD** = defined daily dosage; **ICD** = International Classification of Diseases; **OR** = odds ratio; **PAN** = population-based amyotrophic lateral sclerosis study in the Netherlands; **UMCU** = University Medical Center Utrecht.

The association between polyneuropathy and statins has been the subject of debate.[1] Case reports have described patients who developed polyneuropathy after initiation of statin use, and symptoms were sometimes reversible after cessation of the statin. However, outcomes from controlled studies have been conflicting and most of these studies focused on statins. Some studies also investigated the effect of other cholesterol-lowering medication separately, mostly fibrates. Results were usually similar, despite small numbers of users compared to statins.[2–4] Establishing causality remains difficult due to confounding factors, because statins are prescribed for cardiovascular diseases and associated risk factors like the metabolic syndrome, conditions that also have a demonstrated association with cryptogenic axonal polyneuropathy.[5–10] The increasing frequency of metabolic syndrome and cardiovascular diseases will result in more people requiring cholesterol-lowering treatment, especially with treatment guidelines becoming more stringent.[11–13] If cholesterol-lowering treatment is associated with an increased risk of polyneuropathy, then limiting the use of these drugs could have far-reaching implications for cardiovascular risk management. It is therefore important to know whether an association really exists.

We provide a literature overview of all available studies, and present findings from our prospective case-control study to establish whether cholesterol-lowering medication use, and specifically statin use, is associated with an increased risk of polyneuropathy. A patient group of cryptogenic axonal polyneuropathy, also known as chronic idiopathic axonal polyneuropathy, was used to assess this relation to reduce the chance of confounding of the effect of cholesterol-lowering medication by other known causes of polyneuropathy.

## Methods

### Literature review

We searched PubMed, Embase, and The Cochrane library for controlled clinical intervention studies or controlled observational studies that investigated the relation between cholesterol-lowering medication and chronic polyneuropathy. The search strategy is outlined in appendix 2 (links.lww.com/WNL/A839). All identified studies were assessed on the following 3 criteria (table 1):

1. A clinical diagnosis of polyneuropathy had to be explicitly defined as both the presence of distal symmetrical sensory or sensorimotor symptoms as well as signs compatible with polyneuropathy upon neurologic examination. Preferably, the diagnosis was also confirmed by nerve conduction studies. A diagnosis solely based on ICD codes (or electronic registries) was considered insufficient, because these encompass a substantial number of misclassified cases.[14]
2. Common causes of polyneuropathy had to have been excluded, or corrected for in the analyses. Common causes include diabetes mellitus, excessive alcohol consumption, exposure to neurotoxic medication or chemotherapy, thyroid disease, renal function disorder, connective tissue disease, and vitamin deficiencies. We found this criterion relevant, because in the presence of concomitant causes of polyneuropathy, an additional relation with statin use cannot be reliably assessed.
3. Exposure to cholesterol-lowering medication had to have been prior to onset of symptoms of polyneuropathy; if the medication was started after symptom onset, the development of polyneuropathy may not be related to it.

Studies that did not fulfill these 3 criteria are considered to have a high risk of bias. Their results should be interpreted with caution and will be presented separately from studies that fulfill all 3 criteria.

### Design of case-control study

This work was carried out as part of a prospective controlled study on the etiology of cryptogenic axonal polyneuropathy, initiated in 2008 at the University Medical Center Utrecht (UMCU).[15] Patients newly diagnosed with cryptogenic axonal polyneuropathy between October 2008 and July 2012 at the neuromuscular outpatient clinic in the UMCU were included. At study inclusion, all participants completed standardized questionnaires that encompassed use of cholesterol-lowering medication, dosage, year started, and, if applicable, year when medication was stopped. Missing data was obtained from pharmacies or family physicians, if participants gave consent for this.

Questionnaires also included questions on the presence of cardiovascular medical history, hypertension, use of antihypertensive medication, waist circumference, weight, and height.

We established the index date; this was the self-reported date of onset of polyneuropathy symptoms for patients, and date of questionnaire completion for controls. We assessed if cholesterol-lowering medications were initiated before the index date. Cholesterol-lowering medication use was divided into current use at index date, current use or past use prior to index date combined (ever use), and never use prior to index date. To investigate a dose–response effect, we used the defined daily dosage (DDD). This is a typical adult's daily maintenance dosage for each separate cholesterol-lowering

**Table 1** Literature review: Characteristics of 13 identified studies

| Design, citation | Year | N | Clinical diagnostic criteria for PNP[a] | Excluded/adjusted for common causes of PNP[b] | Exposure prior to PNP symptom onset | Outcomes |
|---|---|---|---|---|---|---|
| **Study fulfilling criteria** | | | | | | |
| **Case-control, database**[1] | 2017 | 238 IPNP patients; 1,760 controls | Yes | Yes | Yes[c] | Statins: OR 1.30 (CI 0.88–1.92) |
| **Studies not fulfilling criteria** | | | | | | |
| **Nondiabetic polyneuropathy** | | | | | | |
| **Case-control study**[23] | 2018 | 39 Statin; 39 controls | No | All except thiamine deficiency | No | No difference in PNP prevalence |
| **Observational cohort study**[28] | 2012 | 1,372 Statin; 7,773 no statin | No | No | No | OR 1.3 (CI 1.1–1.6) |
| **Intervention cohort study**[29] | 2007 | 42 Simvastatin; 50 placebo | No | No | Yes | No between-group comparison |
| **Case-control, database**[30] | 2005 | 272 PNP patients; 1,360 controls | No | No | No | Statins: OR 1.3 (CI 0.82–2.08) |
| **Case-control, database**[4] | 2004 | 2,040 Hospitalized PNP patients; 36,041 controls | No | No | No | Statins: OR 1.22 (CI 1.03–1.45); fibrates: OR 1.54 (CI 1.07–2.23) |
| **Case-control, database**[22] | 2002 | 35 Definite IPNP; 4,150 controls | No[38] | Yes | No | Statins: OR 14.2 (CI 5.3–38) |
| **Cohort study, database**[2] | 2001 | 17,086 All cholesterol-lowering medication users; 14,437 statins; 2,58,405 controls | No | No | No | Cholesterol-lowering medication users: OR 1.6 (CI 0.2–8.8); statins: OR 2.5 (CI 0.3–14.2) |
| **Diabetic polyneuropathy** | | | | | | |
| **RCT**[25] | 2015 | DPNP patients: 25 ezetimib and simvastatin; 25 rosuvastatin; 24 placebo | Yes | No | No | NCS outcomes: no differences; PNP severity scores: no between-group comparison |
| **RCT**[26] | 2014 | DPNP patients: 17 rosuvastatin; 17 placebo | Yes | No | No | DPNP stage: improved for rosuvastatin, no between-group comparison; PNP severity scores: no differences |
| **RCT**[24] | 2012 | 32 DPNP patients; atorvastatin; no statin | Yes | No | No | MCV improved for atorvastatin, M/F ratio no difference |

Continued

**Table 1** Literature review: Characteristics of 13 identified studies *(continued)*

| Design, citation | Year | N | Clinical diagnostic criteria for PNP[a] | Excluded/adjusted for common causes of PNP[b] | Exposure prior to PNP symptom onset | Outcomes |
|---|---|---|---|---|---|---|
| **Cross-sectional and longitudinal cohort study[3]** | 2008 | DM patients; cross-sectional: 382 DPNP; 855 no DPNP; longitudinal: 248 new DPNP; 147 no DPNP | Yes | No | Unclear[d] | Fibrates: OR 0.30 (CI 0.10–0.86); statins: HR 0.70 (CI 0.49–0.997); fibrates: HR 0.51 (CI 0.27–0.97) |
| **Case-control, database[27]** | 2014 | DM patients: 15,679 statin; 47,037 no statin | No | No | Unclear[e] | HR 0.66 (CI 0.57–0.75) |

Abbreviations: CI = 95% confidence interval; DM = diabetes mellitus; DPNP = diabetic polyneuropathy; HR = hazard ratio; ICD = International Classification of Diseases; IPNP = idiopathic polyneuropathy; MCV = mean corpuscular volume; NCS = nerve conduction study; OR = odds ratio; PNP = polyneuropathy; RCT = randomized controlled trial.
[a] Presence of distal sensory or sensorimotor symptoms and signs compatible with polyneuropathy upon neurologic examination.
[b] Common causes of polyneuropathy: DM, excessive alcohol consumption, exposure to neurotoxic medication, thyroid disease, renal function disorder, connective tissue disease, vitamin deficiencies.
[c] Statin use was before index date; this was self-reported date of symptom onset for patients, if this was not available this was date of registration of ICD diagnosis, or first hospital visit for polyneuropathy.
[d] Not for cross-sectional data, for longitudinal data only assessed at baseline, cholesterol-lowering medication use increased during 5 years follow-up from 14% to 45.3%.
[e] Statin use before ICD diagnosis of diabetic polyneuropathy.

medicine: simvastatin 30 mg, pravastatin 30 mg, fluvastatin 60 mg, rosuvastatin 10 mg, atorvastatin 20 mg, cerivastatin 0.2 mg, gemfibrozil 1,200 mg, ezetimibe 10 mg, bezafibrate 600 mg.[16] We calculated the cumulative dosage as the total amount of DDD to which participants were exposed prior to index date. For each participant, we determined exposure duration, by calculating the total time of exposure to cholesterol-lowering medication prior to index date in years.

Study participants underwent laboratory investigations for lipid spectrum, HbA1c, glucose, and measurements of blood pressure. With these investigations and waist circumference measurements we assessed the presence of the metabolic syndrome, defined as fulfilling at least 3 criteria of the Adult Treatment Panel III (ATP-III).[17] In addition, if study participants used antihypertensive or cholesterol-lowering medication, they were considered to fulfill the ATP-III criteria for, respectively, hypertension or increased triglycerides and decreased high-density lipoprotein cholesterol.

## Patients

The diagnosis of cryptogenic axonal polyneuropathy was made in a standardized fashion by an experienced neuromuscular neurologist in accordance with diagnostic criteria as previously described.[5] In short, patients were over 40 years old, they had to have both distal symmetrical sensory or sensorimotor symptoms as well as signs compatible with polyneuropathy upon neurologic examination, and nerve conduction study outcomes had to be consistent with axonal polyneuropathy. A comprehensive diagnostic workup and patient history excluded other known causes of polyneuropathy.

## Controls

We used healthy persons from the prospective population-based amyotrophic lateral sclerosis study in the Netherlands (PAN) as controls.[18] A subgroup of controls who were included in the same time period as patients underwent additional investigations for the purpose of this study.[18] Exclusion criteria for controls were age under 40 years, a known diagnosis of polyneuropathy, or a major risk factor for polyneuropathy, such as diabetes mellitus, excessive alcohol consumption (≥4 drinks per day), or thyroid disease.

## Statistical analyses

All statistical analyses were performed using Software Package for Social Sciences (SPSS version 22.0; SPSS Inc., Chicago, IL). Results were considered statistically significant when $p$ value was lower than 0.05.

We compared participant characteristics between groups with $\chi^2$ statistics or Fisher exact test for ordinal and nominal variables and Student $t$ test or Mann-Whitney $U$ test for continuous variables. Missing data were imputed by multiple imputations (n = 10) using predictive mean matching. The imputation model contained all available covariates and endpoints. Results across statistical methods were pooled using Rubin Rules.[19]

A binary logistic regression was used to model the association between cryptogenic axonal polyneuropathy and cholesterol-lowering drug use. The propensity score was used to adjust odds ratios (ORs) for potential confounders.[20] The propensity model contained all variables that resulted in a more than 5% change in the log (OR) for statin use. Lipid spectrum values were not included in the model as these values are influenced by cholesterol medication use. The propensity scores were calculated per imputed dataset and included as covariate in the binary logistic regression to calculate adjusted ORs. To assess the balance among the propensity scores, we split the propensity score into 10 equally sized strata. We estimated within the propensity strata the mean for various potential confounders for the patients and controls.

We assessed a possible dose–response effect by calculating ORs for cumulative dosage and exposure duration as a continuous variable. Furthermore, we assessed the change in OR for increasing categories of cumulative dosage and exposure duration to assess the dose–response effect.

All analyses were carried out separately for all cholesterol-lowering medication combined and statins alone. If numbers allowed for this, a subgroup analysis was planned for statins and other types of cholesterol-lowering medication.

In order to rule out an effect of selection bias for the control group, we carried out a sensitivity analysis in which we repeated all analyses after including all controls enrolled in PAN from 2010 through 2013 who fulfilled our inclusion criteria. This included controls who did not undergo laboratory investigations and blood pressure measurements. Results for these investigations were imputed with the previously described methods. We decided on the inclusion date limitation of 2013, as prescription guidelines for cholesterol-lowering medication became more stringent in November 2013, which could result in an increase of statins use compared to our original study period.[21]

## Standard protocol approvals, registration, and patient consents

This study was approved by the Medical Ethics Committee of the UMCU. All study participants gave written informed consent before inclusion.

### Classification of evidence

The primary research question of this study is whether cholesterol-lowering drug use, and statin use specifically, is associated with an increased risk of cryptogenic axonal polyneuropathy. This study provides Class III evidence that statin use prior to onset of symptoms does not convey an increased risk of cryptogenic axonal polyneuropathy in 2008–2012 (OR 0.6, 95% confidence interval 0.3–0.9, $p = 0.02$).

## Data availability statement

All study data are available on request.

# Results

## Literature review

The literature search yielded 1,301 citations, and we identified 13 studies that investigated the association between cholesterol-lowering medication use and polyneuropathy.[1–4,22–30] These studies showed conflicting results, and do not provide sufficient evidence that cholesterol-lowering medication use is a risk factor for polyneuropathy. A review of the literature is given in table 1.

There was one study that met all 3 of our criteria.[1] This study neither found an association between statin use and cryptogenic polyneuropathy nor was there a dose–response effect between statins and polyneuropathy.

## Case-control study

There were 662 potential participants who underwent investigations for this study: 345 patients with axonal polyneuropathy and 308 controls. After re-evaluation of clinical data, 12 patients were excluded due to presence of exclusion criteria (n = 4 alcohol overuse, n = 2 thyroid disease, n = 5 diabetes, n = 1 age under 40 years at symptom onset), 22 controls were excluded because they did not fulfill inclusion criteria (n = 6 alcohol overuse, n = 12 diabetes mellitus, n = 2 age under 40 years, n = 3 polyneuropathy), and 3 controls were excluded because they did not complete the questionnaire. Table 2 presents characteristics of the included 616 participants: 333 patients with cryptogenic axonal polyneuropathy and 283 controls. At inclusion, patients were older, but at index date (date of symptom onset) patients were younger than controls, and there was a higher percentage of male participants in the patient group. Other differences between patients and controls were current smoking status and alcohol intake.

In table 3, cardiovascular risk factors and history at inclusion date are shown. Patients had larger waist circumference and higher body mass index (BMI) than controls; they more often fulfilled criteria for hypertriglyceridemia and metabolic syndrome. Potential confounders that influenced the relation between polyneuropathy and cholesterol-lowering medication use were age, alcohol intake, current smoking, waist circumference, BMI, metabolic syndrome, cardiovascular history, and hypertension (use of antihypertensive medication or a known diagnosis of hypertension). These variables were included in the propensity score. Sex was also included in the propensity score as this differed between patients and controls.

## All cholesterol-lowering medication

Cholesterol-lowering medication consisted mainly of statins (94%). There were only 6 participants who used fibrates or ezetimibe prior to index date, of whom 3 had also been exposed to statins, and these numbers were too small to perform a subgroup analysis for statins and other cholesterol-lowering medication. Conclusions on the effect of individual cholesterol-lowering drug groups are therefore limited to statins, and the

**Table 2** Characteristics of study participants

| | Patients | Controls | *p* Value |
|---|---|---|---|
| **No. of participants** | 333 | 283 | |
| **% Men** | 71 | 63 | 0.04 |
| **Age at inclusion, y** | 66 (9) | 64 (9) | <0.005 |
| **Age at index date, y[a]** | 59 (9) | 64 (9) | <0.005 |
| **Alcohol units/wk** | 5 (0–25) | 7 (0–25) | <0.005 |
| **Smoking status, %** | | | <0.005 |
| **Current** | 5 | 14 | |
| **Past** | 61 | 59 | |
| **Never** | 34 | 28 | |
| **Level of education, %** | | | 0.76 |
| **Primary/middle** | 37 | 34 | |
| **Secondary** | 28 | 32 | |
| **College/university** | 34 | 34 | |

Outcomes are mean (SD), except for alcohol intake, which is median (range).
[a] Index date = date of symptom onset for patients, date of first study visit for controls.

**Table 3** Metabolic syndrome and cardiovascular risk factors at inclusion

| | Patients, n = 333 | Controls, n = 283 | *p* Value |
|---|---|---|---|
| **Metabolic syndrome** | 50[b] | 44[b] | 0.02 |
| **Decreased HDL[a] or medication** | 37[b] | 35 | 0.32 |
| **Hypertriglyceridemia[a] or medication** | 42[b] | 38 | 0.08 |
| **Glucose, mmol/L** | 5.4 (0.5) | 5.4 (0.5) | 0.58 |
| **Increased fasting glucose[a]** | 39[b] | 39[b] | 0.97 |
| **Increased blood pressure[a] or medication** | 81[b] | 81[b] | 0.16 |
| **Waist circumference, cm** | 101 (10) | 97 (11)[b] | <0.005 |
| **Abdominal obesity[a]** | 59 | 43 | <0.005 |
| **BMI** | 26 (17–43) | 25 (17–41) | 0.01 |
| **Cardiovascular history** | 22 | 17 | 0.10 |
| **Antihypertensive medication** | 32 | 31 | 0.75 |
| **Hypertension diagnosis or medication** | 45 | 39 | 0.08 |
| **Statin use at inclusion** | 20 | 21 | 0.75 |
| **All cholesterol-lowering medication use at inclusion** | 20 | 21 | 0.81 |

Abbreviations: BMI = body mass index; HDL = high-density lipoprotein.
Outcomes are % or mean (SD), except for BMI, which is median (range).
[a] According to Adult Treatment Panel III criteria.
[b] Missing data >5%: metabolic syndrome patients 15%, controls 11%, ATP triglycerides and HDL 7%, fasting glucose patients 5%, controls 8%, waist circumference 6%, increased blood pressure patients 13%, controls 11%, antihypertensive medication use 23%, cardiovascular history 29%.

outcomes of all cholesterol-lowering medication combined are largely driven by the effect of statins. Table 4 shows the frequency of statin use and all cholesterol-lowering medication with the corresponding ORs for polyneuropathy. Results for all cholesterol-lowering medication were similar to when statins alone were assessed, except for current use, which did not remain statistically significant.

### Statins

Patients were less often exposed to statins before index date than controls. Exposure to statins prior to symptom onset was not associated with an increased risk of cryptogenic axonal polyneuropathy, in fact, it was associated with decreased odds of cryptogenic polyneuropathy compared to no exposure to statins. Results were similar when only current statin users were assessed. There was an association between exposure duration to statins and polyneuropathy: adjusted OR 0.75 (95% confidence interval [CI] 0.59–0.94, $p = 0.01$). Figure 1 shows that when exposure duration increases, the OR for polyneuropathy decreases. There was no dose–response effect: adjusted OR 0.93 (95% CI 0.87–1.00, $p = 0.052$) for cumulative dosage of statins as a continuous outcome, and as shown in figure 2, the OR for polyneuropathy does not show a decreasing trend with increasing cumulative dosage categories.

For the sensitivity analyses, 145 additional controls with incomplete data were included, resulting in 428 controls in total. Baseline characteristics of controls were similar after inclusion of the additional controls, and the results of all analyses did not change.

## Discussion

We found that exposure to cholesterol-lowering medication, and statins specifically, prior to symptom onset is not a risk factor for cryptogenic axonal polyneuropathy. In fact, exposure to statins conveyed a decrease in the odds of developing polyneuropathy compared to no exposure. Because of the low number of other cholesterol-lowering medication users, we can only draw conclusions on the effects of statin use.

The studies identified through our literature review differed too greatly to allow the results to be pooled. We used relatively stringent criteria for the literature review to reduce risk of bias. The fact that only one study fulfilled all criteria underlines the methodologic limitations of the studies performed so far. To provide a complete overview of the literature, we presented the findings of all studies, also including those that did not fulfill all criteria. The fact that most studies did not assess whether statins were started before onset of symptoms, and did not exclude, or correct for, known causes of polyneuropathy and confounders such as cardiovascular diseases, can lead to an overestimation of the effect of statins on the risk of polyneuropathy. This could explain why some studies found an

**Table 4** Exposure to cholesterol-lowering medication prior to index date, with corresponding odds ratios (ORs)

| Patients (n = 333), controls (n = 283) | Statins | All cholesterol-lowering medication |
|---|---|---|
| **Ever use**[a] | | |
| **Patients/controls, n (%)** | 43 (13)/60 (21) | 45 (14)/61 (22) |
| **OR (95% CI) (*p* value)** | 0.55 (0.36–0.85) ($p = 0.01$) | 0.57 (0.37–0.87) ( $p = 0.01$) |
| **Adjusted OR[b] (95% CI) (*p* value)** | 0.56 (0.34–0.95) ($p = 0.03$) | 0.59 (0.35–0.98) ($p = 0.04$) |
| **Current use**[c] | | |
| **Patients/controls, n (%)** | 38 (11)/55 (19) | 41 (12)/56 (20) |
| **OR (95% CI) (*p* value)** | 0.53 (0.34–0.84) ($p = 0.01$) | 0.57 (0.37–0.88) ($p = 0.01$) |
| **Adjusted OR[b] (95% CI) (*p* value)** | 0.55 (0.32–0.93) ($p = 0.03$) | 0.60 (0.35–1.01) ($p = 0.06$) |

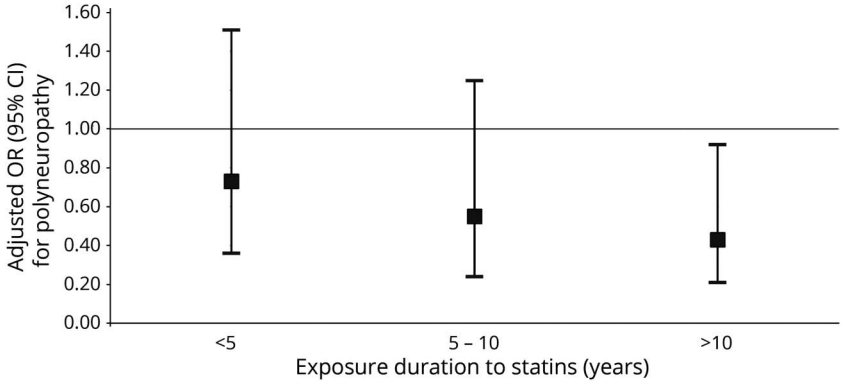
Abbreviation: CI = confidence interval.
[a] Participants who have ever been exposed to statins prior to index date (date of symptom onset for patients, date of completion of questionnaire for controls), including those who stopped using statins before index date (past users).
[b] OR adjusted for propensity score, including age, sex, current smoking status, alcohol intake, waist circumference, body mass index, hypertension (hypertension diagnosis, or medication), metabolic syndrome, cardiovascular history.
[c] Participants who were currently using medication at the index date.

increased risk of polyneuropathy in statin users. Our study shows the importance of accurately establishing the time relation between statin use and the development of polyneuropathy; we found that many patients started using statins after onset of symptoms (statin use was almost doubled at inclusion date compared to date of onset of symptoms). The study that met all our inclusion criteria found statins do not increase the risk of polyneuropathy. Strengths of this study are the population-based design, large study size, and low risk of recall bias due to retrieval of information on medication use from a national pharmacy database.[1] There were also some limitations. No adjustments were made for confounders such as cardiovascular diseases and metabolic syndrome. In 33% of patients who used statins, it was unclear whether statins were started before onset of symptoms, because date of onset was unknown. Exclusion of these patients would decrease the OR from 1.3 to 0.8 (95% CI 0.53–1.26). The inclusion of 42 patients with (possible) demyelinating polyneuropathy is questionable, as these patients most probably had an immune-mediated or hereditary demyelinating polyneuropathy. The effect of excluding these 42 patients would be limited and results in the same OR 1.4 (95% 0.98–2.10). These factors could explain the difference in outcomes with our study.

Our findings are in line with 2 large randomized controlled trials assessing the safety and efficacy of statins. Neither study found an increased incidence of polyneuropathy; however, the presence of polyneuropathy was self-reported and not systematically assessed.[31,32]

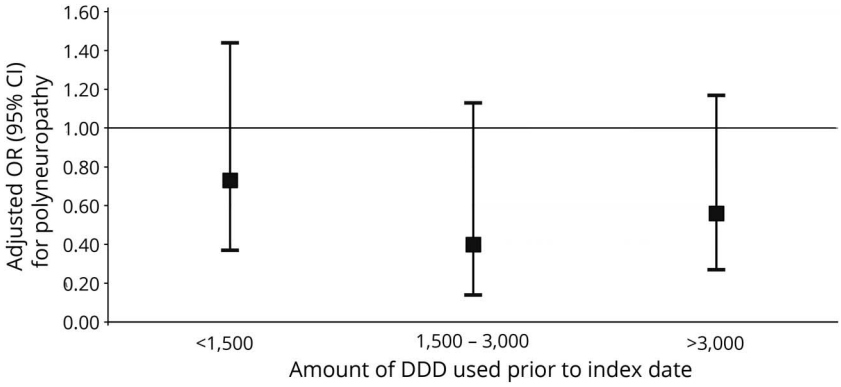
Studies in diabetic patients have indicated a protective effect of statin use on the development of diabetic polyneuropathy.[3,27] Suggested mechanisms for this protective effect are a reduction of microvascular damage to peripheral nerves, reduction of oxidative stress, and immunomodulation.[33] A microvascular pathophysiology has also been suggested for cryptogenic

**Figure 1** Effect of exposure duration to statins on risk of polyneuropathy




CI = confidence interval; OR = odds ratio.

**Figure 2** Dose–response effect of statin use on risk of polyneuropathy




CI = confidence interval; DDD = defined daily dosage; OR = odds ratio.

axonal polyneuropathy, because of its association with the metabolic syndrome and cardiovascular diseases.[5–10,34] A protective effect of statins may therefore also be applicable to cryptogenic axonal polyneuropathy. However, with our study design we are not able establish a causal relation between statin use and the decrease in odds of polyneuropathy.

Strengths of our study are the stringent clinical diagnostic criteria for cryptogenic polyneuropathy, the adjustments for potential confounders, and the exclusion of other possible causes of polyneuropathy, which limits the risk of confounding of the effect of statin use. A causal relation between the metabolic syndrome and cryptogenic axonal polyneuropathy has not been established; therefore, participants with polyneuropathy and metabolic syndrome were still considered to have cryptogenic axonal polyneuropathy.[5] The metabolic syndrome is, however, an important risk factor for cryptogenic axonal polyneuropathy and also for statin use, which is why it was included in the propensity score. We also carefully assessed whether statins had indeed been started before onset of symptoms. Our study population is an accurate reflection of the population, as we found a similar prevalence of statin use compared to prescription prevalence data in the Netherlands in 2008.[35] A limitation is the observational study design. A prospective incidence study does not seem feasible; the relatively low incidence of cryptogenic axonal polyneuropathy (~30/100,000 person-years) would necessitate a very large number of study participants and long follow-up time.[36] There is a risk of recall bias for date of symptom onset and starting date of statins, which could lead to an underestimation of the amount of patients who were exposed to statins prior to symptom onset. However, even when we considered all patients who used statins, including those who started using statins after symptom onset, we still did not find an increased risk of polyneuropathy in statin users (adjusted OR 1.1, 95% CI 0.48–2.4, $p = 0.86$). Thus it seems that the effect of this bias could at its worst result in no association between statin use and polyneuropathy. Another limitation is the relatively small control group compared to the patient group. We repeated the analyses with additional controls who did not undergo laboratory investigations to increase control group size, and this did not change our results.

Our study was not designed to investigate polyneuropathy as a rare side effect of statin use. We are aware that there may be patients who have an idiosyncratic reaction to statins, which could explain why in some case reports, patients experienced improvement of symptoms after discontinuation and exacerbation upon reexposure to statins.[37] Also, symptoms such as muscle cramps can present a challenge in patients with polyneuropathy who use statins, as this is both a common symptom of polyneuropathy as well as a known side effect of statins. Distinguishing the cause of muscle cramps can, therefore, be difficult, and may lead to discontinuation of statins. However, based on our findings and current literature, the use of statins is not a risk factor for cryptogenic axonal polyneuropathy. Therefore, statins should not routinely be withheld or, in the absence of known side effects, discontinued in patients with cryptogenic axonal polyneuropathy.

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## Disclosure

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| Name | Location | Role | Contributions |
|---|---|---|---|
| **Janna K. Warendorf, MD** | Brain Center Rudolf Magnus, UMC Utrecht, the Netherlands | Author | Literature review, data collection, statistical analyses, writing manuscript |
| **Alexander F.J.E. Vrancken, MD, PhD** | Brain Center Rudolf Magnus, UMC Utrecht, the Netherlands | Author | Daily supervision, review of manuscript, outline of the study |
| **Ruben P.A. van Eijk, MD** | Brain Center Rudolf Magnus, UMC Utrecht, the Netherlands | Author | Advisor for epidemiology, review of manuscript |
| **Nora A. Visser, MD, PhD** | Brain Center Rudolf Magnus, UMC Utrecht, the Netherlands | Author | Data collection, review of manuscript |
| **Leonard H. van den Berg, MD, PhD** | Brain Center Rudolf Magnus, UMC Utrecht, the Netherlands | Author | Review of manuscript |
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