Statins and risk of poststroke hemorrhagic complications

Jan F. Scheitz, MD
Rachael L. MacIsaac, PhD
Azmil H. Abdul-Rahim,
MBCbB, MRCP
Bob Siegerink, PhD
Philip M. Bath, FRCP,
DSc
Matthias Endres, MD
Kennedy R. Lees, MD,
FRCP
Christian H. Nolte, MD
On behalf of the VISTA
collaboration

Correspondence to
Dr. Scheitz:
jan-friedrich.scheitz@charite.de

ABSTRACT

Objective: To assess whether statin treatment before or after acute ischemic stroke (AIS) affects the risk of acute intracerebral hemorrhage (ICH), postacute ICH, and mortality within 90 days.

Methods: Data were sought from the Virtual International Stroke Trials Archive, an international repository of clinical trials data. Using propensity score matching, we retrospectively compared patients with prior statin treatment and newly initiated statin within 3 days after AIS to patients without statin exposure. Outcomes of interest were acute symptomatic ICH (sICH), any acute ICH, postacute ICH, and mortality during follow-up of 3 months.

Results: A total of 8,535 patients (mean age 70 years, 54% male, median baseline NIH Stroke Scale score 13) were analyzed. After propensity score matching, prior statin use was not strongly associated with sICH (adjusted odds ratio [OR] 1.33, 95% confidence interval [CI] 0.83–2.14) or any ICH (adjusted OR 1.35, 95% CI 0.92–1.98). There was no evidence of an interaction between prior statin use and thrombolysis. New initiation of statins was not associated with postacute ICH (adjusted hazard ratio [HR] 1.60, 95% CI 0.70–3.65). There was a signal towards lower 90-day mortality in patients with prior statin use (adjusted HR 0.84, 95% CI 0.70–1.00) and especially early initiation of statins (adjusted HR 0.67, 95% CI 0.46–0.97).

Conclusions: Statin use prior to AIS was not associated with early hemorrhagic complications, irrespective of treatment with thrombolysis. New initiation of statin treatment early after AIS did not affect risk of postacute ICH, but might be associated with reduced mortality. *Neurology*® 2016;86:1590–1596

GLOSSARY

ACE = angiotensin-converting enzyme; **AE** = adverse event; **ATC** = Anatomical Therapeutic Chemical; **CI** = confidence interval; **HR** = hazard ratio; **ICH** = intracerebral hemorrhage; **IQR** = interquartile range; **mRS** = modified Rankin Scale; **NIHSS** = NIH Stroke Scale; **OR** = odds ratio; **PPM** = propensity score matching; **RCT** = randomized controlled trial; **SAE** = severe adverse event; **sICH** = symptomatic intracerebral hemorrhage; **SPARCL** = Stroke Prevention by Aggressive Reduction in Cholesterol Levels; **VISTA** = Virtual International Stroke Trials Archive.

Statins (HMG-CoA-reductase inhibitors) are lipid-lowering drugs that are widely prescribed for the primary and secondary prevention of cardiovascular and cerebrovascular events.¹ Treatment with statins before and after ischemic stroke has been associated with improved functional outcomes and survival.² Despite the overall benefit of statins for secondary stroke prevention, there are persisting concerns regarding the potential increased risk of intracerebral hemorrhage (ICH) among statin users.^{3–5} The skepticism derives from the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial and Heart Protection Study, which observed more ICH events in patients with a history of stroke who were randomized to statins for secondary prevention,^{6,7} the inverse correlation between cholesterol levels and ICH,⁸ and the pleiotropic effects of statins on hemostasis and coagulation.^{9,10} Further, there might be a higher risk of symptomatic hemorrhagic transformation after IV thrombolysis, especially with higher

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From the Center for Stroke Research Berlin (J.F.S., B.S., M.E., C.H.N.), Klinik für Neurologie (J.F.S., M.E., C.H.N.), Clinical Epidemiology and Health Services Research in Stroke (CEHRIS) (B.S.), Excellence Cluster NeuroCure (M.E.), German Center for Cardiovascular Research (DZHK) (M.E.), and German Center for Neurodegenerative Diseases (DZNE) (M.E.), Charité-Universitätsmedizin Berlin, Germany; Stroke Research (R.L.M., A.H.A.-R., K.R.L.), Institute of Cardiovascular & Medical Sciences, University of Glasgow; and Stroke Trials Unit (P.M.B.), Division of Clinical Neuroscience, University of Nottingham, UK.

Coinvestigators are listed on the *Neurology*® Web site at [Neurology.org](#).

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doses of statins.^{11,12} However, there is a paucity of data on the safety and efficacy of early initiation of statin treatment acutely following ischemic stroke with regards to new hemorrhagic stroke events and poststroke survival.

Using anonymized clinical trial data from the Virtual International Stroke Trials Archive (VISTA), we aimed to investigate (1) whether statin use prior to stroke affects the risk of early symptomatic ICH, (2) whether statin use prior to stroke affects the safety of thrombolysis, and (3) whether early initiation of statins after stroke affects the occurrence of ICH during follow-up and mortality within 90 days.

METHODS **Data source, design, and patients.** Anonymous data of patients with acute ischemic stroke were sought from the VISTA Acute database (www.vistacollaboration.org). VISTA Acute collates and provides access to anonymized data of 28,130 acute stroke patients treated in randomized controlled trials (RCTs).¹³ For the present analysis, all trials with available core data (age, sex, stroke severity according to NIH Stroke Scale [NIHSS], treatment with thrombolysis, adverse events [AEs], prior and concurrent medication, medical history of hypertension, atrial fibrillation, diabetes mellitus, history of stroke, history of myocardial infarction, and follow-up modified Rankin Scale [mRS]) were included. We conducted a retrospective analysis of raw AE and severe AE (SAE) data as well as concurrent medication data. A project proposal with definitions of the outcome parameters was reviewed prior to analysis by the independent VISTA steering committee.

Statin use and type was defined as any record matching Anatomical Therapeutic Chemical (ATC) codes C10AA, C10BA, or C10BX on available prior or current medication datasets. Patients with statin treatment prior to stroke onset (prevalent users) were compared with patients with no recorded prior statin treatment. Regarding statin type, potent statins (rosuvastatin, atorvastatin, cerivastatin) were compared with less potent statins (simvastatin, fluvastatin, lovastatin, pravastatin). Potency was evaluated using IC50 values for inhibition of HMG-CoA-reductase and comparative efficacy regarding low-density lipoprotein-lowering capacity at lowest available doses.^{10,14,15} In addition, we compared patients having early initiation of statin treatment after stroke with patients without statin exposure during the acute phase. Statin exposure was defined as start day of treatment within the first 3 days. Treatment had to be continued during the first 30 days, until occurrence of a SAE leading to discontinuation, or until 7 days prior to death. Other prior and current medication analyzed included oral anticoagulants (ATC code B01AA), antiplatelet agents (ATC code B01AC), and angiotensin-converting enzyme (ACE) inhibitors (ATC codes C09AA, C09B, C09BA, C09BB) in order to account for confounding by indication bias.

Outcome measures. Hemorrhagic complications were extracted from AE and SAE datasets. Primary outcome was occurrence of symptomatic ICH (sICH). In accordance with a previous study using VISTA data and in approximation to criteria used in the European Cooperative Acute Stroke Study II, sICH was defined as any ICH recorded within 4 days together with (1)

clinical worsening as indicated by ≥ 4 point increase between baseline and follow-up NIHSS at 24 hours, (2) ICH leading to death within 7 days thereafter, or (3) ICH considered to be a SAE.¹⁶ Secondary outcomes were occurrence of any ICH recorded to be an AE within 4 days and postacute ICH (sICH according to abovementioned criteria detected >7 days after randomization). Subarachnoid hemorrhage, subdural/epidural hemorrhages, or unspecified hemorrhages were excluded because of different pathophysiology (i.e., due to aneurysms or trauma).

Statistical methods. For univariate group comparisons regarding binary, categorical, or continuous variables, the Pearson χ^2 , Mann-Whitney *U*, or Student *t* tests were used where appropriate. In order to test the association between prior statin use and sICH or any ICH, a multiple logistic regression was computed. Cox proportional hazards regression analysis was conducted to analyze the association between early statin exposure after stroke with occurrence of postacute ICH and 90-day mortality. Ordinal regression analysis was used to assess the association between statin exposure and distribution of functional outcome on the mRS at 3 months. The regression analyses included all variables associated with the respective outcomes of interest at a *p* value < 0.10 in univariate comparison. Variables had to be available in $>90\%$ of the cohort to minimize reduction of endpoints for analysis. In order to account for potential heterogeneity between the trials, we used stratified logistic regression to analyze the sICH endpoint. Furthermore, we adjusted for trials in Cox regression and ordinal regression analyses. In addition, we used propensity score matching (PPM) to account for imbalances regarding baseline characteristics of patients with and without statin exposure. Details regarding the matching procedure are described in the e-Methods on the *Neurology*[®] Web site at Neurology.org. Statistical analyses were performed using SPSS Statistics version 23 and SAS version 8.3.

RESULTS A total of 8,535 patients across 5 VISTA Acute trial sources were included in the analysis (mean age 70 ± 12 years, 54% male, median NIHSS 13 [interquartile range (IQR) 8–18]). Table 1 shows the baseline characteristics of the cohort according to prior statin use. Prior statin use was recorded in 15.3% of patients (*n* = 1,309). The most common statin types used were simvastatin (*n* = 560, 42.8%), atorvastatin (*n* = 416, 31.8%), and pravastatin (*n* = 170, 13.0%). Patients with prior statin use differed significantly from patients without prior statin use in several baseline characteristics (table 1). As shown in table 1, baseline differences in age, sex, stroke severity, prior antiplatelet use, prior oral anticoagulation, and medical history of diabetes, myocardial infarction, or hypertension were balanced in the PPM cohort. Among statin-naïve patients at the time of stroke (*n* = 7,226), data on time of initiation were available in 7,116 patients (98.5%). New initiation of statin treatment within 3 days was documented in 626 patients (8.8%). Simvastatin (*n* = 294, 47.0%), atorvastatin (*n* = 264, 42.2%), and pravastatin (*n* = 45, 7.2%) were the statins most commonly started shortly after stroke. Table e-1 shows baseline

Table 1 Baseline characteristics of patients with and without prior statin use before and after matching according to propensity scores

	Entire cohort (n = 8,535)	Unmatched cohort		p	PPM cohort		p
		Prior statin (n = 1,309)	No prior statin (n = 7,226)		Prior statin ^a (n = 1,308)	No prior statin (n = 1,308)	
Age, y, mean ± SD	69.8 ± 12.4	71.0 ± 9.6	69.6 ± 12.9	<0.001	71.0 ± 9.6	71.4 ± 11.2	0.43
Male sex, % (n)	54.3 (4,631)	58.1 (760)	53.6 (3,871)	0.003	58.1 (760)	58.1 (760)	0.99
NIHSS on admission, median (IQR)	13 (8–18)	13 (9–18)	12 (8–18)	0.001	13 (9–18)	13 (9–18)	0.86
Hypertension, % (n)	72.4 (6,183)	85.7 (1,122)	70.0 (5,061)	<0.001	85.8 (1,122)	87.4 (1,143)	0.21
Atrial fibrillation, % (n)	27.6 (2,357)	25.9 (339)	27.9 (2,018)	0.13	25.9 (339)	31.3 (409)	0.002
Previous stroke, % (n)	27.4 (2,342)	29.1 (381)	27.1 (1,961)	0.14	29.1 (381)	35.3 (462)	<0.001
Diabetes, % (n)	23.4 (1,983)	31.5 (412)	21.7 (1,571)	<0.001	31.4 (411)	29.9 (391)	0.40
Previous MI, % (n)	15.4 (1,311)	31.1 (407)	12.5 (904)	<0.001	31.1 (407)	30.7 (402)	0.87
Onset to randomization time, h, mean ± SD (n = 8,459)	4.3 ± 1.5	4.0 ± 1.2	4.4 ± 1.6	<0.001	4.0 ± 1.2	4.39 ± 1.43	<0.001
Systolic blood pressure, mm Hg, mean ± SD (n = 8,448)	155.4 ± 26.1	152.8 ± 25.7	155.9 ± 26.2	<0.001	152.8 ± 25.7	157.6 ± 26.0	<0.001
Treatment with thrombolysis, % (n)	30.3 (2,583)	43.0 (563)	28.0 (2,020)	<0.001	43.0 (563)	26.0 (340)	<0.001
Glucose, mmol/L, mean ± SD (n = 5,300)	7.6 ± 3.1	7.7 ± 3.0	7.6 ± 3.1	0.36	7.7 ± 3.0	8.1 ± 3.4	0.008
Platelet count, 10 ⁹ /L, mean ± SD (n = 7,024)	233.2 ± 76.7	228.5 ± 72.8	234.1 ± 77.4	0.03	228.4 ± 72.8	232.1 ± 80.8	0.27
Creatinine, μmol/L, mean ± SD (n = 7,613)	84.0 ± 27.1	89.9 ± 30.3	82.8 ± 26.3	<0.001	89.9 ± 30.3	87.6 ± 29.2	0.06
Antiplatelets, % (n)	32.2 (2,748)	60.0 (786)	27.2 (1,962)	<0.001	60.0 (785)	59.6 (780)	0.71
Single antiplatelets, % (n)	30.5 (2,601)	54.8 (717)	26.1 (1,884)		54.8 (717)	55.1 (721)	
Dual antiplatelets, % (n)	1.7 (147)	5.3 (69)	1.1 (78)		5.2 (68)	4.5 (59)	
Oral anticoagulation, % (n)	7.1 (610)	10.2 (134)	6.6 (476)	<0.001	10.2 (133)	10.6 (139)	0.70
ACE inhibitors, % (n)	25.7 (2,195)	42.4 (555)	22.7 (1,640)	<0.001	42.4 (554)	31.4 (411)	<0.001

Abbreviations: ACE = angiotensin-converting enzyme; IQR = interquartile range; MI = myocardial infarction; NIHSS = NIH Stroke Scale; PPM = propensity score matched cohort.

^aOne patient could not be matched due to missing data on medical history.

characteristics of patients with and without early statin initiation before and after matching according to propensity scores.

Prior statin use and early hemorrhagic complications. sICH was recorded in 221 patients (2.6%). In univariate comparison, occurrence of sICH was more likely in patients with prior statin use (3.9% vs 2.4%, $p = 0.002$, odds ratio [OR]_{unadjusted} 1.56, 95% confidence interval [CI] 1.13–2.15; figure 1). After additional adjustment for confounders in a multiple regression analysis in which we stratified for trial affiliation, there was no evidence of a significant association between prior statin use and sICH (OR_{adjusted} 1.30, 95% CI 0.92–1.83). Older age, higher NIHSS, treatment with thrombolysis, atrial fibrillation, and the use of dual antiplatelets prior to stroke were associated with sICH (table e-2). In the PPM cohort, the occurrence of sICH was observed in 100 patients (3.8%) and was not associated with prior statin use (OR_{PPM} 1.33, 0.83–2.14).

Similar results were observed regarding any ICH within 4 days poststroke (n = 354, 4.1%). In univariate comparison, any ICH occurred more often in

patients with prior statin use (6.5% vs 3.7%, $p < 0.001$). This association was not significant in multiple regression analysis (OR_{adjusted} 1.28, 95% CI 0.97–1.69) and within the PPM cohort (OR_{PPM} 1.35, 95% CI 0.92–1.98). There was no significant association between potent statin types and severe hemorrhagic complications, although the overall association was stronger for more potent statins with an adjusted OR 1.59 (95% CI 0.99–2.55) for the risk of any ICH (data shown in table e-3).

Safety of thrombolysis in patients with prior statin use.

Overall, 2,583 (30.3%) patients received treatment with thrombolysis (mean age 68 ± 13 years, 56.5%, median NIHSS 14 [IQR 10–18]), including 563 patients with prior statin use. Rate of sICH was 4.6% (n = 120) in the thrombolysis group and 1.7% (n = 101) in the nonthrombolysis group. Thrombolysis was independently associated with occurrence of sICH (OR_{adjusted} 2.65, 95% CI 1.91–3.66). There was no evidence of an excess risk of sICH due to interaction between prior statin use and treatment with thrombolysis (table 2). In the unmatched cohort, our interaction analysis showed that patients

Figure 1 Models for the association between prior statin use and symptomatic intracerebral hemorrhage (ICH)

Models of acute symptomatic ICH

^aStratified logistic regression accounting for trial affiliation. ^bStratified logistic regression accounting for trial affiliation; adjusted for age, sex, baseline NIH Stroke Scale (NIHSS), atrial fibrillation, previous stroke, onset to treatment time, prior use of antiplatelets, and thrombolysis. ^cAdjusted for variables used for matching (age, sex, baseline NIHSS, diabetes, hypertension, previous myocardial infarction, prior oral anticoagulation, prior use of antiplatelets) and atrial fibrillation, onset to treatment time, and thrombolysis.

who have concurrent statin use and receive thrombolysis therapy have a threefold increase in sICH (OR_{adjusted} 3.24, 95% CI 2.06–5.09). This risk seemed to be driven by the effect of thrombolysis therapy alone (OR_{adjusted} 2.55), and not by any increase in risk seen in the patients who are treated with statins at the moment of the event (OR_{adjusted} 1.24). Similar results were obtained under propensity matching. Addition of prior statin use did not improve the capacity of the regression model for prediction of sICH that included patient-related risk factors (table e-4).

New initiation of statins and hemorrhagic stroke during follow-up. A total of 52 patients had a postacute ICH during follow-up of 90 days (0.7%). Median time between stroke onset and occurrence of postacute ICH was 20 days (IQR 16–40). In univariate comparison, rate of postacute ICH was not higher among patients with new initiation of statins (1.1% vs 0.7%, $p = 0.23$). New initiation of statins was not

strongly associated with postacute ICH (hazard ratio [HR]_{adjusted} 1.60, 95% CI 0.70–3.65, figure 2) in a Cox regression analysis that accounted for age, sex, NIHSS, hypertension, atrial fibrillation, new initiation of antiplatelets or anticoagulation, and trial affiliation. Due to the low event rate, no reasonable analysis could be performed in the cohort matched according to propensity scores.

Statin use before and newly initiated after stroke and outcome at 90 days. Ninety-day mortality was 19.1% ($n = 1,628$). In the propensity matched cohort, patients with prior statin use were less likely to die within 3 months (19.7% vs 24.2%, $p = 0.005$, figure e-1). In a multiple Cox regression analysis, prior statin use was not associated with a strong effect on the risk of mortality (adjusted HR 0.84, 95% CI 0.70–1.00, figure 2), with larger effects found with more potent statin types as compared to no statin (table e-3). Prior statin use was associated with a small shift toward better 90-day outcomes on the mRS in an adjusted ordinal regression analysis (OR_{unadjusted} 0.95, 0.86–1.06; OR_{adjusted} 1.13, 1.01–1.27; OR_{PPM} 1.14, 0.99–1.31, figure e-1).

Patients newly started on statins early after stroke had a lower mortality at 90 days (HR_{unadjusted} 0.49, 95% CI 0.38–0.62; HR_{adjusted} 0.68, 95% CI 0.52–0.88; HR_{PPM} 0.67, 95% CI 0.46–0.97, figure 2). When categorized according to potency, highly potent statins were associated with reduced mortality ($p = 0.04$), but less potent statin types were not ($p = 0.11$). New initiation of statin treatment within 3 days after stroke was associated with a more favorable distribution of 90-day mRS (OR_{unadjusted} 1.63, 95% CI 1.41–1.89), which attenuated after adjustment for confounding or PPM (OR_{adjusted} 1.20, 95% CI 1.03–1.40; OR_{PPM} 1.21, 95% CI 0.98–1.50; figure e-1).

DISCUSSION In this large sample of anonymized clinical trial data, we reported 4 major observations. First, although crude comparisons suggested a potential association between prior statin use and acute hemorrhagic complications after stroke, the association was attenuated when multiple regression analysis

Table 2 Interaction analysis between prior statin use and treatment with thrombolysis regarding early symptomatic intracerebral hemorrhage (sICH)

Prior statin use	Thrombolysis treatment	Unmatched cohort			PPM cohort		
		No.	sICH rate, %	Adjusted OR (95% CI)	No.	sICH rate, %	Adjusted OR (95% CI)
No	No	5,206	1.6	1 (Reference)	968	2.1	1 (Reference)
Yes	No	746	2.3	1.24 (0.73–2.12)	745	2.3	1.14 (0.57–2.28)
No	Yes	2,020	4.3	2.55 (1.79–3.64)	340	4.1	2.04 (0.91–2.55)
Yes	Yes	563	6.0	3.24 (2.06–5.09)	563	6.0	3.12 (1.08–6.16)

Abbreviations: CI = confidence interval; OR = odds ratio; PPM = propensity matched cohort.

Figure 2 Models for the association between new initiation of statins and postacute intracerebral hemorrhage (ICH) (A) and the association between statin exposure and mortality within 90 days (B)

^aCox regression analysis adjusted for age, sex, NIH Stroke Scale (NIHSS), atrial fibrillation, hypertension, new initiation of antiplatelets, new initiation of oral anticoagulation, and trial affiliation. ^bCox regression analysis adjusted for variables used for matching (age, sex, baseline NIHSS, hypertension, diabetes, previous myocardial infarction, prior use of antiplatelets, prior oral anticoagulation) and atrial fibrillation, history of stroke, onset to treatment time, thrombolysis, and trial affiliation. ^cCox regression adjusted for variables used for matching (age, sex, baseline NIHSS, thrombolysis, atrial fibrillation, previous stroke, new initiation of antiplatelets, angiotensin-converting enzyme inhibitors, and oral anticoagulation) and diabetes, hypertension, myocardial infarction, onset to treatment time, and trial affiliation.

or PPM adjusted for baseline differences. Second, the overall safety of thrombolysis was not altered among patients with and without prior statin use. Third, early initiation of statin treatment poststroke in statin-naïve patients was not significantly associated with occurrence of postacute hemorrhagic stroke during 90 days of follow-up. Fourth, statin exposure in the acute phase poststroke was associated with reduced mortality at 90 days.

We did not find an excess risk of early hemorrhagic transformation with prevalent statin treatment at stroke onset. There was no evidence of an additional risk of acute hemorrhagic complications after thrombolysis attributable to statin treatment compared to the baseline risk observed in thrombolysed patients. Of note, all unadjusted point estimates indicated a positive association between prior statin use and hemorrhagic complications. However, these associations were reduced in size and lost statistical significance after adjustment for patient-related characteristics. Therefore, we conclude that the observed crude association is mainly caused by the

characteristics of the typical patient on statins that indicate a high-risk constellation for sICH. Altogether, our findings suggest that statin use is probably a marker, but not the cause of an increased risk of ICH. Our observation that point estimates were higher in patients using more potent statins also fits within this concept. Recently, observational data from 2 large European thrombolysis centers suggested an increased risk of sICH among patients using high-dose statins (i.e., capable of reducing cholesterol of more than 45%).¹² Because no exact data on statin dosages were available in our cohort, the analyses were based on average cholesterol-lowering potency of the respective statin types. Therefore, these findings have to be considered exploratory in nature and interpreted with caution.

To date, data on the acute effects of early statin treatment after an ischemic stroke on postacute hemorrhagic complications are sparse. We found no evidence of a strongly increased risk of postacute ICH among patients started on statins shortly after stroke (HR 1.6, 95% CI 0.7–3.7). Overall, this reinforces the safety of early initiation of statins early after ischemic stroke, particularly since we analyzed a cohort with relatively severe strokes, median NIHSS >10. In accordance with our observations, no increased risk of ICH within 7 days was found among patients allocated to statins within 12 hours after stroke in a pilot randomized trial.¹⁷ Our findings are also in line with the growing body of literature suggesting that statin therapy in general is probably not associated with a clinically relevant risk of future ICH, also in cohorts of patients with recent history of ischemic and even hemorrhagic stroke.^{18–20}

The potential neuroprotective role of early statin treatment after stroke is still debated.^{21,22} In this non-randomized study using PPM, we observed a signal towards lower 90-day mortality and improved functional outcomes among prevalent statin users at stroke onset and newly started on statins early after stroke, especially when more potent statins were used. This finding is in accordance with a growing body of literature suggesting improved outcomes in stroke patients treated with statins. Recently, an observational study conducted in hospitals operated by Kaiser Permanente Northern California found that lower mortality was observed when statin treatment was initiated during hospitalization for ischemic stroke.²³ In addition, a meta-analysis found an association of statin treatment after stroke with lower mortality within 90 days if limited to observational studies only. Interestingly, however, this meta-analysis did not observe such an association in existing pilot RCTs.² This suggests that uncontrolled bias may be relevant in previous observational studies and emphasizes the need for appropriate adjustment for

severity markers or sufficiently matched analyses in the future. In contrast to prior observational studies, we used PPM, which also included matching for early initiation of other medications like oral anticoagulation or ACE inhibitors in order to account for potential confounding by indication bias. Still, we cannot exclude that unobserved bias, especially those confounded by indication, may have influenced our findings.

Besides the size of the VISTA Acute database, other major advantages are the high proportion of severe strokes presenting in an early time window and the high standard of data collection that is required in clinical trials. The limitations of our study are inherent to the design, since we retrospectively analyzed pooled data from trials that were not primarily designed to address our research question. As a consequence, the outcomes were dependent on raw AE or SAE data records. Although rigorously documented, our definition of sICH was not founded on neuroimaging data and details of the characteristics and immediate clinical consequences of the events are missing. Patients not treated with IV thrombolysis generally did not undergo follow-up routine cerebral imaging for detection of hemorrhagic transformation or minor recurrent strokes unless there was symptomatic deterioration. Therefore, sICH and in particular asymptomatic ICH events may have been underreported in the patients without thrombolysis. However, the definition used in our cohort achieved a frequency of sICH similar to that in RCTs.²⁴ Although we did not consider subdural and subarachnoid hemorrhage for analysis, our findings regarding postacute ICH are limited by the fact that we did not have information on the exact pathophysiology and location of postacute ICH. It has been suggested that risk of lobar ICH and of lobar cerebral microbleeds might be higher among statin users.^{4,25} Moreover, the length of follow-up may have been too short to detect such long-term effects. Furthermore, the frequency of prior statin use in our study was lower than expected from contemporary observational data.¹¹ This might be inherent to the age of available trial data within VISTA, with some conducted before the SPARCL trial era.²⁶ Although medical adherence is likely to be high under controlled trial settings, data about statin adherence were not available. Statin discontinuation results in an overshoot reversal of many beneficial pleiotropic effects in experimental settings.²⁷ Previous clinical studies showed that stroke patients who discontinued their statin treatment early after ischemic stroke were at an increased risk of unfavorable outcome and mortality after 3 months.^{28,29} Thus, nonadherence to statins during follow-up may have reduced our observed beneficial effects on mortality and functional outcome.

Taken together, prior statin use was not associated with early poststroke hemorrhagic complications. There was no evidence of excess risk of sICH in the setting of treatment with IV thrombolysis, which supports overall safety of thrombolysis among prevalent statin users. In addition, our data reassure on the safety of early initiation of statin treatment after stroke with regard to postacute hemorrhagic strokes and support an association of statin treatment with lower 90-day mortality. Whether early poststroke initiation of statins improves outcomes and reduces mortality has yet to be proven in RCT settings.

AUTHOR CONTRIBUTIONS

Dr. Scheitz had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Drs. Scheitz, Nolte, Siegerink, MacIsaac, Endres, Lees, VISTA collaborators. Analysis or interpretation of data: all authors. Acquisition of data: VISTA collaborators. Drafting of the manuscript: Dr. Scheitz. Critical revision of the manuscript for important intellectual content: all authors. Statistical plan and analysis: Drs. Scheitz, Siegerink, MacIsaac. Administrative, technical, or material support: Drs. Endres, MacIsaac, Abdul-Rahim, Lees. Obtained funding: Drs. Scheitz, Lees. Study supervision: Drs. Endres, Lees, Nolte.

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