

Supplement

Statin intensity after ischemic stroke

Stroke Vasc Neurol 2024

**Supplement****Supplemental Methods**Outcome definitions:

- All-cause death: Death by any cause. Follow-up available up to December 31<sup>st</sup> 2020.
- Recurrent ischemic stroke: ICD-10 code I63\* as primary diagnosis in new hospital admission or as any cause of death. Follow-up available up to December 31<sup>st</sup> 2018.
- Cardiovascular death: Death with ICD-10 code I\* as the underlying cause of death.
- Intracerebral hemorrhage: ICD-10 code I61\* as primary diagnosis in new hospital admission or as any cause of death. Follow-up available up to December 31<sup>st</sup> 2018.

Data sources:

The following mandated-by-law nationwide registry data were collected and combined from all study patients:

- All hospital admissions, all outpatient visits in specialist medical care, and all emergency room admissions (International Classification of Diagnosis / ICD-10) and operational codes (Nordic Classification of Surgical Procedures) collected from the CRHC registry. Received from the National Institute for Health and Welfare of Finland. Available from Jan 1<sup>st</sup> 2004.
- Prescription medication purchases including Anatomical Therapeutic Chemical (ATC)-codes and purchase dates. Available from Jan 1<sup>st</sup> 2004.
- Cancer data from the Finnish Cancer Registry. Available from Jan 1<sup>st</sup> 1980.
- Entitlements to special reimbursements for prescription medication expenses including entitlement codes and underlying ICD diagnoses. Available from Jan 1<sup>st</sup> 1964.
- Mortality data including date and causes of death. Received from the Statistics Finland. Available from Jan 1<sup>st</sup> 2005.

Co-morbidities were detected from the data of index IS admission and data available prior to event.

Recanalization and neurosurgical operations were detected from the data of index IS admission.

Adherence to statin therapy

Usage of statin therapy during the 12-year follow-up after index IS was studied by yearly intervals with data available up to December 31<sup>st</sup> 2020. Statin usage was defined as at least two statin purchases during the time-period (365 days). Intensity of used statin was determined from the first statin purchase of each follow-up year. Patients with less than two statin purchases who's follow-up lasted at least 6 months in the examined year were determined be nonadherent.

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	Intensity			ATC codes
	High	Moderate	Low	
<b>Atorvastatin</b>	40-80 mg	10-20 mg	-	C10AA05, C10BA05, C10BX03, C10BX08, C10BX11, C10BX12, C10BX15
<b>Fluvastatin</b>	-	80 mg	20-40 mg	C10AA04
<b>Lovastatin</b>	-	40 mg	20 mg	C10AA02, C10BA01
<b>Pitavastatin*</b>				C10AA08
<b>Pravastatin</b>	-	40-80 mg	10-20 mg	C10AA03, C10BA03, C10BX02
<b>Cerivastatin*</b>				C10AA06
<b>Simvastatin</b>	80 mg	20-60 mg	10 mg	C10AA01, C10BA02, C10BA04, C10BX01, C10BX04
<b>Rosuvastatin</b>	20-40 mg	10 mg	-	C10AA07, C10BA06, C10BX05, C10BX07, C10BX09, C10BX10, C10BX13, C10BX14

\* Not used by study patients

**Supplemental Table 1.** Classification of statin intensity and Anatomical Therapeutic Classification (ATC) codes used for detection of statins.

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Variable	Intensity of statin therapy			P-value Between groups
	High N = 7,284	Moderate N = 33,588	Low N = 4,640	
Age, years (SD)	68.4 (10.7)	70.2 (11.5)	73.3 (11.1)	<0.0001
Men	62.2%	55.1%	48.6%	<0.0001
<b>Co-morbidities</b>				
Alcohol abuse	4.6%	3.9%	2.5%	<0.0001
Anemia	2.7%	2.7%	3.1%	0.280
Atrial fibrillation	20.7%	21.6%	24.9%	<0.0001
Chronic pulmonary disease	13.6%	13.5%	14.2%	0.448
Coagulopathy	0.7%	0.5%	0.3%	0.005
Dementia	2.6%	4.3%	6.3%	<0.0001
Depression	11.5%	11.0%	11.3%	0.397
Diabetes	27.2%	22.5%	23.0%	<0.0001
Insulin dependent	8.2%	6.0%	6.5%	<0.0001
Non-insulin dependent	19.0%	16.5%	16.5%	<0.0001
Drug abuse	0.3%	0.4%	0.2%	0.351
Heart failure	11.9%	11.5%	13.2%	0.002
Heart valve disease	5.5%	4.8%	4.8%	0.067
Hypertension	65.7%	60.3%	61.5%	<0.0001
Liver disease	1.1%	1.0%	0.7%	0.047
Malignancy	13.1%	12.7%	12.8%	0.682
Myocardial infarction	14.2%	9.1%	7.8%	<0.0001
Peripheral vascular disease	9.7%	5.8%	5.5%	<0.0001
Prior cerebrovascular disease	24.8%	21.8%	24.0%	<0.0001
Psychotic disorder	3.1%	3.4%	3.8%	0.065
Rheumatic disease	5.2%	5.4%	5.8%	0.454
Renal failure	2.8%	1.9%	2.1%	<0.0001
Recanalization	13.8%	7.7%	5.9%	<0.0001
Thrombolysis	11.9%	7.2%	5.6%	<0.0001
Thrombectomy	3.7%	1.0%	0.5%	<0.0001
Neurosurgery	0.1%	0.1%	0.2%	0.254
<b>Medication after IS*</b>				
ACEi/ARB	70.0%	63.1%	58.8%	<0.0001

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<b>ADP-inhibitor</b>	38.5%	25.1%	16.8%	<0.0001
<b>Any antihypertensive</b>	87.3%	83.3%	83.4%	<0.0001
<b>Dipyridamole</b>	25.8%	34.7%	36.2%	<0.0001
<b>Ezetimibe</b>	3.4%	1.5%	1.2%	<0.0001
<b>Oral anticoagulant</b>	28.5%	27.8%	29.8%	0.016
<b>Treatment in university hospital</b>	64.2%	44.7%	46.4%	<0.0001

**Supplemental Table 2.** Baseline features of study patients by intensity of statin therapy after ischemic stroke. ACEi = angiotensin-converting-enzyme inhibitor, ADP = adenosine diphosphate, ARB = angiotensin receptor blocker, IS = ischemic stroke. \*None of the patients used PCSK9 inhibitor.

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Patient Subgroup	Intensity of statin therapy					
	High vs. Moderate		Moderate vs. Low		High vs. Low	
	adj.HR (95% CI)	P-value	adj.HR (95% CI)	P-value	adj.HR (95% CI)	P-value
<b>Age (years)</b>						
<80	0.91 (0.86-0.97)	0.004	0.93 (0.88-0.99)	0.023	0.85 (0.78-0.92)	0.0001
≥80	0.90 (0.82-1.00)	0.050	0.90 (0.84-0.96)	0.002	0.81 (0.73-0.91)	0.0004
<b>Sex</b>						
Men	0.91 (0.85-0.97)	0.004	0.90 (0.84-0.95)	0.0006	0.81 (0.75-0.89)	<0.0001
Women	0.94 (0.86-1.02)	0.148	0.91 (0.86-0.97)	0.005	0.86 (0.77-0.95)	0.003
<b>Atrial fibrillation</b>						
Yes	0.88 (0.80-0.98)	0.015	0.90 (0.83-0.97)	0.009	0.79 (0.70-0.89)	0.0002
No	0.93 (0.87-0.99)	0.025	0.91 (0.86-0.96)	0.001	0.85 (0.78-0.92)	<0.0001
<b>Diabetes</b>						
Yes	0.87 (0.80-0.95)	0.003	0.94 (0.86-1.03)	0.172	0.82 (0.73-0.92)	0.001
No	0.94 (0.88-1.00)	0.060	0.89 (0.85-0.94)	<0.0001	0.84 (0.77-0.90)	<0.0001
<b>Antithrombotic medication</b>						
Yes	0.91 (0.85-0.98)	0.012	0.89 (0.84-0.95)	0.001	0.82 (0.74-0.89)	<0.0001
No	0.89 (0.82-0.97)	0.005	0.91 (0.85-0.97)	0.002	0.81 (0.74-0.89)	<0.0001
<b>Oral anticoagulation</b>						
Yes	0.90 (0.82-0.99)	0.034	0.90 (0.83-0.97)	0.007	0.81 (0.72-0.91)	0.0003
No	0.92 (0.87-0.99)	0.017	0.91 (0.87-0.96)	0.001	0.84 (0.78-0.91)	<0.0001
<b>Prior statin use</b>						
Yes	0.86 (0.79-0.94)	0.001	0.88 (0.82-0.94)	0.0004	0.76 (0.68-0.84)	<0.0001
No	0.96 (0.89-1.02)	0.203	0.92 (0.87-0.98)	0.007	0.88 (0.81-0.96)	0.004

\* After MI.

**Supplemental Table 3.** Association of all-cause mortality with intensity of statin therapy after ischemic stroke in subgroups during 12-year follow-up. Multivariable adjusted analyses. Models are adjusted for age, sex, comorbidities (listed in Supplemental Table 2), recanalization, neurosurgery, other pharmacotherapies after IS (listed in Supplemental Table 2), and treatment in university hospital.

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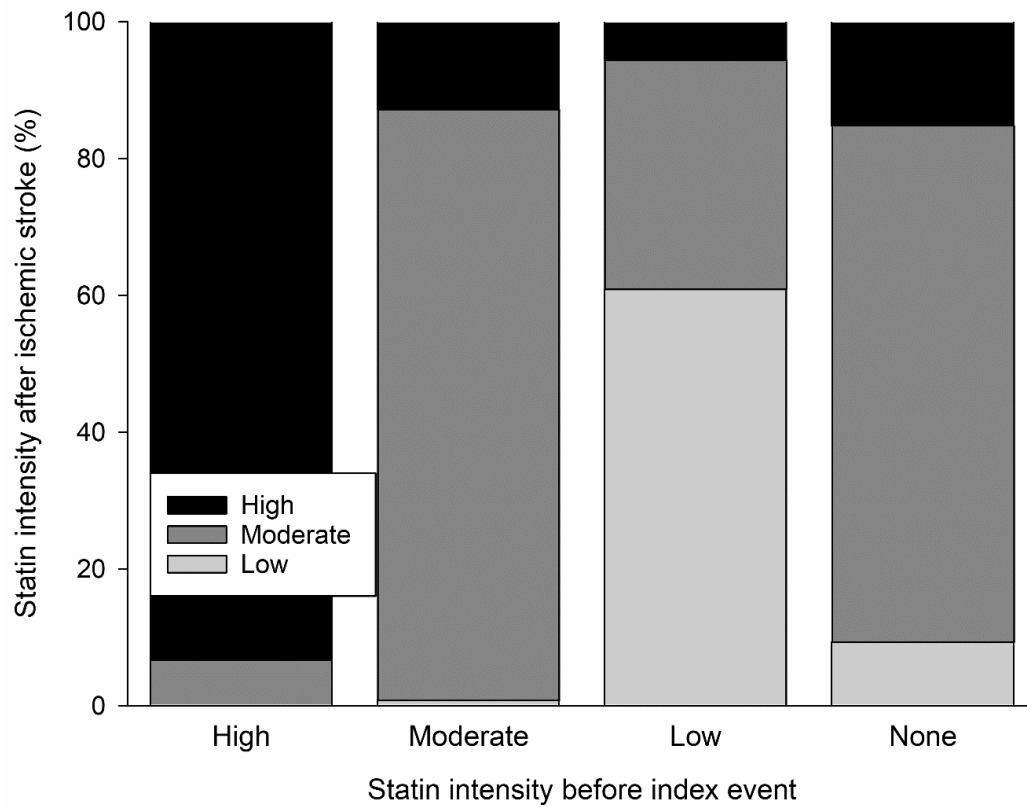
Patient Subgroup	Intensity of statin therapy					
	High vs. Moderate		Moderate vs. Low		High vs. Low	
	adj.sHR (95% CI)	P-value	adj.sHR (95% CI)	P-value	adj.sHR (95% CI)	P-value
<b>Age (years)</b>						
<80	0.90 (0.70-1.15)	0.403	0.98 (0.78-1.23)	0.855	0.88 (0.64-1.21)	0.430
≥80	0.95 (0.57-1.58)	0.843	1.13 (0.77-1.65)	0.527	1.07 (0.59-1.96)	0.819
<b>Sex</b>						
Men	0.94 (0.71-1.25)	0.688	1.04 (0.78-1.37)	0.797	0.98 (0.67-1.42)	0.910
Women	0.85 (0.59-1.23)	0.385	1.02 (0.77-1.35)	0.887	0.87 (0.56-1.34)	0.520
<b>Atrial fibrillation</b>						
Yes	0.95 (0.71-1.25)	0.681	1.09 (0.80-1.31)	0.423	1.10 (0.59-2.05)	0.759
No	1.07 (0.78-1.30)	0.957	0.89 (0.72-1.11)	0.300	0.90 (0.65-1.23)	0.498
<b>Diabetes</b>						
Yes	0.97 (0.64-1.47)	0.874	0.81 (0.55-1.19)	0.275	0.78 (0.46-1.33)	0.359
No	0.88 (0.68-1.15)	0.357	1.10 (0.87-1.38)	0.415	0.97 (0.70-1.35)	0.862
<b>Antithrombotic medication</b>						
Yes	0.97 (0.71-1.31)	0.829	0.87 (0.66-1.13)	0.296	0.84 (0.57-1.23)	0.364
No	0.84 (0.61-1.17)	0.303	1.19 (0.89-1.59)	0.247	1.00 (0.66-1.51)	0.995
<b>Oral anticoagulation</b>						
Yes	0.90 (0.62-1.32)	0.585	1.29 (0.88-1.72)	0.189	1.16 (0.70-1.91)	0.562
No	0.91 (0.69-1.20)	0.489	0.93 (0.74-1.17)	0.529	0.84 (0.60-1.18)	0.322
<b>Prior statin use</b>						
Yes	0.82 (0.57-1.17)	0.274	1.09 (0.78-1.52)	0.626	0.89 (0.56-1.41)	0.621
No	0.96 (0.72-1.27)	0.755	0.98 (0.77-1.26)	0.902	0.94 (0.66-1.34)	0.736

**Supplemental Table 4.** Association of intracerebral hemorrhage with intensity of statin therapy after ischemic stroke in subgroups during 12-year follow-up. Multivariable adjusted competing risk analyses. Models are adjusted for age, sex, comorbidities (listed in Supplemental Table 2), recanalization, neurosurgery, other pharmacotherapies after IS (listed in Supplemental Table 2), and treatment in university hospital.

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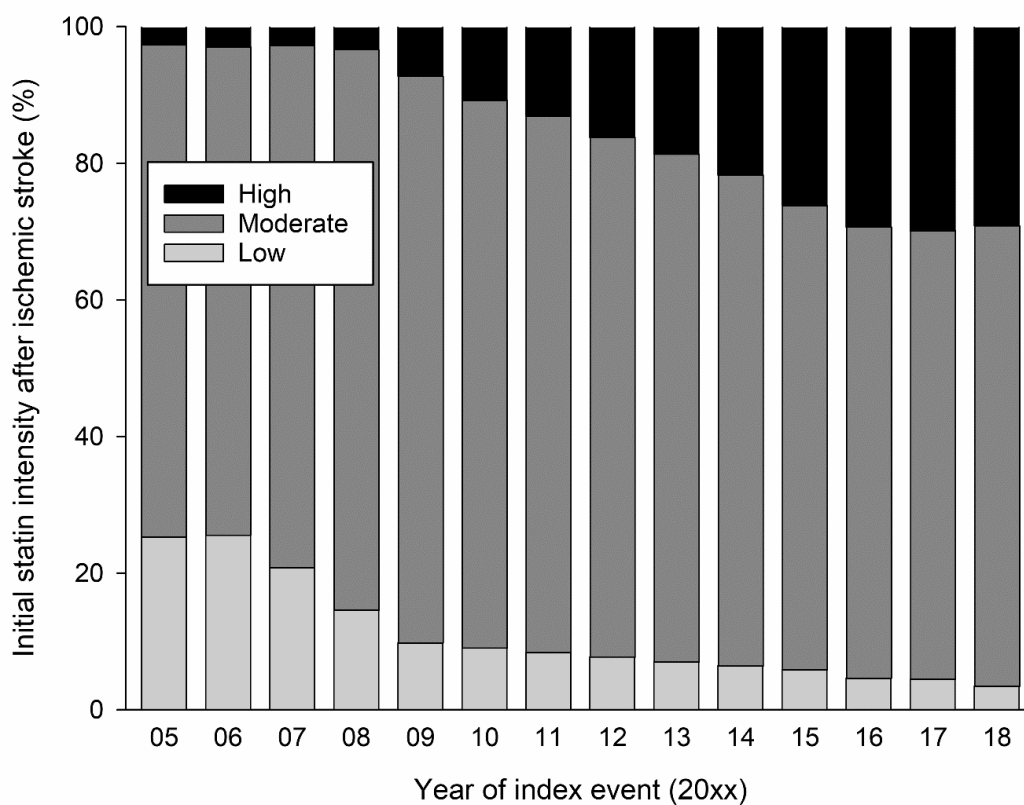


**Supplemental Figure 1.** Association of statin intensity before and early after ischemic stroke.

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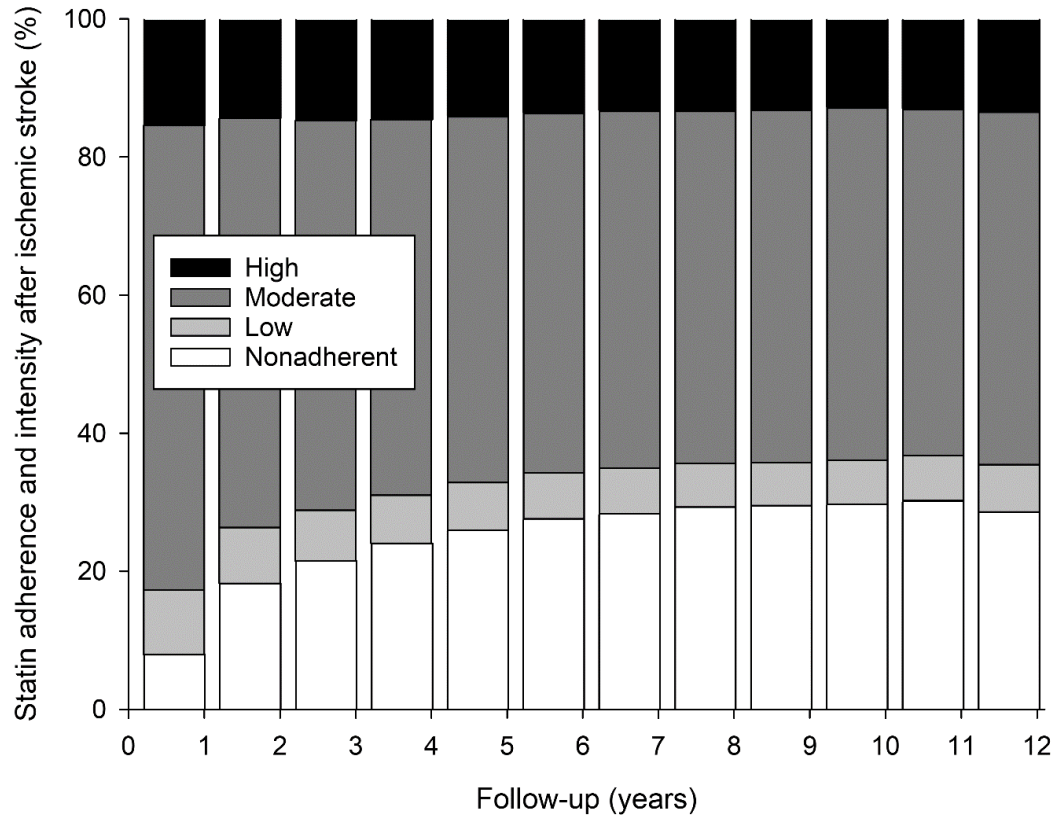
**Supplemental Figure 2.** Trends for the intensity of the first statin used after ischemic stroke during the study period.



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**Supplemental Figure 3.** Adherence to statins and intensity of used statin after ischemic stroke.