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Statin use and peripheral nerve function - a prospective follow-up study

Running title: Statins and peripheral nerve function

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All authors have completed the Unified Competing Interest Form at http://www.icmje.org/coi_disclosure.pdf (available on request from the submitting author) and declare: Drs. Svendsen, Krøigård, Wirenfeldt, Schrøder, Bak and Möller have no disclosures; Drs. Hallas and Sindrup received grants from Pfizer unrelated to this work; Dr. Gaist received fees from Astra Zenica (Sweden) for participation as a coinvestigator in a research project unrelated to this work.

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ABSTRACT

Purpose: To examine the association between use of statins and risk of deterioration of peripheral nerve function.

Methods: We prospectively followed patients who initiated statin treatment and compared them with statin never-users (non-users). At the time of inclusion and at 1-year follow-up, participants underwent tests for peripheral nerve function (i.e., nerve conduction studies, quantitative sensory testing), skin biopsies, and ratings of symptoms and signs of neuropathy. We selected five tests of nerve function and the intraepidermal nerve fiber density (IENFD) *a priori* as primary outcomes. We used linear regression to test for differences between statin users and non-users with Holm-Bonferroni-corrected statistical significance level of 0.05.

Results: Comparisons were based on 57 statin users and 46 non-users. Changes in nerve function test results during follow-up were not uniform with regard to direction and were statistically not significant with the exception of IENFD (change in IENFD: statin users 1 fiber/mm vs. non-statin users -2 fibers/mm; *P*-value = 0.006). None of the participants developed overt peripheral neuropathy. However, five statin users developed neuropathy-like symptoms and a *post-hoc* analysis showed a significant decrease in vibration sensitivity compared to asymptomatic statin users.

Conclusion: Statin use was not clearly associated with increased risk of deterioration of peripheral nerve function analysed at a group level. However, given the sample size limitations of our study and the findings of our *post-hoc* analysis, we cannot preclude that peripheral nerve function may be affected in some individuals exposed to statins.

INTRODUCTION

HMG-CoA-reductase inhibitors (statins) are extensively used in the prevention of cardiovascular disease. In 2015, 35% of all Danes aged 65+ years used statins (1). Given the widespread use of statins, it is crucial to investigate even rare potential side effects of this class of drugs. Polyneuropathy is a disorder of the peripheral nerves that causes considerable morbidity in terms of sensory or motor symptoms, is frequently painful, and has a major impact on the quality of life (2). Polyneuropathy is estimated to affect approximately 2% of the general population, and the prevalence of this disorder increases with age (3). Although statin use has been reported as a possible cause of polyneuropathy in case studies (4–7), epidemiological studies of this putative association have provided equivocal results (8–17). Moreover, animal studies have reported a neuroprotective effect of statins against peripheral nerve injury (18,19).
To date, the majority of epidemiological studies of the association between statin use and risk of polyneuropathy have utilized secondary data collected for other purposes (7–11,16,17). Primary data, collected *ad hoc*, might provide further insight. We conducted the present study, where we prospectively collected detailed clinical data among patients initiating statin therapy and followed them for a year. Changes in the function of the peripheral nerve system were assessed through several methods in these patients and in a comparison group of non-users of statins.

METHODS

This is a prospective follow-up study of peripheral nerve function among patients exposed to statins (statin users), compared with individuals not exposed to statins (non-users).

Statin users and non-users

Statin users were recruited among patients with a verified diagnosis of cerebral infarction or transient ischemic attack (TIA) evaluated for these cerebrovascular events as in-patients or outpatients at our Department of Neurology. The cholesterol-lowering regimen recommended by department guidelines at the time of the study was simvastatin 40 mg daily. We recruited non-users of statins through advertisements in the local community and among spouses of patients included in the statin user group. Individuals aged 40-80 years with no previous use of statins or other cholesterol-lowering drugs were eligible for inclusion in either group. Subjects with a history of polyneuropathy or symptoms or signs suggestive of this disorder were excluded. Inclusion and exclusion criteria are further detailed in **eTable 1**.
Medical history and neurological examination of all participants was conducted by two study physicians. Baseline blood tests were used to rule out diabetes, hypothyroidism and renal insufficiency (creatinine > 150 μmol/L), and to measure cholesterol levels, i.e. total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL) and triglycerides.

Written informed consent was obtained from all participants. Participants in the statin user group received no financial compensation, while non-user participants received a minor remuneration (250 DKK ≈ 40 US dollars per visit). The study was conducted in accordance with the Basic & Clinical Pharmacology & Toxicology policy for experimental and clinical studies (20). The study was further approved by the Ethics Committee, Region of Southern Denmark (Project ID: S-20140089), and the Danish Data Protection Agency (Project ID: 14/47400).

Tests:

Each participant was tested at baseline and after 12 months with nerve conduction studies, skin biopsy for determination of the intraepidermal nerve fiber density (IENFD), quantitative sensory testing (QST) and rating of symptoms and signs of neuropathy (**Supplementary Methods**).

Based on the nerve conduction study and the rating scales, we determined the reduced version of the Total Neuropathy Score (TNSr) (21). As participants in the statin user group had suffered a cerebrovascular incident that could cause unilateral motor and sensory symptoms or signs, we adapted rating scales and QST accordingly for this group, i.e., by only rating extremities that were not affected by the stroke. Rating of symptoms and signs of neuropathy and definition of new onset polyneuropathy as clinical outcome are detailed in the **Supplementary Methods**.

At follow-up, patients were asked about any diseases diagnosed since baseline and any changes in medication within the last year, including statin use; cholesterol levels were measured once again. We excluded participants who fulfilled any exclusion criteria at follow-up (**eTable 1**).

We aimed at conducting all baseline tests within 7 days from the date of onset of statin use (for exposed participants), and the follow-up test one year (±30 days) after the baseline date. Evaluation of nerve conduction studies and counting of the nerve fibers in the skin biopsies was performed blinded with regard to patients' medication and previous test results.

Outcomes and sample size

We *a priori* selected changes in five tests of nerve function (peroneal nerve MCV and CMAP, sural nerve SCV and SNAP, and tibial nerve F-wave) and changes in IENFD as the primary outcome variables. Secondary outcomes comprised changes in all other measures conducted, i.e., nerve conduction variables not mentioned above (peroneal nerve dML and F-wave, tibial nerve dML and CMAP), QST results, rating scales, and new onset polyneuropathy.

Sample size calculations based on a previous study (22) indicated that 80 participants (40 statin users and 40 non-users) were required to demonstrate a clinically meaningful difference in the primary outcomes (*alpha* = 0.05 , *beta* = 90%). Holm-Bonferroni correction was applied to *P*-values regarding primary

outcomes. Based on our expectations with regard to drop outs and non-adherence to statin therapy, we aimed at including approximately 65 statin users and 50 non-users.

Analyses

In the analysis of nerve conduction data, we calculated an average of left and right extremity for each test of nerve function – missing values were disregarded.

For analyses of participant characteristics at baseline, we used chi-square-test, Fisher's exact test and independent group t-test, as appropriate. We used linear regression to calculate difference in changes in primary and secondary outcomes among statin users compared with non-users. In supplementary analyses, we performed the above analyses 1) adjusting for age and sex and 2) using only statin compliant participants.

Statistical analyses were carried out using Stata SE 15.0 (Stata Corp, College Station, TX, USA).

RESULTS

Of a total of 116 statin-naïve individuals recruited at the outset, 57 statin users and 46 non-users completed the study (**Figure 1**). Compared with non-users, statin users were older (mean age, years: 61 vs. 54; *P*-value = 0.001), more frequently smokers (*P*-value 0.034), and had higher blood levels of HbA1c at baseline (mean, mmol/mol: 37.8 vs. 35.8; *P*-value = 0.018). The two groups were similar with regard to other characteristics (**Table 1**). All statin users were initially prescribed simvastatin 40 mg, but during follow-up some patients had their dose reduced (n=2) or were switched to other statins (n=13) by their primary care physicians. Self-reported adherence to statins was high, e.g. 86% of patients used any type of statin for at least 10 months. Among patients in the statin group, cholesterol levels were lower at follow-up compared with baseline (mean total cholesterol 4.4 vs. 5.8; *P*-value = < 0.001; mean LDL 2.2 vs 3.7; *P*-value = < 0.001).

Nerve conduction studies were available for all participants except 1 statin user who declined to undergo the test. Reduction of sensory action potential of the sural nerve during follow-up was apparent among both statin users and non-users, but there was no statistical difference between the groups (–2 μV vs. –0.4 μV; *P*-value = 0.5 – Holm-Bonferroni-corrected). The differences between statin users and non-users regarding other nerve function test results included as primary outcomes were even smaller and were not uniform with regard to direction (**Table 2**).

Skin biopsies were available for 44 non-users (2 biopsies not available for analyses for technical reasons) and 49 statin users (7 biopsies not available for analyses for technical reasons; 1 declined follow-up biopsy). IENFD increased among statin users and decreased among non-statin users (change in IENFD:

statin users 1 fiber/mm vs. non-statin users -2 fibers/mm; *P*-value = 0.006 – Holm-Bonferroni corrected) (**Table 2**).

Changes in secondary outcomes among statin users did not differ from those observed among non-users, apart from the rating with Neurological Symptom Score, which showed borderline significant difference between groups (change 0.1 vs. 0.0; *P*-value = 0.052) (**Table 3**). None of the participants developed overt peripheral neuropathy. However, five of the 57 statin users developed distal, symmetric, neuropathy-like symptoms (pain and/or paresthesia) versus none of the non-users (*P*-value = 0.063). Another *post-hoc* analysis of the symptomatic statin users versus non-symptomatic statin users showed significant differences regarding vibration sensation as measured by biothesiometer (symptomatic users: change 9.5 vs. non-symptomatic users 0.6; *P*-value <0.001) but not sural nerve SNAP (**Table 4**).

In secondary analyses of primary outcomes, adjusting for the influence of age and sex had no major impact on study results (data not shown). Sub-analyses only including participants with more than 10 months of statin use in the exposed group returned results similar to those of the main analyses (data not shown).

DISCUSSION

We found no clear association between statin use and risk of deterioration of peripheral nerve function according to our pre-defined main outcome. However, a minority of patients (n=5) treated with statins did develop neuropathy-like symptoms and in a *post-hoc* analysis, these patients had developed a significant deterioration of vibration sensitivity measured with biothesiometer, compared with asymptomatic patients on statins.

Previous studies that reported data on peripheral nerve function in patients taking statins were either cross-sectional (23), or reported data on changes in pre-existing peripheral neuropathy among patients with diabetes (14,24). To date, we are aware of only one other study of individuals with no history of peripheral neuropathy or diabetes that were prospectively followed for changes in peripheral nerve function over time, as assessed through neurophysiological tests (42 patients on statins versus 50 non-statin users) (12). In that study, patients were assessed with nerve conduction tests four times in 24 months, during which period none of the patients developed symptoms compatible with polyneuropathy. Compared with non-users (whose data were not presented), significant changes over time in measurements of the peroneal nerves and F-waves of the tibial nerves could be demonstrated, but, importantly, not of the sural nerve. Involvement of the sural nerve is frequent in polyneuropathy to a degree that it constitutes an essential part of the acknowledged criteria for diagnosing the disorder (25). Lack of involvement of the sural nerve in that study may, therefore, raise concern as to whether the remaining neurophysiological findings truly demonstrate clinically silent electrophysiological damage to peripheral nerves, as suggested

by the authors, particularly since patients were asymptomatic. Differences in design prevent further comparisons between the above-mentioned study and the present one.

Our study has a number of strengths. We used multiple established tests to assess participants' peripheral nerve function and symptoms suggestive of polyneuropathy. Evaluation of nerve conduction studies and skin biopsies were performed blinded with regard to statin use. We secured a high degree of follow-up and included a comparison group in our study.

The results of skin biopsies in our study do not support a deleterious effect of statin on peripheral nerves. In fact, as IENFD increased among statin users and decreased among non-statin users, a protective effect of statins could be hypothesized. However, the IENFD finding was not supported by changes in the QST variables testing for small fiber function, i.e. temperature and heat pain sensation, which were left unchanged and with no difference between groups. Furthermore, we caution against the skin biopsy results as repeated evaluation of samples with outlier values performed *post hoc* and by the same staff that originally assessed the skin biopsies, revealed considerable inter- and intra-observer variation. This may, at least partially, underlie the findings of our study concerning IENFD. Another potential source of variation was a change in primary anti-PGP9.5-antibody during the study due to end of production – although comparison of IENFD analysed using the two antibodies showed no difference. Further, we did not measure IENFD in skin biopsies from the thigh, a site reported to be possibly affected in statin users (as a sign of non-length dependent involvement of peripheral nerves) in a cross-sectional study (26). Another potential weakness of our study was our choice of patients for the statin-exposed group (i.e. patients with cerebrovascular disease). Cardiovascular disease (CVD) risk factors, which have been associated with increased risk of idiopathic polyneuropathy in a single observational study (27), are highly prevalent in this patient group. We did not find convincing evidence of such an association in our univariate *post-hoc* analyses comparing CVD risk factors in patients taking statins versus asymptomatic statin users. While somewhat reassuring, these crude analyses do not rule out that the study design may have biased our results towards non-protective effects of statins on peripheral nerve function. We note that HbA1c levels were slightly higher in patients taking statins compared with non-statin users. Statin use has been associated with development of diabetes (28). As we did not measure HbA1c at follow-up, we cannot rule out that some patients taking statins experienced increases in their HbA1c to a degree that may have had a negative impact on their neurophysiological test results, e.g, as seen in diabetes. Confounding by indication is another issue of concern, as this particular CVD risk factor has been linked with risk of polyneuropathy. However, we find it reassuring that baseline cholesterol levels were similar in patients exposed to statins compared with non-users in our study. Also, in another study of the effects of statin use on peripheral nerve function, the comparison group comprised patients that suffered from hyperlipidaemia who were not treated with statins; yet these patients did not develop evidence of peripheral nerve damage over the 24-month follow-up period (12).

The sample size of our study can be criticized. Although adequate to address our primary outcome, it is insufficiently powered to robustly address the presented secondary and *post-hoc* analyses. Further, it is possible that one-year follow-up may be too short to demonstrate negative effects of statins on nerve function, although the results of previous studies involving repeated neurophysiological testing for up to 3 years do not seem to support this (12,13). We excluded patients with known risk factors for polyneuropathy from our study. While this reduced the generalizability of the study, it served the purpose of reducing potential confounding. However, due to the observational nature of our study, we cannot rule out that unmeasured or insufficiently adjusted confounders influenced our results. With these caveats in mind, we conclude that statin use was not clearly associated with increased risk of deterioration of peripheral nerve function analysed at a group level. We caution, however, that our results do not preclude that peripheral nerve function may be affected in some individuals exposed to statins.

Further research exploring the possible link between cardiovascular risk factors and peripheral neuropathy is warranted.

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Table 1. Baseline characteristics of study participants.

Characteristic	**Statin users (n=57)**	**Non-users (n=46)**	***P*-value[a]**
Male sex, n (%)[a]	31 (54)	18 (39)	0.1
Age, years, mean±SD[a,b]	61±9	54±11	0.001*
Height, cm, mean±SD[a,b]	171±9	174±10	0.2
Weight, kg, mean±SD[a,b]	82±13	82±15	1
Alcohol, units/week, mean±SD[a,b,c]	5.8±6.7	4.9±5.1	0.4
Smoking			
Current, n (%)[a]	12 (21)	8 (17)	
Past, n (%)[a]	23 (40)	9 (20)	0.034*
Never, n (%)[a]	22 (39)	29 (63)	
Baseline tests done within 7 days, n (%)[a]	56 (98)	46 (100)	1
Examination interval[d], days, mean (range)[a]	386 (342-454)	381 (306-469)	0.4
Examination interval[d]			
300-400 days, n (%)[a]	44 (77)	34 (74)	
>400 days, n (%)[a]	13 (23)	12 (26)	0.7
Cholesterol levels[e] – baseline, mean±SD[b], mmol/L			
Total cholesterol[a,f]	5.8±1	5.5±1.1	0.2
Low-density lipoprotein[a,f]	3.7±0.8	3.4±1	0.1
High-density lipoprotein[a,f]	1.4±0.3	1.4±0.4	0.4
Triglycerides[a,f]	1.7±1.1	1.6±0.8	0.5
HbA1c, mean±SD[b], mmol/mol[a,e]	37.8±3.3	35.8±2.9	0.018*

*statistically significant results (*P*-value <0.05)

[a]Chi2-test or Fisher's exact test for proportions and t-test for means.

[b]SD: standard deviation.

[c]Missing values for 2 non-users of statins.

[d]Days between testing at baseline and follow-up.

[e]Missing values for 1 non-user of statins.

[f]Corresponding mean values±SD for statin users at follow-up were total cholesterol 4.4±0.9, low-density lipoprotein 2.2±0.8, high-density lipoprotein 1.4±0.3, and triglycerides 1.7±1.

Table 2. Changes in primary outcome measures among statin users and non-users during follow-up.

	Statin user (n=57)			Non-user of statins (n=46)				
Test	**Baseline**	**1-year follow-up**	**Change**	**Baseline**	**1-year follow-up**	**Change**	***P*-value[a,b]**	**Coefficient[b] (95% CI)**
Nerve conduction study[c,d]								
Peroneal Nerve								
MCV, m/s	45.6±4.2	45.8±4	0.2±2.9	46.8±4.2	46.6±5.7	-0.2±5.6	1	0.5 (-1.2 to 2.2)
CMAP, mV	7.4±2.8	6.9±2.7	-0.5±1.8	7.2±2.8	6.6±2.8	-0.6±1.9	1	0.1 (-0.6 to 0.9)
Sural Nerve[e]								
SCV, m/s	51.3±6	53±5	1.8±5.5	51.3±4.6	52.7±4.9	1.4±4.3	0.7	0.3 (-1.6 to 2.3)
SNAP, µV	11.6±7.3	9.6±5.2	-2±5.3	11.1±4.9	10.7±4.9	-0.4±4.1	0.5	-1.6 (-3.5 to 0.3)
Tibial Nerve								

F-wave, ms	52.3±4.8	52.6±4.9	0.4±2.7	52.2±6.3	53.1±5.8	0.9±3.5	1	-0.6 (-1.8 to 0.7)
Skin biopsy[f,g]								
IENFD	6.8±3	7.8±3.1	1±3.7	8.2±4.3	6.2±2.8	-2±4.8	0.006*	3 (1.3 to 4.8)

Values are means plus minus standard deviation.

*statistically significant results (*P*-value <0.05).

Abbreviations: CI: confidence interval; CMAP: compound motor action potential amplitude; IENFD: intraepidermal nerve fiber density; MCV: motor conduction velocity; SNAP: sensory nerve action potential amplitude; SCV: sensory conduction velocity.

[a]*P* indicating statistical significance 0.05. Holm-Bonferroni correction is applied.

[b]Estimated through linear regression of Δdifference, i.e., difference in change from baseline to follow-up in statin users compared with non-users.

[c]Average of left and right extremity measures.

[d]Subject who did not want to undergo nerve conduction study (1 statin user and 0 non-users)

[e]Subject with missing variables for both right and left extremity at either baseline or follow up not included (0 statin users and 1 non-user).

[f]Done on distal leg (10 cm above lateral malleolus).

[g]Subjects where skin biopsies were not obtained or could not be analysed for technical reasons not included (statin users: 8; non-statin users: 2)

Table 3. Changes in secondary outcome measures among statin users and non-users during follow-up.

Test	Statin users (n=57)			Non users of statins (n=46)			*P*-value	Coefficient[b] (95% CI)
	Baseline[a]	1-year follow-up[a]	Change[a]	Baseline[a]	1-year follow-up[a]	Change[a]		
Quantitative sensory testing, mean±standard deviation								
Cold Detection Threshold	25.7±3	26.9±5.1	1.2±4.6	27.3±3.4	28±3.4	0.6±2.4	0.4	0.6 (-0.9 to 2.1)
Warm Detection Threshold	40.4±4	40.6±3.5	0.2±3.5	39±3.4	39.1±3.5	0.1±2.7	0.9	0.1 (-1.1 to 1.3)
Heat Pain Threshold	45.9±3.2	46.6±2.7	0.7±3	46.4±2.7	46.6±2.5	0.2±2.8	0.4	0.5 (-0.6 to 1.6)
Mechanical Detection Threshold	15.2±30.5	16.3±28.8	1±31	5.4±4.1	6.5±8.4	1.1±7.5	1	-0.1 (-9.4 to 9.2)
Mechanical Pain Threshold	43.7±59.8	51.5±77.1	7.8±62.5	41.8±31.4	35.1±31.3	-6.7±29.4	0.2	14.5 (-5.4 to 34.3)
Vibration Detection Threshold	5.4±1.8	5.6±1.8	0.2±1.2	6.1±1.7	6.1±1.7	0±0.9	0.3	0.2 (-0.2 to 0.7)
Biothesiometer[c]	14.7±8.8	16.1±10.1	1.4±5.7	11.7±8.2	11.4±8.3	-0.3±3.8	0.1	1.7 (-0.2 to 3.7)
Ratings of neuropathy symptoms & signs, median (range)								

Neurological Symptom Score[d]	0 (0 – 2)	0 (0 – 1)	0 (-1 – 1)	0 (0 – 0)	0 (0 – 0)	0 (0 – 0)	0.052[e]	0.1 (-0.001 to 0.2)
Neuropathy Impairment Score[f]	0 (0 – 6)	0 (0 – 6)	0 (-2 – 2)	0 (0 – 11)	0 (0 – 12)	0 (-5 – 1)	0.6	0.1 (-0.2 to 0.4)
Overall Disability Sum Score[g]	0 (0 – 0)	0 (0 – 0)	0 (0 – 0)	0 (0 – 0)	0 (0 – 0)	0 (0 – 0)	---	--- (---)
INCAT Sensory Sum Score[h,i]	0 (0 – 1)	0 (0 – 2)	0 (0 – 1)	0 (0 – 1)	0 (0 – 2)	0 (0 – 1)	0.3	0.1 (-0.04 to 0.1)
Total Neuropathy Score[j,k], median (range)								
Total score	0 (0 – 6)	0 (0 – 7)	0 (-4 – 3)	0 (0 – 5)	0 (0 – 7)	0 (-2 – 5)	0.7	-0.1 (-0.5 to 0.4)

Abbreviations: CI: confidence interval. INCAT: Inflammatory Neuropathy Cause and Treatment.

[a]Rounded to one decimal.

[b]Estimated through linear regression of Δdifference, i.e., difference in change from baseline to follow-up in statin users compared with non-users – unadjusted values.

[c]Subject with missing variables not included (1 non-user).

[d]Score range in rating instrument: 0 to 8 (women) or 0 to 9 (men).

[e]*Post-hoc* analyses using Fisher's exact test revealed; 5 symptomatic statin users out of 57 vs. 0 symptomatic non-users out of 46; *P-value* = 0.063.

[f]Score range in rating instrument: 0 to 32 (age>69); 0 to 42 (age50 to 69); 0 to 52 (age<50).

[g]Score range in rating instrument: 0 to 12.

[h]Score range in rating instrument: 0 to 20.

[i]Subject with missing variables not included (2 non-users).

[j]Subjects with missing information not included (1 statin user; 2 non-users).

[k]Reduced version. Score range in rating instrument: 0 to 28.

Table 4. *Post-hoc* analyses among statin users by emergence of neuropathic symptoms during follow-up.

Test	**Non-symptomatic (n=52)**	**Symptomatic (n=5)**	***P*-value[a,b]**	**Difference[c] (95% CI)**
Sural Nerve, SNAP, µV, change[a,d,e,f]	-2.1±5.5	-0.8±0.5	0.6	1.3 (-4.3 to 6.8)
Biothesiometer, change[a,f]	0.6±4.8	9.5±8.2	0.0006*	8.8 (4 to 13.7)
Characteristics				
Male sex, n (%)[a]	29 (56)	2 (40)	0.7	
Age, years, mean ±SD[a,g]	60±9	71±7	0.0149*	
Body mass index (weight/hight^2) , mean ±SD[a,g]	28.1±4.1	26.2±1.7	0.3	
Hypertension, n (%)[a]	18 (35)	4 (80)	0.067	
Cholesterol levels – mean±SD[g], mmol/L[a]				
Total cholesterol – baseline	5.9±1	5.2±0.7	0.1	
Total cholesterol – change[f]	-1.3±1.1	-1.7±0.6	0.5	
Low density lipo-protein – baseline	3.7±0.9	3.2±0.5	0.2	
Low density lipo-protein – change[f]	-1.4±1	-1.6±0.4	0.7	
High density lipo-protein – baseline	1.4±0.3	1.4±0.4	0.6	
High density lipo-protein – change[f]	0.1±0.3	-0.2±0.4	0.0416*	

Triglycerides – baseline	1.7±1.1	1.3±0.5	0.4
Triglycerides – change[f]	0±1	0.1±0.6	0.8
HbA1c, mean ±SD[g], mmol/mol[a]	37.7±3.3	39.0±3.9	0.4
Diagnosis[a]			
Cerebral infarction, n (%)	31 (60)	3 (60)	
Transient ischemic attack, n (%)	19 (37)	1 (20)	0.4
Other[h], n (%)	2 (4)	1 (20)	

*statistically significant results (*P*-value <0.05).

Abbreviations: CI: confidence interval; SNAP: sensory nerve action potential amplitude.

[a]Fisher's exact test for proportions and t-test for means.

[b]*P* indicating statistical significance 0.05. Unadjusted values.

[c]Estimated through t-test of Δdifference, i.e., difference in changes in statin-users with neuropathic symptoms compared with statin-users without these symptoms.

[d]Average of left and right extremity measures.

[e]One symptomatic participant who did not want to undergo nerve conduction study not included.

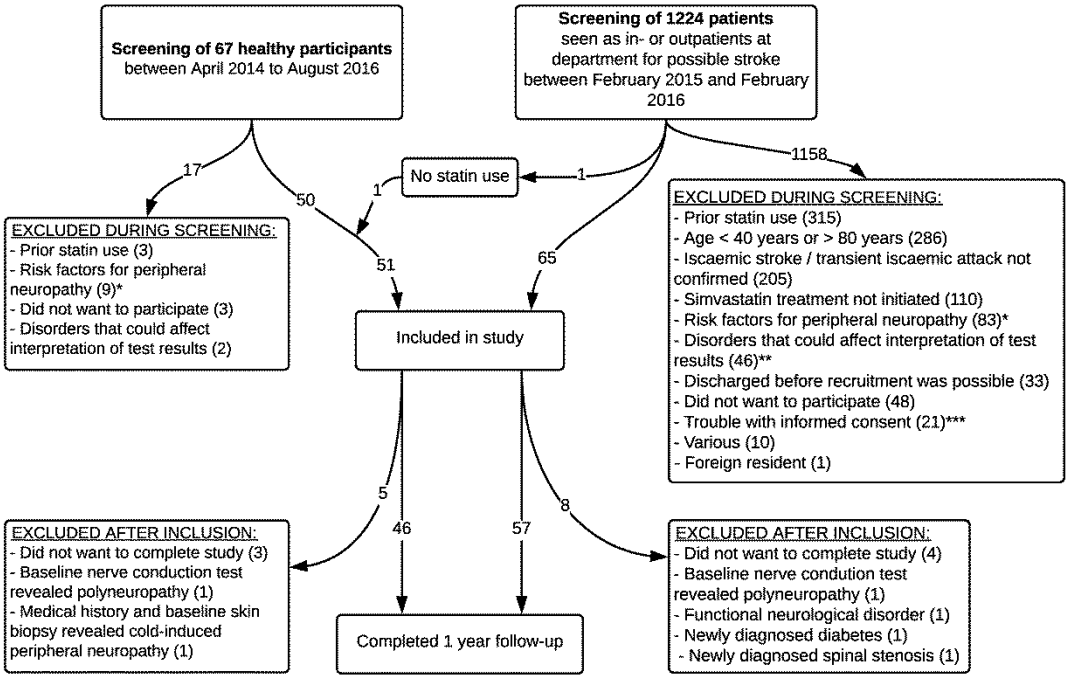
[f]"Change" = follow-up values minus baseline values.

[g]SD: standard deviation

[h]One non-symptomatic patient had central retinal artery occlusion. Two patients had infarction sequela(e) (one symptomatic, one non-symptomatic).

LEGENDS

Figure 1. Flowchart of participant selection process



* Alcohol abuse, diabetes, cancer, hypothyroidism, connective tissue disease, renal insufficiency, monoclonal gammopathy of unknown significance, neurotoxic medication (eg, chemotherapy) .

** Previous known or suspected polyneuropathy, or other disorders (eg. multiple sclerosis, spinal stenosis) with neuropathy-like symptoms or signs.

*** Neuropsycological sequlae including aphasia, mentally disabled, non-Danish-speakers, severe psychiatric disease.