The THRombolysis and STatins (THRaST) study

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ABSTRACT

Objective: To assess the impact on stroke outcome of statin use in the acute phase after IV thrombolysis.

Methods: Multicenter study on prospectively collected data of 2,072 stroke patients treated with IV thrombolysis. Outcome measures of efficacy were neurologic improvement (NIH Stroke Scale [NIHSS] ≤ 4 points from baseline or NIHSS = 0) and major neurologic improvement (NIHSS ≤ 8 points from baseline or NIHSS = 0) at 7 days and favorable (modified Rankin Scale [mRS] ≤ 2) and excellent functional outcome (mRS ≤ 1) at 3 months. Outcome measures of safety were 7-day neurologic deterioration (NIHSS ≥ 4 points from baseline or death), symptomatic intracerebral hemorrhage type 2 with NIHSS ≥ 4 points from baseline or death within 36 hours, and 3-month death.

Results: Adjusted multivariate analysis showed that statin use in the acute phase was associated with neurologic improvement (odds ratio [OR] 1.68, 95% confidence interval [CI] 1.26–2.25; $p < 0.001$), major neurologic improvement (OR 1.43, 95% CI 1.11–1.85; $p = 0.006$), favorable functional outcome (OR 1.63, 95% CI 1.18–2.26; $p = 0.003$), and a reduced risk of neurologic deterioration (OR: 0.31, 95% CI 0.19–0.53; $p < 0.001$) and death (OR 0.48, 95% CI 0.28–0.82; $p = 0.007$).

Conclusion: Statin use in the acute phase of stroke after IV thrombolysis may positively influence short- and long-term outcome. ***Neurology*® 2013;80:655–661**

GLOSSARY

CI = confidence interval; **MCA** = middle cerebral artery; **mRS** = modified Rankin Scale; **NIHSS** = NIH Stroke Scale; **OR** = odds ratio; **OTT** = onset to treatment; **rtPA** = recombinant tissue plasminogen activator; **sICH** = symptomatic intracerebral hemorrhage; **SITS-MOST** = Safe Implementation of Thrombolysis in Stroke-Monitoring Study; **THRaST** = THRombolysis and STatins study.

Statins are recommended for primary and secondary stroke prevention in patients at risk of cerebrovascular events.[1] In addition to reducing the risk of first and recurrent ischemic stroke, statin treatment may also improve outcome through pleiotropic non-cholesterol-dependent effects.[2]

An association between statin use before stroke and favorable outcome has been previously reported.[3–5] Moreover, a prospective clinical trial showed that statin withdrawal during the first 3 days after a stroke event was associated with increased risk of death or dependency at 3 months.[6]

To date, very few studies have investigated the effect of statin use in the acute phase on ischemic stroke outcome.[7–9] The Stroke Prevention with Aggressive Reductions in Cholesterol Levels (SPARCL) trial showed a trend toward less severity for outcome 90 days after stroke with atorvastatin administration (80 mg), compared with placebo, in patients having a stroke during the trial.[10]

So far, few studies have assessed the efficacy and safety of statin treatment in ischemic stroke patients treated with IV thrombolysis. Two recent meta-analyses showed that prior statin use may increase the risk of symptomatic intracerebral hemorrhage (sICH) within 36 hours after IV recombinant tissue plasminogen activator (rtPA), though without influencing 3-month functional outcome.[11,12] Two large observational studies reported that previous treatment with statin was not an independent predictor of functional outcome or of ICH.[13,14]

The aim of the THRombolysis and STatins (THRaST) study was to assess the impact of statin use in the acute phase of ischemic stroke on clinical outcome in patients treated with IV thrombolysis.

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METHODS THRaST was a retrospective multicenter study based on data prospectively collected from 2,072 acute ischemic stroke patients who had received IV thrombolysis, after informed consent. All patients were registered in the Safe Implementation of Thrombolysis in Stroke–International Stroke Thrombolysis Register (SITS-ISTR)[15] by 45 Italian centers as of October 2010.

The statin group was defined as patients receiving statin within 72 hours after IV thrombolysis; the no statin group was defined as patients who had started statin therapy before the stroke event but had discontinued its use after IV rtPA or those who had never used statins. The choice of statin administration regimen was at the discretion of the treating physician, who decided to start statin treatment in the acute phase after IV thrombolysis (started group), or to continue with previous treatment using the same type and dose (continued group), or to switch to a higher dose or another type of statin in the acute phase after IV rtPA (switched group), via oral administration or nasogastric tube. All patients treated with statin in the acute phase continued to receive the same type and dosage of statin at least until hospital discharge.

Exclusion criteria were those of the Safe Implementation of Thrombolysis in Stroke–Monitoring Study (SITS-MOST) protocol,[16] except for the 80-year age limit, onset to treatment (OTT) time for IV rtPA from 3 to 4.5 hours from symptom onset, prior stroke within the last 3 months, history of stroke and concomitant diabetes, and aggressive management (IV medication) to reduce blood pressure (systolic blood pressure ≤185 mm Hg or diastolic blood pressure ≤110 mm Hg) before IV rtPA.

Patients with a modified Rankin Scale (mRS) score >2 before the stroke event were excluded. Patients were also excluded if they had started statin therapy before stroke but continued or switched therapy after discontinuation during the first 72 hours poststroke or had started statin therapy after 72 hours poststroke.

Clinical characteristics of the patients. Clinical characteristics of the patients included 1) demographic findings; 2) functional dependence (mRS score ≥ 1) before stroke; 3) OTT time for IV rtPA; 4) deviations from the SITS-MOST protocol; 5) vascular risk factors; 6) therapy before stroke; 7) data before IV rtPA, including the degree of stroke severity according to the NIH Stroke Scale (NIHSS), and CT findings before thrombolysis such as early signs of ischemia (loss of gray/white matter distinction, hypodensity, or sulcal swelling) or middle cerebral artery (MCA) hyperdensity; 8) lipid profile within 72 hours after stroke; 9) statin group and no statin group; 10) statin administration regimen, i.e., starting, continuing, or switching statins in the acute phase; 11) type/dose of statin administered in the acute stroke phase; 12) OTT time for statin in the acute phase.

The primary efficacy and safety endpoints included short- and long-term outcome.

The short-term efficacy endpoints were neurologic improvement (NIHSS ≤4 points from baseline or NIHSS score of 0)[17] and major neurologic improvement (NIHSS ≤8 points from baseline or NIHSS score of 0)[18] at 7 days. The long-term efficacy endpoints were favorable functional outcome (mRS ≤ 2)[16] and excellent functional outcome (mRS ≤ 1)[13] at 3 months.

The short-term safety endpoints were neurologic deterioration (NIHSS ≥4 points from baseline or death)[19] at 7 days and sICH (local or remote parenchymal hematoma type 2 on the imaging scan obtained 22 to 36 hours after treatment, with NIHSS score increase of ≥4 points from baseline or the lowest value in the first 24 hours or leading to death).[16] The long-term safety endpoint was death at 3 months.[16]

Statistical analyses. We performed all statistical analyses using the Statistical Package for Social Sciences v 16.0 for Windows (SPSS, Chicago, IL). We examined differences between the 2 groups stratified according to statin use in the acute phase of stroke using the χ^2 test and Kruskal-Wallis one-way analysis of variance.

We estimated the prognostic importance of statin use by calculating the odds ratio (OR) with 2-sided 95% confidence interval (CI) for each efficacy and safety endpoint, establishing statistical significance at 2-tailed 0.05 level ($p < 0.05$). Due to the nonrandomized design of the study, we performed a post hoc adjusted analysis (logistic regression) of the efficacy and safety endpoints using a forward stepwise method that included established predictors (age, OTT time for IV rtPA, SITS-MOST deviations, baseline NIHSS score), all the unbalanced clinical characteristics between the statin group and the no statin group, and all variables with a probability value <0.10 on univariate analysis.

We then performed univariate statistical analysis of the factors associated with 7-day major neurologic improvement and those associated with 3-month excellent outcome using the χ^2 test (Fisher exact test) for different statin administration regimen, statin type/dose, and OTT time in the statin group. To identify independent predictors of 7-day major neurologic improvement and those associated with 3-month excellent outcome, we performed multivariate analysis including in the analysis the established predictors (age, OTT time for IV rtPA, SITS-MOST protocol violations, baseline NIHSS score) and the clinical variables with a probability value <0.10 on univariate analysis.

Finally, because statin withdrawal is associated with increased risk of death or dependence at 3 months, we repeated all the analyses after excluding from the no statin group those patients who had stopped statin therapy after rtPA.

RESULTS Of the 2,072 patients who entered into the study, 839 (40.5%) were treated with statins in the acute phase of stroke: 542 (26.2%) in the started group, 203 (9.8%) in the continued group, and 94 (4.5%) in the switched group. The statin type and dose were atorvastatin 10–20 mg/day in 260 (12.5%) patients, atorvastatin 40–80 mg/day in 262 (12.6%), simvastatin 10–40 mg/day in 238 (11.5%), and other statins in 79 (3.8%). Statin administration was started within 24 hours after IV thrombolysis in 531 (25.6%) patients, between 24 and 48 hours in 153 (7.4%), and between 48 and 72 hours in 155 (7.5%). In the no statin group, 1,170 (56.5%) patients had never used statins, either before the stroke event or after thrombolysis, and 63 (3%) had used statins before stroke but discontinued the treatment after IV rtPA.

Table 1 shows the clinical characteristics of the cohort and of 2 groups of patients.

Hypertension and hypercholesterolemia were more frequent in the statin group, whereas atrial fibrillation was more frequent in the no statin group. The statin group patients were more often treated with antiplatelet and antihypertensive therapy before the stroke event, and more frequently received thrombolysis beyond 3 hours after stroke onset. Total cholesterol and low-density lipoprotein levels within 72 hours after stroke were higher in the statin group. The patients not receiving statins had a higher baseline NIHSS score and presented more often with a hyperdense MCA sign before thrombolysis.

Supplemental data at www.neurology.org

Table 1 Clinical characteristics of the THRaST patients[a]

	All patients (n = 2,072)	Acute statin (n = 839)	No acute statin (n = 1,233)	p Value
Demographics				
Age, y	66.6 ± 12.5	67.3 ± 10.6	66.1 ± 13.7	0.919
Male	1,210 (58.4)	505 (60.2)	705 (57.2)	0.174
mRS >0 prestroke	210 (10.1)	79 (9.4)	131 (10.6)	0.415
OTT time for IV rtPA	156.9 ± 39.9	157.9 ± 41.6	156.1 ± 38.7	0.579
SITS-MOST deviations				
Age >80 y	140 (6.8)	49 (5.8)	91 (7.4)	0.182
OTT time for IV rtPA 3–4.5 h	327 (15.8)	160 (19.1)	167 (13.5)	0.001
Prior stroke <3 mo	22 (1.1)	11 (1.3)	11 (0.9)	0.388
Prior stroke and diabetes	32 (1.5)	10 (1.2)	22 (1.8)	0.365
IV antihypertensive pre-IV rtPA	99 (4.8)	46 (5.5)	53 (4.3)	0.248
Vascular risk factors				
Hypertension	1,301 (62.9)	595 (71.0)	706 (57.3)	<0.001
Diabetes mellitus	344 (16.6)	147 (17.5)	197 (16.0)	0.367
Hypercholesterolemia	786 (38.0)	478 (57.0)	308 (25.0)	<0.001
Current smoking	503 (24.3)	209 (24.9)	294 (23.9)	0.602
Atrial fibrillation	462 (22.3)	146 (17.4)	316 (25.6)	<0.001
Prior stroke >3 mo	178 (8.6)	65 (7.7)	113 (9.2)	0.265
Congestive heart failure	137 (6.6)	57 (6.8)	80 (6.5)	0.788
Prestroke therapy				
Antiplatelet	735 (35.5)	344 (41.1)	391 (31.7)	<0.001
Antihypertensive	1,034 (50.0)	467 (55.7)	567 (46.0)	<0.001
Data before IV rtPA				
NIHSS score	12.6 ± 6.0	11.7 ± 5.9	13.3 ± 6.1	<0.001
CT sign of current infarct	138 (7.4)	66 (8.5)	72 (6.6)	0.151
MCA hyperdensity	392 (20.2)	138 (17.6)	254 (22.0)	0.021
Blood glucose, mg/dL	129.7 ± 43.2	129.6 ± 41.1	129.7 ± 44.6	0.323
SBP, mm Hg	146.6 ± 20.2	146.6 ± 19.6	146.6 ± 20.7	0.779
DBP, mm Hg	80.3 ± 12.0	80.6 ± 11.8	80.2 ± 12.2	0.389
Lipid profile <72 h				
Total cholesterol, mg/dL	192.0 ± 44.3	201.9 ± 47.5	184.9 ± 40.4	<0.001
LDL, mg/dL	119.2 ± 40.0	126.7 ± 44.4	112.8 ± 34.7	<0.001
HDL, mg/dL	49.5 ± 20.3	49.0 ± 17.7	49.9 ± 22.2	0.354

Abbreviations: DBP = diastolic blood pressure; HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; MCA = middle cerebral artery; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; OTT = onset to treatment; rtPA = recombinant tissue plasminogen activator; SBP = systolic blood pressure; SITS-MOST = Safe Implementation of Thrombolysis in Stroke–Monitoring Study; THRaST = THRombolysis and STatins study.
[a] Results are expressed as number (%) or mean ± SD.

We collected data on neurologic improvement, major neurologic improvement, and neurologic deterioration at 7 days in 2,055 (99.2%) patients, sICH within 36 hours in 2,054 (99.1%), and mRS score at 3 months in 1,844 (89%).

At 7 days, neurologic improvement was noted in 1,405 (68.4%) patients, major neurologic improvement in 922 (44.8%), and neurologic deterioration in 218 (10.6%). On adjusted multivariate analysis, statin use in the acute phase was associated with neurologic improvement (OR 1.68, 95% CI 1.26–2.25; $p < 0.001$), major neurologic improvement (OR 1.43, 95% CI 1.11–1.85; $p = 0.006$), and reduced risk of neurologic deterioration (OR 0.31, 95% CI 0.19–0.53; $p < 0.001$) (table 2).

At 3 months, favorable functional outcome was noted in 1,099 (59.6%) patients and excellent

Table 2 Multivariate analysis: Efficacy and safety of statin use in the acute phase of stroke[a]

	Statin use in the acute phase		Unadjusted analysis		Adjusted analysis	
	Yes (n = 839)	No (n = 1,233)	OR (95% CI)	p Value	OR (95% CI)	p Value
Short-term efficacy						
Neurologic improvement	632/832 (76.0)	773/1,223 (63.2)	1.61 (1.19–2.18)	0.002	1.68 (1.26–2.25)	<0.001
Major neurologic improvement	422/832 (50.7)	500/1,223 (40.9)	1.54 (1.16–2.04)	0.003	1.43 (1.11–1.85)	0.006
Long-term efficacy						
Favorable functional outcome	523/746 (70.1)	576/1,098 (52.5)	1.62 (1.14–2.30)	0.008	1.63 (1.18–2.26)	0.003
Excellent functional outcome	402/746 (53.9)	438/1,098 (39.9)	1.29 (0.92–1.80)	0.141	1.28 (0.94–1.73)	0.121
Short-term safety						
Neurologic deterioration	42/832 (5.0)	176/1,223 (14.4)	0.27 (0.16–0.46)	<0.001	0.31 (0.19–0.53)	<0.001
sICH	10/832 (1.2)	47/1,222 (3.8)	0.56 (0.21–1.53)	0.261	0.52 (0.20–1.34)	0.176
Long-term safety						
Death	43/746 (5.8)	166/1,098 (15.1)	0.45 (0.26–0.79)	0.005	0.48 (0.28–0.82)	0.007

Abbreviations: CI = confidence interval; OR = odds ratio; sICH = symptomatic intracerebral hemorrhage.
[a] Results are expressed as the number of events divided by the total number minus the missing cases (%) or OR (95% CI).

functional outcome in 840 (45.5%). On adjusted multivariate analysis, statin use in the acute phase was associated with favorable functional outcome (OR 1.63, 95% CI 1.18–2.26; $p = 0.003$), but not with excellent functional outcome (table 2).

Neurologic deterioration at 7 days was noted in 218 (10.5%) patients and sICH within 36 hours in 57 (2.8%). On adjusted multivariate analysis, statin use in the acute phase was associated with a reduced risk of neurologic deterioration (OR 0.31, 95% CI 0.19–0.53; $p < 0.001$), but without affecting the risk of sICH occurrence (table 2).

Within 3 months, 209 (10.1%) patients died. On adjusted analysis, statin use in the acute phase was associated with a reduced risk of death (OR 0.48, 95% CI 0.28–0.82; $p = 0.007$) (table 2).

Outcome according to statin regimen, statin type/dose, and OTT time for the statin group is reported in tables 3 and 4. We collected data on major neurologic improvement at 7 days in 832 (99.2%) patients, and

Table 3 Univariate and multivariate analysis: 7-day major neurologic improvement according to statin administration regimen, statin type/dose, and OTT time for statin administration in the acute phase[a]

	Major neurologic improvement		Univariate analysis, p value	Multivariate analysis	
	Yes (n = 422)	No (n = 410)		OR (95% CI)	p Value
Administration regimen					
Starting statins	272 (64.5)	265 (64.6)	0.507	1.18 (0.70–1.99)	0.531
Continuing statins	103 (24.4)	99 (24.1)	0.936	1.01 (0.60–1.72)	0.968
Switching statins	47 (11.1)	46 (11.2)	0.529	0.79 (0.43–1.44)	0.438
Statin type/dose, mg					
Atorvastatin 10–20	129 (30.6)	126 (30.7)	0.510	0.87 (0.57–1.32)	0.502
Atorvastatin 40–80	150 (35.5)	110 (26.8)	0.007	1.52 (1.04–2.23)	0.032
Simvastatin 10–40	104 (24.6)	134 (32.7)	0.011	0.80 (0.53–1.22)	0.303
Other statins	39 (9.2)	40 (9.8)	0.814	1.08 (0.48–2.41)	0.860
OTT time for statin administration, h					
<24	279 (66.1)	251 (61.2)	0.150	1.19 (0.78–1.84)	0.421
24–48	75 (17.8)	76 (18.5)	0.788	0.96 (0.57–1.61)	0.868
48–72	68 (16.1)	83 (20.2)	0.127	0.80 (0.46–1.37)	0.406

Abbreviations: CI = confidence interval; OR = odds ratio; OTT = onset to treatment.
[a] Results are expressed as number (%) or OR (95% CI).

Table 4 Univariate and multivariate analysis: 3-month excellent functional outcome according to statin administration regimen, statin type/dose, and OTT time for statin administration in the acute phase[a]

	Excellent functional outcome		Univariate analysis, *p* value	Multivariate analysis	
	Yes (n = 402)	No (n = 344)		OR (95% CI)	*p* Value
Administration regimen					
Starting statins	264 (65.7)	216 (62.8)	0.443	1.03 (0.56–1.89)	0.933
Continuing statins	95 (23.6)	90 (26.2)	0.445	1.11 (0.60–2.08)	0.738
Switching statins	43 (10.7)	38 (11.0)	0.906	0.84 (0.41–1.72)	0.630
Statin type/dose, mg					
Atorvastatin 10–20	126 (31.3)	99 (28.8)	0.472	1.06 (0.64–1.76)	0.811
Atorvastatin 40–80	130 (32.3)	93 (27.0)	0.128	0.89 (0.53–1.50)	0.665
Simvastatin 10–40	110 (27.4)	112 (32.6)	0.128	1.27 (0.77–2.08)	0.352
Other statins	36 (9.0)	40 (11.6)	0.274	0.49 (0.18–1.30)	0.151
OTT time for statin administration, h					
<24	285 (70.9)	195 (56.7)	<0.001	1.88 (1.20–2.96)	0.006
24–48	62 (15.4)	75 (21.8)	0.029	0.65 (0.29–1.42)	0.278
48–72	55 (13.7)	74 (21.5)	0.006	0.79 (0.42–1.51)	0.480

Abbreviations: CI = confidence interval; OR = odds ratio; OTT = onset to treatment.
[a] Results are expressed as number (%) or OR (95% CI).

excellent functional outcome at 3 months in 746 (88.9%), in the statin group. Major neurologic improvement was noted in 422 (50.7%) patients and excellent functional outcome in 402 (53.9%).

There was no difference in statin regimens on major neurologic improvement. Although the association between statin treatment and excellent functional outcome tended to be greater when started within 24 hours, the 95% CIs overlapped with OTT times for statin administration of up to 72 hours.

The results did not change when the analyses were repeated after excluding the 63 patients in the no statin group who had stopped statin therapy after thrombolysis (table e-1 on the *Neurology*® Web site at www.neurology.org).

DISCUSSION Our study shows that, in patients treated with IV thrombolysis, statin use in the acute phase of stroke was associated with neurologic improvement, major neurologic improvement, and decreased risk of neurologic deterioration at 7 days, and with favorable functional outcome and decreased risk of death at 3 months, while the risk of sICH was similar. The results did not change when the no statin group patients who had stopped statins after rtPA administration were excluded from the analysis.

These findings are in line with those from a recent single-center study involving a smaller cohort of patients which showed that starting statin treatment in the acute phase after IV thrombolysis, compared with no use of statin, either before or in the acute phase, may improve short- and long-term outcome.[20] In addition, our data also agree with previous observations in nonthrombolysed patients which showed that statin continuation in the acute phase of stroke, compared with discontinuation of previous treatment or no statin use, was associated with improved outcome and decreased risk of short-term neurologic deterioration and long-term death.[6,9]

A weakness of the present study is that there were some intergroup imbalances in variables known to be related to unfavorable outcome after IV rtPA. Specifically, stroke severity and prevalence of atrial fibrillation were both higher in the no statin group, while prior antihypertensive use and history of hypercholesterolemia were higher in the statin group. Indeed, recent studies have reported a possible negative impact of a history of hypercholesterolemia on outcome,[21] and a possible association between prior antihypertensive treatment and poorer outcome in patients with low baseline systolic blood pressure.[22] However, the patients in the one study had received intra-arterial thrombolysis with mechanical embolectomy[21] and those in the other had received no thrombolytic treatment.[22]

Our data also agree with a previous study which did not report an increased risk of sICH in thrombolysed patients receiving statin treatment in the acute phase.[20] Admittedly, since we assessed sICH within 36 hours after IV thrombolysis but not later, we might have underestimated the risk of occurrence of sICH in the statin group, because some patients started or continued or switched the treatment beyond 36 hours. However, since statin use was associated with a decreased risk of neurologic deterioration at 7 days, we speculate that such treatment in the acute phase may not have favored the development

of sICH, in accordance with the SITS-MOST definition, which we adopted, and which includes intracerebral hemorrhage type 2 and an NIHSS ≥4-point increase from baseline or death within 36 hours.[16]

Our study also shows that, in thrombolysed patients, there was no difference in the effect of different statin regimens on major neurologic improvement at 7 days, and that statin use within 72 hours, whatever the type or dose, was associated with excellent functional outcome at 3 months, although the benefit might be greater when started within 24 hours.

In rat embolic stroke models, a combination of short-term high-dose atorvastatin and tPA significantly reduced infarct volume and improved neurologic function. Atorvastatin favored the maintenance of cerebral vascular patency and integrity, most likely by reducing thrombosis secondary to tPA administration.[23] In other models, statin administration in the acute stroke phase enhanced vascular endothelial growth factor expression, neurovascularization, proliferation of neural progenitor cells, and synaptogenesis.[24]

We suggest that these potential neuroprotective effects suggested by experimental models may be more effective if statin treatment is given starting from the very early phase of stroke, thus limiting brain damage and favoring tissue repair after ischemic injury in patients treated with IV thrombolysis, though not impacting on vessel patency.

This is the largest ever study to address the prognostic value of statin use in the acute phase in stroke patients treated with IV thrombolysis. The large sample size permitted correction for several potentially confounding variables, including age, OTT time for IV rtPA, SITS-MOST deviations, and baseline NIHSS score. Nevertheless, we are aware of several limitations of the study. It was an exploratory analysis and not a randomized controlled trial designed to investigate the benefits vs the risk of statin use during the acute phase in stroke patients receiving IV thrombolysis. The statin group differed from the no statin group with regard to several prognostic variables. We tried to address these imbalances by conducting an adjusted analysis for efficacy and safety endpoints. Moreover, adherence to statin therapy prescribed during hospitalization was not assessed after discharge, so we cannot exclude that patients who started high-dose statin therapy during hospitalization may have switched to a lower dose after discharge, or may have resumed therapy with the same statin type they had been taking before the stroke event. Finally, as mentioned above, the occurrence of sICH evaluated only within the first 36 hours after IV thrombolysis is an additional limitation.

Nonetheless, the present study suggests that statin use in the acute phase after IV thrombolysis may be safe and may have a favorable impact on short- and long-term outcome. The early initiation of statin therapy might be the treatment of choice for thrombolysed patients. A large-scale clinical trial will be needed to validate these results.

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DISCLOSURE

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REFERENCES

1. Prinz V, Endres M. Statins and stroke: prevention and beyond. Curr Opin Neurol 2011;24:75–80.
2. Endres M. Statins and stroke. J Cereb Blood Flow Metab 2005;25:1093–1110.
3. Lakhan SE, Bagchi S, Hofer M. Statins and clinical outcome of acute ischemic stroke: a systematic review. Int Arch Med 2010;3:22.
4. Sacco S, Toni D, Bignamini AA, et al. Effect of prior medical treatments on ischemic stroke severity and outcome. Funct Neurol 2011;26:133–139.
5. Biffi A, Devan WJ, Anderson CD, Cortellini L, Furie KL, Rosand J, et al. Statin treatment and functional outcome after ischemic stroke: case-control and meta-analysis. Stroke 2011;42:1314–1319.
6. Blanco M, Nombela F, Castellanos M, et al. Statin treatment withdrawal in ischemic stroke: a controlled randomized study. Neurology 2007;69:904–910.
7. Montaner J, Chacón P, Krupinski J, et al. Simvastatin in acute phase of ischemic stroke: a safety and efficacy pilot trial. Eur J Neurol 2008;15:82–90.
8. Lampl Y, Lorberboym M, Gilad R, et al. Early outcome of acute ischemic stroke in hyperlipidemic patients under atorvastatin versus simvastatin. Clin Neuropharmacol 2010;33:129–134.
9. Ní Chróinín D, Callaly EL, Duggan J, et al. Association between acute statin therapy, survival, and improved functional outcome after ischemic stroke: the North Dublin Population Stroke Study. Stroke 2011;42:1021–1029.
10. Goldstein LB, Amarenco P, Zivin J, et al. Statin treatment and stroke outcome in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial. Stroke 2009;40:3526–3531.
11. Martinez-Ramirez S, Delgado-Mederos R, Marín R, et al. Statin pretreatment may increase the risk of symptomatic intracranial haemorrhage in thrombolysis for ischemic stroke: results from a case-control study and a meta-analysis. J Neurol 2012;259:111–118.
12. Cordenier A, De Smedt A, Brouns R, et al. Pre-stroke use of statins on stroke outcome: a meta-analysis of observational studies. Acta Neurol Belg 2011;111:261–267.
13. Engelter ST, Soinne L, Ringleb P, et al. IV thrombolysis and statins. Neurology 2011;77:888–895.
14. Rocco A, Sykora M, Ringleb P, Diedler J. Impact of statin use and lipid profile on symptomatic intracerebral haemorrhage, outcome and mortality after intravenous thrombolysis in acute stroke. Cerebrovasc Dis 2012;33:362–368.
15. Wahlgren N, Ahmed N, Dávalos A, et al. Thrombolysis with alteplase 3-4.5 h after acute ischaemic stroke (SITS-ISTR): an observational study. Lancet 2008;372:1303–1309.
16. Wahlgren N, Ahmed N, Dávalos A, et al. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. Lancet 2007;369:275–282.
17. Kharitonova T, Mikulik R, Roine RO, Soinne L, Ahmed N, Wahlgren N; Safe Implementation of Thrombolysis in Stroke Investigators. Association of early National Institutes of Health Stroke Scale improvement with vessel recanalization and functional outcome after intravenous thrombolysis in ischemic stroke. Stroke 2011;42:1638–1643.
18. Saposnik G, Di Legge S, Webster F, Hachinski V. Predictors of major neurologic improvement after thrombolysis in acute stroke. Neurology 2005;65:1169–1174.
19. Delgado MG, Michel P, Naves M, et al. Early profiles of clinical evolution after intravenous thrombolysis in an unselected stroke population. J Neurol Neurosurg Psychiatry 2010;81:282–285.
20. Cappellari M, Deluca C, Tinazzi M, et al. Does statin in the acute phase of ischemic stroke improve outcome after intravenous thrombolysis? A retrospective study. J Neurol Sci 2011;308:128–134.
21. Restrepo L, Bang OY, Ovbiagele B, et al. Impact of hyperlipidemia and statins on ischemic stroke outcomes after intra-arterial fibrinolysis and percutaneous mechanical embolectomy. Cerebrovasc Dis 2009;28:384–390.
22. Ntaios G, Lambrou D, Michel P. Blood pressure change and outcome in acute ischemic stroke: the impact of baseline values, previous hypertensive disease and previous antihypertensive treatment. J Hypertens 2011;29:1583–1589.
23. Zhang L, Chopp M, Jia L, Cui Y, Lu M, Zhang ZG. Atorvastatin extends the therapeutic window for tPA to 6 h after the onset of embolic stroke in rats. J Cereb Blood Flow Metab 2009;29:1816–1824.
24. Chen J, Zhang ZG, Li Y, et al. Statins induce angiogenesis, neurogenesis, and synaptogenesis after stroke. Ann Neurol 2003;53:743–751.