Statin usage, vascular diagnosis, and vascular risk factors in Parkinson's disease.

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Abstract

Background and Aims:

Vascular disease is a common comorbidity in Parkinson's disease (PD) patients. Statins are potentially neuroprotective for PD through non-vascular mechanisms. We investigated prevailing statin use in a PD cohort.

Methods and Results:

Data on diagnostic indication for statins, antiparkinson therapy, vascular risk factors, and statin prescription, were obtained from electronic medical record review for consecutive PD patients. The ASSIGN (ASsessing cardiac risk using Scottish Intercollegiate Guidelines Network) system was used to calculate future cardiovascular risk, and identify those warranting statin use. Of 441 patients included, 59.9% were male, with a mean age of 68.9 years (SD 10.3). 174 patients (39.5%) had at least one diagnostic indication for statin use, of whom 136 (78.2%) were prescribed a statin. In the 267 cases (60.5%) without a diagnostic indication, 54 (20.2%) were excluded owing to age-limitations defined in ASSIGN. Of the remaining 213, 62 (29.1%) had an ASSIGN score in the recommended range for statin therapy, of whom 15 (24.1%) were prescribed statins.

Conclusion:

There is suboptimal implementation of statin therapy in PD patients. Given the possible neuroprotective effects of statins in PD in addition to reducing

cardiovascular risk, reasons for suboptimal implementation warrant further investigation.

(196/200 words)

Keywords:

Parkinson’s disease, statin, cardiovascular disease, cardiovascular risk, neuroprotection.

Background

Parkinson's disease (PD) and cerebrovascular disease (CVD) both increase significantly with age and have overlapping symptomatology, in particular for cognition and gait impairment. PD patients with vascular risk factors, or brain imaging features of subclinical CVD, have greater gait impairment and worse motor symptoms, which has implications for prognosis and treatment [1-4].

Statins are proven to reduce the risk of vascular events when used as secondary preventive treatment (eg. after ischaemic stroke or myocardial infarction) or in the presence of a high future vascular risk as primary prevention [5, 6]. The known adverse effects of CVD on cognition and gait are likely to contribute to morbidity in PD, and might be diminished by optimising the implementation of statins and other vascular preventive treatment approaches.

Cholesterol is also implicated in neurodegenerative diseases including PD, being associated with several neuropathological processes [7, 8]. The potential of statins as neuroprotective for PD is increasingly recognised, and a UK-based study (PD-STAT) is underway; this randomises PD patients to high-dose statin or placebo, when statin therapy is not indicated by increased vascular risk [9].

In view of the possible advantages of statin use in PD patients as described above, we sought to establish statin usage rates in a clinic-based cohort of

PD patients, to define rates of vascular comorbidity and risks, and assess the implementation of cholesterol-lowering therapy according to Scottish guidelines.

Methods

Drug-treated PD patients, aged over 18 years, diagnosed clinically but with diagnoses supported by structural and dopaminergic functional neuroimaging performed on clinical grounds were included. This was a convenience sample of all consecutive cases attending the regional movement disorder clinic between February 2008 and March 2015. Patient demographics and characteristics, laboratory results and list of medications were obtained from electronic medical records. The study was approved by the clinical governance office of the local Health Board.

Standard diagnostic indications for statin use (cardiovascular, cerebrovascular, chronic kidney disease, diabetes and peripheral vascular disease [PVD]) were identified from coding and clinical records. For cases without a diagnostic indication for statin therapy, the 10-year cardiovascular risk was calculated using the ASsessing cardiac risk using Scottish Intercollegiate Guidelines Network (ASSIGN) scoring system, version 1.5.1[10]. Where information on smoking, systolic blood pressure, total and HDL cholesterol was unavailable, mean values based on age and sex for each parameter, and calculated by the ASSIGN scoring system, were imputed. 169 (79.3%) patients had data on their systolic blood pressure, 151 (70.9%) on total cholesterol, 142 (66.7%) on HDL cholesterol, 169 (79.3%) on smoking habits and 199 (93.4%) on estimated glomerular filtration rate. ASSIGN is applicable to patients aged 30 to 74 years who do not have diagnostic indication for statins [11]. A cut-off for ASSIGN of 20% or more as a vascular risk score warranting statin therapy

was used, based on current recommendations [11], and in addition, an exploratory calculation was based on an ASSIGN score of 10% or more, given recent downward adjustment of the recommendation level from 20% to 10% for the similar QRISK vascular risk calculator, in England and Wales [12]. Diabetes is not considered a risk factor in the current study as it is already considered as an indication for statin use by ASSIGN. The L-dopa equivalent daily doses (LEDD) were calculated using standard formulae [13].

Statistics

Chi-square tests were used for categorical data (and for trend when appropriate), 2 sample t-tests and ANOVA for parametric data and Mann-Whitney U and Kruskal-Wallis test for non-parametric data. Correction for confounding variables was performed with bivariate and partial correlations. SPSS 22 (SPSS Inc., Chicago, IL, USA) was used. Statistical significance was set at $P<0.05$.

Results

Out of 441 patients with PD and prescribed antiparkinson therapy, 174 (39.5%) had one or more diagnostic indication for statin therapy, and 54 patients (12.2%) were aged over 74 years, leaving 213 patients (48.2%) for ASSIGN vascular risk calculation. The majority of patients were male (59.9%) with a mean age of 68.9 years (SD 10.3). The most common vascular risk factor was hypertension (32.9%). Levodopa-based therapy was used by the majority of patients (94.6%). 43.8% of PD patients were prescribed statins, most commonly simvastatin.

Vascular risk factors and medication use were assessed according to diagnostic indication for statin use (Table 1). Patients with a diagnostic indication for statin use were significantly older by approximately 7 years ($p<0.0005$). A significantly higher proportion of patients with a diagnostic indication for statins had smoked tobacco, had hypertension, were prescribed statin and antiplatelet therapy, even after age adjustment compared to patients without any diagnostic indication for statin use (Table 1). Patients with a diagnostic indication for statin use were significantly less likely to be prescribed mono-amine oxidase type B inhibitors (5.2% vs. 15.4%, $p=0.001$) (Table 1).

Of patients with a diagnostic indication for statin use, 69.0% had a single indication (Table 2). Considering the indication, 80.0% of patients with cardiac disease, 76.5% with diabetes and 71.9% with CVD were prescribed statins. Neither of 2 patients with PVD as their only diagnostic indication was prescribed a statin.

Figure 1 shows the breakdown of PD patients who were prescribed antiparkinson therapy. 174 patients had a diagnostic indication for statin use, the most common being cardiac disease. Of these patients, 78% patients were prescribed statins. Of the 213 patients eligible for ASSIGN calculation, 10% patients with low risk (ASSIGN ≤ 10), 19% with moderate risk (ASSIGN 11-19) and 24% with high risk (ASSIGN ≥ 20) were prescribed statins.

Discussion

This is the first paper reporting the use of statins in PD patients in Scotland. We report that a high proportion of patients with a diagnostic indication received statin therapy, but that the proportion of patients with a high future cardiovascular risk being treated with statins was considerably lower.

Our results are consistent with other studies performed in a more general population; namely higher rates of statin use in those with a diagnostic indication than in those with a risk status indication. A UK survey showed that 93% of patients with coronary disease and 61% of high-risk individuals (by a definition including elevated cholesterol) were treated with statins [14]. European studies have reported that 81% of coronary patients and 47% of patients with elevated total cholesterol were treated with statins [15, 16]. Although one study from Italy found the same rate of 61% for statin use for both patients with established CVD and patients with high future risk of CVD, the latter category was defined by the presence of hyperlipidemia rather than using a risk calculator, which may explain the higher statin use[17]. Some of the differences observed between studies can be explained by patient demographics and variable methods of defining risk, through risk calculators in some studies or according to the prescription of anti-hypertensive, anti-diabetic or lipid-lowering drugs in other studies. Our patient cohort was approximately 8 years older than those in the studies described above [13-16] and fewer were current cigarette smokers, which is expected given the known greater prevalence of PD in non-smokers [18-21]. Our study findings are also

similar to those from a UK PD cohort, which showed underutilisation of statins (75.3% in patients with CVD, 37.2% in patients with high vascular risk and 15.1% in patients with medium vascular risk) in PD patients where risk was assessed using QRISK2 [3]. Our cohort had fewer patients with high vascular risk who were treated with statins compared with the UK study. There are however, differences in the ASSIGN guidelines used in Scotland compared to QRISK2 guidelines used in the rest of UK, so direct comparison of these findings is not straightforward.

Reasons for sub-optimal statin implementation, particularly in the 'at risk' group, deserve further consideration. Patient choice (to take statin therapy or not), therapy persistence (maintenance of treatment once initiated) and awareness and perception of guidelines are all potential factors [22, 23]. A more PD-specific reason for suboptimal implementation of statins is the well-known potential side-effect of muscle pain or cramp, which is a very common symptom from PD, and may be difficult to distinguish from a statin effect. Given that myalgia occurs in only about 10% of those taking statins [24], it is possible that over-attribution of muscle pain to statins occurs in PD patients, and we plan to examine this in a more detailed multicentre study.

In conclusion, a significant proportion of PD patients, particularly those with a high CVD risk that may benefit from statin therapy, are not prescribed such treatment. Given the potential neuroprotective benefits from statins in PD in addition to established reductions in cardiovascular risk, the reasons for this

under-utilisation merit further study, which could be achieved in an observational design.

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Table 1: Demographics, vascular risks, and antiparkinson drug use in 441 Parkinson's disease patients.

Characteristic	Diagnostic indication for statin				All patients
	Yes	No	p-value	Adjusted p-value[a]	
Number of patients	174 (39.5%)	267 (60.5%)			441
Male sex	59.8%	59.9%	1.000	0.124	59.9%
Age, Mean (SD)	73.2 (9.1)	66.0 (10.0)	<0.0005		68.9 (10.3)
Smoking status					
Ever smokers	40.8%	27.0%	0.014	0.008	32.4%
Current smokers	8.6%	9.4%	0.791	0.294	9.1%
Risk Factors					
Hypertension	49.4%	22.1%	<0.0005	<0.0005	32.9%
Atrial fibrillation	8.6%	3.0%	0.009	0.235	5.2%
Heart failure	1.7%	0.4%	0.305	0.504	0.9%
Rheumatoid arthritis	1.1%	0.7%	0.665	0.894	0.9%
Antiparkinson drug type					
Levodopa + DDI	97.7%	92.5%	0.019	0.168	94.6%

Dopamine agonists	27.6%	41.6%	0.003	0.523	36.1%
COMT inhibitors	14.9%	22.1%	0.063	0.124	19.3%
MAOB inhibitors	5.2%	15.4%	0.001	0.024	11.3%
Amantadine	4.0%	6.4%	0.289	0.751	5.4%
Anticholinergics	2.3%	0.7%	0.170	0.126	1.4%
LEDD, median (IQR)	400 (200-600)	450 (260-700)	0.076	0.340	400 (250-665)
Medication					
Statin therapy	78.2%	21.3%	<0.0005	<0.0005	43.8%
Simvastatin	48.9%	16.5%			29.3%
Atorvastatin	23.0%	4.1%			11.6%
Rosuvastatin	3.4%	0.4%			1.6%
Pravastatin	2.3%	0.4%			1.1%
Fluvastatin	0.6%	0%			0.2%
Non-statin therapy	2.9%	0.7%	0.081	0.069	1.6%
Antiplatelets	71.8%	16.1%	<0.0005	<0.0005	38.1%
Anticoagulants	12.1%	4.5%	0.003	0.137	7.5%

[a]adjusted for age

SD = standard deviation, DDI = dopa decarboxylase inhibitor, IQR = interquartile range, COMT = catechol-O-methyl transferase, MAOB = monoamine oxidase type B, LEDD = levodopa equivalent daily dose. Non-statin includes ezetimibe and fibrates.

Table 2: Demographics and medication use in 174 patients with Parkinson's disease, who had one or more diagnostic indication for statin use.

Characteristic	1 indication (N=120, 69.0%)	2 or more indications (N=54, 31.0%)	p-value
Age, mean (SD)	72.9 (9.3)	73.9 (8.6)	0.682
Male sex	58.3%	63.0%	0.620
Smoking status			
Ever smokers	41.2%	55.8%	0.122
Current smokers	10.8%	3.7%	0.208
Antiparkinson drug classes			0.719
1	61.7%	61.1%	
2	29.2%	25.9%	
≥ 3	9.2%	13.0%	
LEDD, median (IQR)	300 (200-600)	410 (300-798)	0.047
Statin use	74.2%	87.0%	0.089

SD = standard deviation, LEDD = levodopa equivalent daily dose, IQR = interquartile range

Figure 1: Flow chart for 441 patients with Parkinson's disease and prescribed antiparkinson therapy. Patients with a diagnostic indication for statin therapy were identified, and the cardiovascular risk score was assessed in remaining patients. The proportions in each category who were prescribed statins were calculated. PD = Parkinson's disease, PVD = peripheral vascular disease, CKD = chronic kidney disease, ASSIGN = ASsessing cardiac risk using Scottish Intercollegiate Guidelines Network