Early in-hospital exposure to statins and outcome after intracerebral hemorrhage

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Results from the Virtual International Stroke Trials Archive

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Abstract

Introduction: Recent data suggest that statin use after intracerebral hemorrhage (ICH) might be beneficial. However, data on the effects of early in-hospital statin exposure are lacking. Therefore, we sought to assess whether 1) early statin exposure during the acute phase after ICH and 2) early continuation of prevalent statin use are associated with favorable functional outcome.

Patients and methods: Data were obtained from the Virtual International Stroke Trials Archive. Patients were categorized according to use patterns of statins during this early in-hospital phase (continuation, discontinuation or new initiation of statins). Univariate and multivariable analyses were conducted to explore the association between early statin exposure and functional outcome.

Results: A total of 919 patients were included in the analysis. Early in-hospital statin exposure (n=89, 9.7%) was associated with better functional outcome (modified Rankin Scale ≤3) compared with 790 patients without statin exposure before or early after the event (66% vs 47%, adjusted OR [adjOR] 2.1, 95% confidence interval [95%CI] 1.3–3.6).

Compared with patients without exposure to statins before and early after the event, early continuation of statin therapy (n=57) was associated with favorable functional outcome (adjOR 2.6, 95%CI 1.3-5.2). The association between early continuation of statins and outcome remained robust in sensitivity analyses restricted to patients able to take oral medication within 72 hours and one-week survivors.

Conclusion: Statin exposure and continuation of prevalent statin therapy early after ICH are associated with favorable functional outcome after 90 days. It is, however, possible that our results are not due to a protective effect of statins after ICH but are confounded by indication bias.

Introduction

Treatment with HMG-CoA-reductase-inhibitors (statins) in patients with acute ischemic stroke is associated with improved survival and better functional outcome.[1, 2] However, in intracerebral hemorrhage (ICH), which constitutes 10-15% of all strokes,[3] use of statins is considered more controversial.[4, 5]

Treatment with statins in patients with recent stroke might be associated with a modestly increased risk for future ICH.[4, 6, 7] On the other hand, there is evidence from observational and animal studies that exposure to statins at any time during hospitalization for ICH is associated with better outcomes and reduced mortality, while discontinuation of statins after ICH is associated with higher rates of poor clinical outcome and mortality.[8-12] However, previous studies did not provide data regarding timing of statin use, specifically continuation of statin during the first few days after ICH.[8-10] This early in-hospital phase is relevant because of potential early rebound effects associated with statin discontinuation.[13-16] Animal model studies in mice with cerebral ischemia, showed loss of protective statin effects as early as two days after their discontinuation.[17]

Altogether, uncertainty remains on how to proceed with pre-existing statin therapy, especially in the early in-hospital phase after ICH. This is mirrored by the current guidelines from the American Heart Association and American Stroke Association on the management of spontaneous ICH, which have no clarity on statin use in patients with recent ICH.[18] There are, however, expert recommendations outside of guidelines suggesting that prevalent statin use should be continued during the early in-hospital phase.[19-21]

Using the Virtual International Stroke Trials Archive (VISTA) database we sought to study whether exposure to statins during the early in-hospital phase, and especially whether continuation of prevalent statin use is associated with a better functional outcome at 90 days.

Methods

Data source, and patients

Data were obtained from the Virtual International Stroke Trials Archive - ICH database (VISTA-ICH, URL: http://www.virtualtrialsarchives.org/vista/). The VISTA database collects data from a variety of clinical trials for exploratory analyses; its design and goals have been published previously.[22] Prior to the data analysis, a project proposal with definitions of our outcome parameters was approved by the independent VISTA steering committee.

We included all patients with primary ICH and having available data on age, prior and concurrent medication, clinical severity as measured by Glasgow Coma Scale (GCS), hematoma volume, systolic blood pressure at baseline and functional outcome after 90 days. Figure 1 shows patient inclusion into our analysis as well as distribution of patients according to statin therapy. Functional outcome was measured using the modified Rankin Scale (mRS). Patients on oral anticoagulation before the event were excluded from the study, as there are differences in clinical outcome in these patients.[23]

Figure 1. Data collection and group allocation

[Insert Figure 1.]

mRS, modified Rankin Scale; ICH, Intracerebral hemorrhage; GCS, Glasgow Coma Scale

Definition of early statin use

We categorized patients into four groups according to early in-hospital statin exposure in the first 48 hours after the event: 1) patients without statin exposure before and early after the event

('no statin use'), 2) patients who continued prevalent statin treatment within 48 hours and continued this therapy at least until day 7 after the event ('early continuation'), 3) patients who discontinued statin use after ICH in the first 48 hours after ICH ('early discontinuation'), and 4) patients newly started on statins within 48 hours after the event and continued this therapy at least until day 7 after the event ('new early initiation'; see figure 2). Early in-hospital statin exposure was defined as documented treatment with statins within the first 48 hours after admission irrespective of prevalent statin therapy before ICH (combination of groups 2 and 4). Group 1 included patients with late initiation of statins after 48 hours but within the first week after ICH, and group 3 included patients with late continuation after 48 hours but within the first week after the event.

Figure 2. Patient groups according to statin exposure

[Insert Figure 2.]

ICH, Intracerebral hemorrhage

Study outcomes

Outcome of interest was favorable functional outcome after 90 days, defined as mRS ≤ 3. This outcome measure was chosen to facilitate comparability with other studies on ICH.[9, 24] Further outcomes were distribution of 90-day mRS and mortality at 90 days.

Statistical analysis

For univariate analysis Pearson's chi-squared test, Mann-Whitney-U-test and student's T-test were used where appropriate. Unadjusted and adjusted multiple logistic regression analyses were conducted to explore the association between statin exposure and favorable functional outcome. Statin use was entered as a 4-group categorical variable. Patients without statin

exposure before and early after ICH ('no statin use') were used as reference. In order to explore the association of early statin therapy after ICH and favorable shift in 90-day mRS, we conducted an ordinal logistic regression analysis. The models were adjusted for age, sex, hematoma volume, history of prior antithrombotic use, Glasgow Coma Scale (GCS) and systolic blood pressure on admission. These variables are established risk factors for unfavorable outcome after ICH and could be linked to clinical decisions regarding statin treatment (re) initiation.[25-28] The variables had to be available for at least 90% of the cohort and were checked for relevant multicollinearity within the model, which was defined as the largest condition index ≥ 30.[29]

We also compared the association between early continued statin exposure ('early continuation') and favorable outcome with patients who discontinued statins ('early discontinuation'). Due to limited numbers, the multiple logistic regression analysis only included age and hematoma volume. Furthermore, we compared functional outcomes of patients who continued statin therapy early after ICH ('early continuation') with those who continued statins later (i.e. between days 3 and 7 after ICH, 'late continuation').

In addition, we performed two sensitivity analyses, restricting our multiple logistic regression to patients with documented intake of oral medication in the first 72 hours in order to try to rule out patients unable to take statins because of dysphagia and to one-week survivors in an attempt to reduce selection bias. In two further sensitivity analyses we 1) replaced GCS with NIHSS into our original model and 2) added intraventricular hemorrhage into our original model.

Two-sided p-values < 0.05 were considered statistically significant. All data were analyzed using SPSS version 25 (IBM, Chicago, USA).

Results

Of 987 ICH patients recorded in VISTA-ICH, 919 fulfilled inclusion criteria. Thirty-five patients were excluded because of missing data on either mRS at 90 days (19 patients), information on early statin exposure (1 patient), baseline GCS and/or hematoma volume (12 patients) and/or systolic blood pressure (3 patients). Another 33 patients were excluded because they were on oral anticoagulant treatment at the time of the event (figure 1).

Of these 919 patients, mean age was 65.6 ± 12.4 years, 66% were male, median baseline GCS was 15 (interquartile range [IQR] 13-15), median baseline NIHSS was 13 (IQR 9-18) median ICH volume was 15 ml (IQR 7-30 ml) and median onset to randomization time was 3.5 hours min (IQR 2.75 – 4.65).

Statin exposure

Prevalent statin use upon hospital admission was present in 97 patients (10.6%). Of these, 57 patients (6.2%) continued statin treatment within 48 hours after ICH, while 40 patients (4.4%) discontinued statin use in the first 48 hours after the event. The latter included 7 patients (0.8%) who continued statins later than 48 hours but within the first week after ICH. New early statin exposure (i.e. new initiation of treatment within 48 hours) was observed in 32 patients (3.5%), while 790 (86.0%) patients were not on statins before and early after the event. The latter included 49 patients (5.3%) with late initiation of statin therapy later than 48 hours but within the first week. Any early in-hospital statin exposure was documented in 89 patients (9.7%). Table 1 shows baseline characteristics according to early in-hospital statin exposure.

Table 1. Baseline characteristics according to early in-hospital statin use

	No statin use n=790	Early continuation of statins n=57	Early discontinuation of statins n=40	New early initiation of statins n=32
Age, years, mean (Std. derivation)	65.2 (±12.6)	67.2 (±8.9)	69.8 (±12.0)	67.0 (±10.6)
Male sex, % (n)	64.3 (509)	63.2 (36)	60.0 (24)	53.1 (17)
GCS base, median (IQR)	15 (13-15)	15 (14-15)	14 (12-15)	15 (12-15)
NIHSS base, Median (IQR)	14 (9-18)	11 (7-15)	14 (11.5-19.5)	11 (7-18.5)
Hematoma volume, ml, median (IQR)	15.7 (8-30.8)	9.5 (4.9-19.3)	20.4 (8.6-44.1)	10.8 (3.4-22.4)
Systolic Blood pressure base, mmHg, median (IQR)	175 (156-195)	160 (144-182)	165 (151- 187)	178 (162 – 200)
History of Diabetes mellitus, % (n)	13.9 (110)	45.6 (26)	35.0 (14)	28.1 (9)
History of hypertension, % (n)	80.1 (633)	94.7 (54)	77.5 (31)	93.8 (30)
Prior use of antithrombotics, %, n	12.5 (99)	43.9 (25)	52.5 (21)	0 (0)

Std. derivation, Standard derivation; IQR, Interquartile Range; NIHSS, National Institute of Health Stroke Scale; GCS, Glasgow Coma Scale

Compared with patients not on statins before and early after the event, patients with continued statin use had lower hematoma volume (median 9.5 ml vs. 15.7 ml, p=0.002), lower systolic blood pressure at admission (median 160 mmHg vs. 175 mmHg, p = 0.003), and were more often on antithrombotic drugs before the event (43.9% vs. 12.5%, p <0.001).

Functional outcome at 90 days

Median mRS at day 90 was 4 (IQR 2-5), and frequency of unfavorable outcome (mRS 4-6) was 50.9% (n=468). Frequency of favorable outcome according to early in-hospital statin exposure is shown in table 2. Early in-hospital statin exposure ('early continuation' and 'new early initiation') was associated with better functional outcome at 90 days compared with no early statin exposure (66.3% vs 47.2%, unadjusted Odds Ratio [OR] 2.20, 95% Confidence Interval [95% CI] 1.39 – 3.48). These results were confirmed after adjusting for age, sex, hematoma volume, prior use of antithrombotics and GCS and systolic blood pressure at initial presentation (adjusted OR 2.13, 95% CI 1.26 – 3.60).

When statin exposure was entered as a categorical variable into the model with patients without statin use ('no statin use') as reference, early continuation of preexisting statin therapy was associated with higher probability of favorable functional outcome (unadjusted OR 2.78, 95% CI 1.53-5.04). After adjustment for age, sex, hematoma volume, prior use of antithrombotics and GCS and systolic blood pressure at initial presentation, early continuation of statins remained significantly associated with favorable functional outcome (adjusted OR 2.64, 95% CI 1.34-5.20), while early discontinuation of statins (adjusted OR 0.75, 95%CI 0.34-1.66) and new early initiation of statins (adjusted OR 1.44, 95% CI 0.64-3.27) were not (table 2). To account for bias conveyed by lower clinical severity in patients with early statin continuation we replaced GCS by NIHSS into our original model, and, second, included presence of intraventricular hemorrhage at baseline (n=265) into our original model. The results regarding

the association between early statin continuation and favorable outcome remained robust (adjusted OR 2.37, 95% CI 1.19 – 4.72 and adjusted OR 2.41, 95% CI 1.20 – 4.88, respectively).

Using ordinal regression analysis there also was an association between early statin continuation and a shift towards a favorable mRS score (adjusted common OR for early statin continuation 2.13, 95% CI 1.30-3.51; table 2 and figure 3).

Table 2. Association between early in-hospital statin use after ICH and functional outcome

	Favorable outcome (mRS 0-3 at 90 days)			Favorable distribution of mRS	
		Logistic Regression		Ordinal Regression	
Statin use	n/N (%)	Unadjusted OR	Adjusted OR*	Unadjusted OR	Adjusted OR*
No statin use	379/790 (48.0)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Early continuation of statins	41/57 (71.9)	2.78 (1.53-5.04)	2.64 (1.34-5.20)	2.35 (1.47-3.75)	2.13 (1.3-3.51)
Early discontinuation of statins	13/40 (32.5)	0.52 (0.27 – 1.03)	0.75 (0.34-1.66)	0.63 (0.37-1.08)	1.00 (0.56 – 1.78)
New early initiation of statins	18/32 (56.3)	1.39 (0.68-2.84)	1.44 (0.64-3.27)	1.49 (0.81-2.76)	1.78 (0.93 – 3.42)

mRS, modified Ranking Scale; OR, Odds Ratio

*adjusted for age, sex, hematoma volume, prior use of antithrombotics and Glasgow Coma Scale and systolic blood pressure at initial presentation

Figure 3. Distribution of mRS at 90 days according to statin exposure

[Insert Figure 3.]

mRS, modified Ranking Scale; OR, Odds Ratio; 95% CI, 95% Confidence Interval

When directly compared with early discontinuation of statin therapy, early continuation of preexisting statin therapy was also associated with higher probability of favorable functional outcome (72 % vs 33%, p < 0.001, unadjusted OR 5.32, 95% CI 2.21-12.21, adjusted OR 3.87, 95% CI 1.46 – 10.27, adjusted for age and hematoma volume). Similarly, early statin continuation was associated with a shift towards favorable mRS score (adjusted common OR for continued statin use 2.75, 95% CI 1.24 – 6.08; versus early discontinuation of statins).

Finally, we compared early and late continuation of statins (n=57 and n=7). Frequency of favorable outcome was higher in the early continuation group (71.9% vs 42.9%, p = 0.117, unadjusted OR 3.4, 95% CI 0.7 – 17.0). Because of the small number of patients with late continuation of statin therapy, we did not perform a multiple logistic regression analysis.

Mortality at 90 days

Within the first 90 days after ICH, 183 patients (19.9%) died. Patients with early in-hospital statin exposure ('early continuation' and 'new early initiation') were less likely to die within 90 days than patients without statin exposure (9% vs. 21%, p=0.007, unadjusted OR 0.37, 95% CI 0.18 – 0.8, adjusted OR 0.4, 95% CI 0.2 – 0.97).

90-day mortality was non-significantly lower in the early continuation group, when compared with the 'no statin' group (21% versus 11%, p=0.074, unadjusted OR 0.4, 95% CI 0.2 – 1.1, adjusted OR 0.6, 95% CI 0.2 – 1.5, table 3), and when compared with the early discontinuation group (11% versus 23%, p=0.108, unadjusted OR 0.4, 95% CI 0.1 – 1.3, adjusted OR 0.7, 95% CI 0.2 – 2.5).

Table 3. Association between early in-hospital statin use after ICH and mortality at 90 days

	Death until day 90		
Statin use	n/N (%)	Unadjusted OR	Adjusted OR*
No statin use	166/790 (21.0)	1 (reference)	1 (reference)
Early continuation of statins	6/57 (10.5)	0.4 (0.12 – 1.1)	0.6 (0.2 -1.5)
Early discontinuation of statins	9/40 (22.5)	1.1 (0.5 – 2.3)	0.7 (0.3 – 1.8)
New early initiation of statins	2/32 (6.3)	0.3 (0.1-1.1)	0.2 (0.1 – 1.0)

OR, Odds Ratio

*adjusted for age, sex, hematoma volume, prior use of antithrombotics and Glasgow Coma Scale and systolic blood pressure at initial presentation

Sensitivity analysis regarding functional outcome

In an attempt to reduce selection bias generated by patients unable to take statins because of dysphagia, we performed a sensitivity analysis regarding favorable 90-day outcome. First, we excluded 313 patients for whom no intake of any oral medication within the first 72 hours was documented. Our results stayed robust (frequency of favorable outcome in patients with early continuation of statins compared with no statin exposure (75% vs 53%, unadjusted OR 2.65, 95% CI 1.27 – 5.54; adjusted OR 2.92, 95% CI 1.26 – 6.75). Similarly, another sensitivity analysis restricted to 839 patients who survived the first week after ICH, showed similar associations in the multiple logistic regression analysis (frequency of favorable outcome in patients with early continuation of statins compared with no statin exposure 73% vs 53%, unadjusted OR 2.40, 95% CI 1.31 – 4.42; adjusted OR 2.55, 95% CI 1.28 – 5.09).

Discussion

In this study, early in-hospital exposure to statins after acute ICH was associated with better functional outcome compared with no statin exposure early after the event. Our data suggests that this association is particularly driven by continuation of pre-existing statin use within the first two days after the event. Thus, our findings provide clinical evidence to support current expert recommendations that prevalent statin use should be continued during the early in-hospital phase.[19-21]

Several hospital-based observational studies have explored the association between in-hospital statin exposure and functional outcome after ICH:[8, 9, 30] In a study of 3218 Chinese patients with ICH, in-hospital statin use (at any time during hospitalization) was associated with a better functional outcome at 3 months and 1 year, in comparison to patients without in-hospital statin use.[30] Data from other studies show more conflicting results.[8, 9] In an analysis of data from the Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) study, a prospective hospital-based multicenter study of 2457 patients with ICH, there was a signal towards better functional outcomes among patients with in-hospital statin use (combined group of patients with continued statin use and new statin use) compared with discontinuation of statins. This was, however, no longer statistically significant when a propensity score accounting for variables that could have influenced the decision to treat with statins was included in the analysis.[8] Similarly, an analysis of data from 2466 patients from the registry of the Canadian stroke network found an association between in-hospital statin discontinuation (at any time) and poor functional short-term outcome which became borderline statistically significant after excluding patients treated palliatively.[7]

Importantly, these studies did not define the timing of in-hospital statin exposure. We hypothesize that any protective or detrimental effects of statins would occur early following index ICH. Clinically, the early phase after ICH is critical because of the risk for hematoma expansion, development of perihematomal edema and re-bleeding.[31-34] Hence, continuation of

statin therapy early after ICH is reasonable to avoid rebound effects associated with statin discontinuation.[13-15] This argument is supported by animal models, where the protective effect of statins was lost within 2 days after their withdrawal.[17] Moreover, clinical data show, that withdrawing statin therapy within the first 24 hours after myocardial infarction is associated with increased in-hospital mortality, compared to patients without statin use.[35] These findings might explain that our observed associations remained stable even after adjusting for strong predictors of outcome after ICH.

It should be mentioned, that a direct comparison between early and late continuation of statins also is of high interest, when assessing the necessity to continue statin therapy early after ICH. However, late continuation of statins was rare in our cohort limiting the statistical power to detect statistically significant differences.

In our study, statin exposure early after ICH was significantly associated with a reduced odds of 90-day mortality compared with patients without statin exposure. Likewise, there was a signal towards lower mortality in patients who continued statins within 48 hours after ICH, though this was not statistically significant. This is in line with most data derived from observational studies focusing on mortality as outcome parameter. In a recent meta-analysis by Lei and colleagues comprising seven studies, in hospital-statin exposure was associated with an approximately 60% reduced odds of mortality.[36] Interestingly, our observed associations fit well within these results and extend these observations to the early in-hospital phase.

Strengths and limitations

The strength of our study is the large sample size of the VISTA ICH database which is based on multicenter randomized controlled trials on (hyper-)acute ICH. The high data quality required in clinical trials with rigorous documentation of time points of drug administration allowed us to define and measure early in-hospital statin use.

There are limitations to this analysis. First, our results could be confounded by indication bias. Patients with presumed good prognosis at index ICH might have received statins more likely compared to those with presumed poor prognosis. This also falls into weight as our database lacked information on the exact reason to start or continue statin treatment, such as prevalence of coronary disease, severe carotid artery disease or history of ischemic stroke. Reassuringly, results from the sensitivity analysis, limited to one-week survivors, remained statistically significant with similar effect measures being detected. Moreover, as our database consists of patients that participated in randomized controlled trials (RCTs), confounding by indication bias could be lower than in registry studies. Patients enrolled in RCTs usually differ from those registered in hospital-based cohorts in particular with regard of co-morbidities and prognosis as patients with a presumably bad prognosis are often not included in RCTs. This presumption is corroborated by the high median GCS in our patient population suggesting an overall mild-to-moderate ICH severity. Thus, our findings may not apply to a more severely affected ICH population.

Second, statins cannot be administered intravenously. Therefore patients with dysphagia, which is a common complication of stroke, are unable to take statins.[37] To account for this, we performed yet another sensitivity analysis, excluding patients for whom no intake of oral medication was documented in the first 72 hours. Again, our results stayed robust in this analysis. However, it has to be noted, that the reason for not administering oral medication was not documented in our database. It is therefore possible, that there were other reasons to withhold oral medication (and therefore statins) than dysphagia.

Third, the number of patients on statins was small, especially in the continuation and discontinuation groups. Therefore, we were not able to study potential effects of statin type or statin dose. This could be important as there is an association between higher dose of statin use and risk of symptomatic ICH after intravenous thrombolysis for ischemic stroke.[38] Moreover,

sample size did not allow us to provide reasonable comparison of early versus late continuation, as well as early versus late new treatment initiation.

Fourth, we have no data on the exact location of ICH, presence and location of cerebral microbleeds, hematoma expansion, and recurrent ICH. This could be of significance as all these factors are associated with outcome and potentially affected by statin exposure.[39-43] Finally, our data lacked information on cholesterol levels of our patients. Therefore, we were unable to interpret the association between outcome and cholesterol levels.[44]

Conclusion

We observed an association between continued statin use during the early in-hospital phase after ICH (<48 hours) and a favorable functional outcome at 90 days. We are unable to differentiate if this association was due to a protective effect of early statin use in ICH patients or whether the use of statins was a surrogate parameter for an expected better prognosis. Still, our results provide clinical evidence supporting current expert recommendations to continue statins early after ICH. Well-designed randomized controlled-trials are warranted to further answer questions about statin continuation in the setting of acute ICH.

Declaration of Conflicting Interests

JID, AHA, BS, and CHN report no disclosures. ME reports grants from Bayer and fees paid to the Charité from Bayer, Boehringer Ingelheim, BMS/Pfizer, Daiichi Sankyo, Amgen, GSK, Sanofi, Covidien, Novartis, all outside the submitted work. KRL reports no relevant disclosure, he has received Fees/expenses from Boehringer Ingelheim (for data monitoring committees); ACI Clinical, Parexel, Nestlé, American Heart Association, and EVER NeuroPharma. JFS has received fees for lectures from Stryker GmbH & Co. KG and BristolMyers Squibb, all outside the submitted work.

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Ethical approval

Not applicable

Informed consent

Not applicable

Guarantor

JFS

Contributorship

Study concept and design: JID and JFS. Acquisition of data: Vista collaboration, JFS. Analysis and interpretation of data: All authors. Drafting of the manuscript: JID and JFS. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: JID, JFS.

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