SVN Stroke & Vascular Neurology

Intensity of statin therapy after ischaemic stroke and long-term outcomes: a nationwide cohort study

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To cite: Kytö V, Åivo J, Ruuskanen JO. Intensity of statin therapy after ischaemic stroke and long-term outcomes: a nationwide cohort study. *Stroke & Vascular Neurology* 2024;**0**. doi:10.1136/svn-2024-003230

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/svn-2024-003230).

European Stroke Organisation Conference 16 May 2024

Received 5 March 2024
Accepted 4 June 2024

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ABSTRACT

Background Statins are essential for secondary prevention after ischaemic stroke (IS). However, statin intensity recommendations differ, and there is a concern about intracerebral haemorrhage (ICH). We studied the long-term impacts of initial statin intensity following IS.

Methods Consecutive patients using high-intensity, moderate-intensity or low-intensity statin early after IS (n=45 512) were retrospectively studied using national registries in Finland. Differences were adjusted using multivariable regression. The primary outcome was all-cause death within 12-year follow-up (median 5.9 years). Secondary outcomes were recurrent IS, cardiovascular death and ICH studied using competing risk analyses.

Results High-intensity therapy was initially used by 16.0%, moderate-intensity by 73.8% and low-intensity by 10.2%. Risk of death was lower with high-intensity versus moderate-intensity (adjusted HR (adj.HR) 0.92; 95% CI 0.87 to 0.97; number needed to treat (NNT) 32.0), with moderate-intensity versus low-intensity (adj.HR 0.91; 95% CI 0.87 to 0.95; NNT 27.5) and with high-intensity versus low-intensity (adj.HR 0.83; 95% CI 0.78 to 0.89; NNT 14.6) statin. There was a dose-dependent association of initial statin intensity with a lower probability of recurrent IS (p<0.0001) and cardiovascular death (p<0.0001). The occurrence of ICH was not associated with initial statin intensity (p=0.646).

Conclusions Following IS, more intense initial statin treatment is associated with improved long-term outcomes but not with the risk of ICH. These findings emphasise the importance of high statin intensity shortly after IS.

INTRODUCTION

Lowering of low-density lipoprotein (LDL) cholesterol improves outcomes after ischaemic stroke (IS).[1] Statins (HMG-CoA reductase inhibitors) are currently the mainstay and first-line LDL-lowering therapy, despite the emergence of PCSK9 inhibitors and other highly effective treatments.[2] However, results on statin intensity in secondary stroke prevention trials[1 3] and in real-life studies are equivocal.[4 5] This is reflected in guidelines that differ in treatment intensities and target groups of statin therapy.[2 6 7] First randomised controlled trials evaluating statins after IS suggested an increase in risk for intracerebral haemorrhage (ICH) but later meta-analyses showed conflicting results.[8 9] Furthermore, large observational studies have shown neutral[10] or beneficial[11] effect of statins regarding the risk of ICH after stroke.[12] The risk of ICH might, however, depend on the statin intensity.[13] Statin intensity is largely determined early after an ischaemic event.[14] We investigated the real-life impact of initial statin intensity on long-term outcomes after IS.

METHODS

Study population

Consecutive adult patients with IS (International Classification of Diseases 10th revision primary diagnosis code I63) in Finland between 1 January 2005 to 30 June 2018 purchasing statins within 90 days following hospital discharge were retrospectively studied.[10] All hospitals treating patients with acute IS in mainland Finland were included in the study (20 hospitals, of which 5 university hospitals with neurosurgical facilities).[10] Patients were designated into study groups by the intensity of the first statin purchase after the index event.

Outcomes and definitions

Statin intensity was categorised as low, moderate or high based on statin type and dose[14] (online supplemental table 1). The primary outcome was all-cause death, and secondary outcomes were recurrent IS, cardiovascular death and ICH (online supplemental methods). Medications, treatments and comorbidities were identified as previously described.[10] Statins and other studied medications used out of hospital can be obtained in Finland only with a prescription, and are dispensed for a maximum usage of 3 months. All purchases are recorded in the database used in the study.[14] Adherence to any statin therapy and statin intensity during follow-up was studied at yearly intervals (online supplemental methods).[14] Patients with less than two statin purchases and follow-up of at least 6 months in the examined year were determined non-adherent.

Data sources and permissions

Individual-level data on hospital admissions, major operations, malignancies, prescription medication purchases, medication reimbursements and mortality of the included patients were combined[10] (online supplemental methods). The data were obtained from Statistics Finland (permission TK-53-484-20) and Findata (permission THL/164/14.02.00/2021), covering the whole Finnish population. Follow-up on primary outcome ended on 31 December 2020 and was complete for all study patients with a median of 5.9 (IQR 3.5–9.2; max 12.0) years. No patients were contacted. The legal basis for processing personal data was public interest and scientific research (EU General Data Protection Regulation 2016/679 (GDPR), Article 6 (1) (e) and Article 9 (2) (j); Data Protection Act, Sections 4 and 6).

Statistical analysis

Study group differences were analysed with χ^2 tests and one-way analysis of variance. The Cochran-Armitage test was used to study trends. The primary outcome was studied using the Kaplan-Meier method and Cox regression. Cumulative incidence function was used to study secondary outcomes with Fine-Gray regression notifying competing risk due to non-endpoint specific death. For multivariable regression models, adjustments included age, sex, the prearranged baseline comorbidities, recanalisation, neurosurgical operations, other medication used within 90 days after the index event and treatment in the university hospital (online supplemental table 2). Subgroup analyses for all-cause death and ICH were performed by age (<80 or ≥80 years), sex, atrial fibrillation, diabetes, usage of antithrombotic medications and prior statin usage. Estimation of potential residual confounding was done by computing the E-value.[10] The adjusted HR was used for calculating the number needed to treat (NNT).[14] The results are presented as mean, median, percentage, HR or subdistribution HR (sHR) with a 95% CI, IQR or±SD. Statistical significance was inferred at p<0.05. SAS V.9.4 was used for the analyses.

RESULTS

A total of 45 512 patients with IS were included in the study. Intensity of first-line statin therapy after IS was high in 16.0%, moderate in 73.8% and low in 10.2% of patients. Baseline features are presented in online supplemental table 2. The intensity of statin therapy decreased with ageing and men received higher intensity statins more frequently than women. There was no statin prior to the index event in 70.8% of patients. The intensity of prior statin therapy remained unaltered during IS admission in 82.0% (online supplemental figure 1).

Usage of initial high-intensity statin after IS increased (from 2.7% to 29.9%) and usage of low-intensity statins decreased (from 25.2% to 3.4%) during the study period (trend p<0.0001) (online supplemental figure 2). Adherence to statins decreased during the follow-up with 28.6% of patients being non-adherent 12 years after the index event (trend p<0.0001). The intensity of used statin treatment remained consistent throughout the follow-up with 18.9% using high, 71.5% moderate and 9.6% low-intensity statin at the end of follow-up (online supplemental figure 3).

A total of 27 647 patients died during the follow-up of 290 556 patient-years. All-cause mortality was 48.2% among those with high-intensity statin, 53.6% with moderate-intensity and 62.3% with low-intensity (figure 1). Higher intensity of treatment is associated stepwise with a lower risk of death (table 1). The NNTs of higher intensity statin after IS for death during follow-up were 32.0 (95% CI 20.1 to 79.8) for high-intensity versus moderate-intensity, 27.5 (95% CI 19.0 to 49.6) for moderate-intensity versus low-intensity and 14.6 (95% CI 10.9 to 22.3) for high-intensity versus low-intensity. The E-value stood at 1.41 (95% CI 1.23 to 1.57) in high-intensity versus moderate-intensity, 1.44 (95% CI 1.30 to 1.58) in moderate-intensity versus low-intensity and 1.70 (CI 1.51 to 1.90) in high-intensity versus low-intensity groups with regard to mortality. Increased statin intensity was associated with a reduced risk of death across all studied subgroups (online supplemental table 3).

Recurrent IS occurred in 7438 patients, and 7280 patients died due to cardiovascular causes. The cumulative incidence of recurrent IS was 22.7% for those with a high-intensity statin, 23.6% for those with a moderate-intensity statin and 25.9% for those with a low-intensity statin (figure 1). Cumulative incidences of cardiovascular death were 26.8%, 28.9% and 34.1%, respectively (figure 1). Higher statin intensity was associated with a lower probability of recurrent IS and cardiovascular death in non-adjusted (figure 1) and adjusted competing risk analyses (table 1). The NNT for recurrent IS was 41.1 (95% CI 26.4 to 100.4) for high-intensity versus moderate-intensity, 35.1 (95% CI 23.9 to 68.5) for moderate-intensity versus low-intensity and 19.1 (95% CI 14.5 to 38.5) for high-intensity versus low-intensity.

Intracerebral haemorrhage occurred in 904 patients with a cumulative incidence of 3.3% during the follow-up (figure 1). Statin intensity was not associated with the probability of ICH in non-adjusted (figure 1) or adjusted competing-risk analyses (table 1). The result was consistent in all studied subgroups (online supplemental table 4).

DISCUSSION

The current study is, to our knowledge, the largest long-term study comparing different statin intensities after IS. We found higher statin-intensity early after IS to be associated with lower mortality and lower risk of recurrent IS. The outcome was better with higher statin intensity regardless of sex, age, diabetes, atrial fibrillation, antithrombotic medications or prior statin use. In our study with 234 778 follow-up years after IS there was no evidence or trend for increased risk of ICH with higher

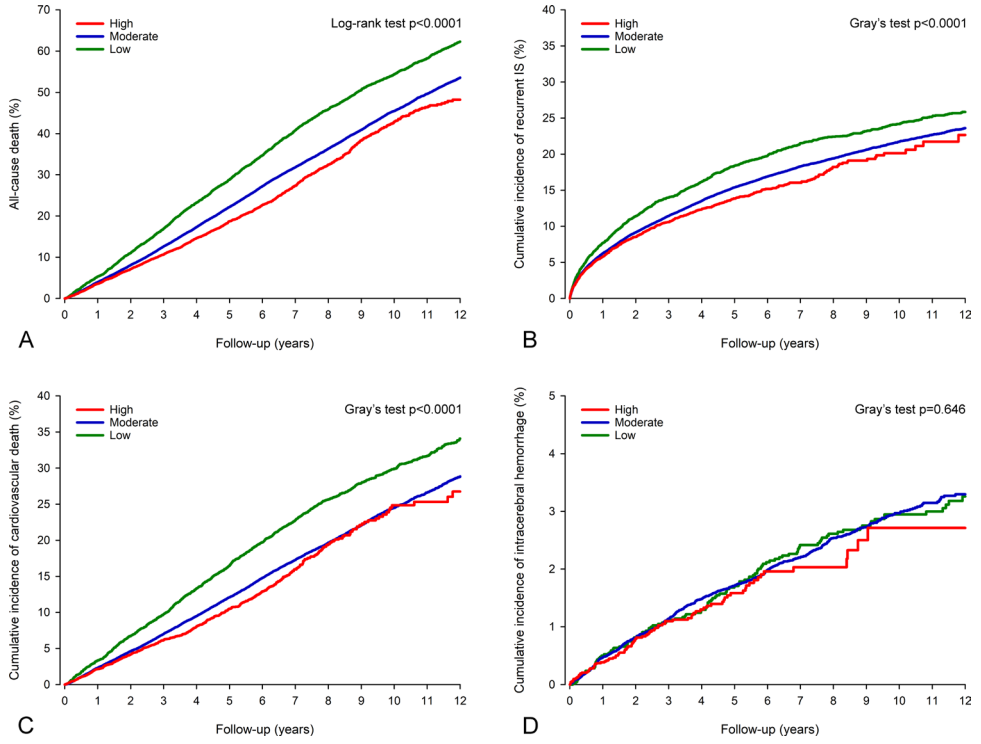

Figure 1 Intensity of initial statin therapy (high, moderate, low) after ischaemic stroke (IS) and incidences of all-cause death (A), recurrent IS (B), cardiovascular death (C) and intracerebral haemorrhage (D) in 45 512 patients. Competing risk plots in panels B–D. Please note the scale differences in y-axis.

statin intensities (sHR 0.93; 95% CI 0.70 to 1.23 for high-intensity vs low-intensity).

Our results support the previous notion that the intensity of statin therapy is mainly determined during index hospitalisation.[14] This underlines the clinical importance of ensuring the usage of high-intensity treatment when discharging patients with IS. A number of patients still use low-intensity statins and more than one-fourth of patients quit statins during follow-up. Although severe adverse effects are rare, mild muscle symptoms are common in statin users.[15] These symptoms, along with the fear they provoke, constitute the primary reason for statin discontinuity.[15]

Importantly, our findings indicate that moderate-intensity statins lead to superior outcomes compared with low-intensity statins. This highlights a crucial notion that, while any statin is preferable to none following IS,[10] the intensity of statin therapy should be the highest tolerated. Our results were adjusted with ezetimibe usage, emphasising the benefits of lowering LDL with higher-intensity statin despite other therapies.[2]

The strengths of the current study include using a nationwide, population-based all-comer retrospective multiregistry study design. The analyses were adjusted for a wide range of potential confounders, although the possibility for residual confounding by unacknowledged factors remains. It is probable that patients with atherosclerosis and high LDL levels have started with higher intensity statins, and at least some patients with probable cerebral amyloid angiopathy started with lower intensity.

Table 1 Association of initial statin intensity after ischaemic stroke (IS) with 12-year outcomes. Multivariable models are adjusted for age, sex, the predetermined baseline comorbidities, recanalisation, usage of neurosurgery, other medication used after the index event and treatment in a university hospital. Secondary outcomes are analysed using competing risk modelling

	Intensity of statin therapy					
	High vs moderate		Moderate vs low		High vs low	
Primary outcome	**adj.HR (95% CI)**	**P value**	**adj.HR (95% CI)**	**P value**	**adj.HR (95% CI)**	**P value**
All-cause death	0.92 (0.87 to 0.97)	0.001	0.91 (0.87 to 0.95)	<0.0001	0.83 (0.78 to 0.89)	<0.0001
Secondary outcomes	**adj.sHR (95% CI)**	**P value**	**adj.sHR (95% CI)**	**P value**	**adj.sHR (95% CI)**	**P value**
Recurrent IS	0.88 (0.82 to 0.95)	0.001	0.87 (0.82 to 0.93)	<0.0001	0.77 (0.70 to 0.84)	<0.0001
Cardiovascular death	0.91 (0.83 to 0.99)	0.021	0.87 (0.81 to 0.93)	<0.0001	0.79 (0.71 to 0.87)	<0.0001
Intracerebral haemorrhage	0.91 (0.73 to 1.14)	0.402	1.02 (0.84 to 1.25)	0.808	0.93 (0.70 to 1.23)	0.619

adj.HR, adjusted HR; adj.sHR, adjusted subdistribution HR.

Thus, important limitations include a lack of access to laboratory values including LDL levels and imaging data, as well as a lack of information on statin intolerance, hospital-level long-term care and socioeconomic status. Statin dosing instructions were not available and usage was presumed to be a unit per day, aligning with 95% of prescriptions in Finland.[14] Based on the E-value, the observed risk reduction in mortality by high-intensity versus moderate-intensity statin could be explained by an unmeasured confounding having an association with both statin intensity and death by a risk ratio of ≥1.4 for each, but not by a weaker confounding.[10]

CONCLUSION

The current results show that a higher intensity of initial statin treatment following IS is associated with lower risks of recurrent IS, cardiovascular death and all-cause death, but not with risk of ICH. These findings underscore the significance of maximising statin intensity shortly after IS.

Contributors VK: Drafting the manuscript, acquisition of data, study concept and design, analysis and interpretation of data. JÅ: Drafting the manuscript, interpretation of data. JOR: Revision of the manuscript for content, study concept and design, interpretation of data. VK had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Funding This work was supported by grant funding from the Finnish Foundation for Cardiovascular Research sr, and the Finnish State research funding.

Disclaimer The funders had no role in the design and conduct of the study, collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript; and decision to submit the manuscript for publication.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Hospital review board, ethical committee approval and informed consent were waived by law due to the study design.

Provenance and peer review Not commissioned; externally peer reviewed.

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