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ORIGINAL COMMUNICATION

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

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Abstract The influence of statins on the results of intravenous thrombolysis for ischemic stroke is controversial. We studied the risks and benefits of statin pretreatment (SP) in patients treated with intravenous alteplase (t-PA) at our institution, and included our data to a meta-analysis of previous related studies. We reviewed prospectively collected data from consecutive patients with acute ischemic stroke treated with IV rt-PA at our institution over the past 9 years. We compared symptomatic intracranial haemorrhage (SICH), favourable short-term outcome (decrease of ≥4 points on the NIHSS score after 24 h from baseline assessment), favourable long-term outcome (mRS score ≤2 at 3 months) and mortality rates between statin-pretreated (SPP) and nonstatin-pretreated patients (NSPP). We performed a systematic search through MEDLINE/PubMed and Embase datasets to identify similar English language studies. A total of 182 patients were included (mean age 68.3 ± 11.4 years, 54.3% men). There were no significant differences between SPP and NSPP regarding SICH (3.3 vs. 1.7%, $p = 0.47$), favourable short-term outcome (44.8 vs 56%, $p = 0.31$) and favourable long-term outcome rates (40 vs 44.1%, $p = 0.84$). In a meta-analysis of 1,055 patients, SP was neither related to long-term functional outcome nor mortality, but it was a risk factor for SICH (OR 1.99, 95% CI 1.03–3.84, $p = 0.04$). Statin pretreatment may increase the risk of SICH in patients receiving IV t-PA for ischemic stroke, though it does not influence the 3 months outcome. Prospective studies are needed to confirm this safety concern.

Keywords Statins · Thrombolysis · t-PA · Outcome · Intracerebral haemorrhage · Meta-analysis

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Introduction

Intravenous tissue plasminogen activator (IV t-PA) is the only thrombolytic drug approved to treat acute ischemic stroke. Despite its effectiveness, only 40–50% of stroke patients show a significant improvement after treatment [1, 2]. In addition, use of t-PA is restricted because symptomatic intracranial haemorrhage (SICH) occurs in 1.7–6.4% of treated patients [1, 3, 4]. When determining those factors modulating the risks and benefits of IV thrombolysis, it may be important to consider some common drugs taken by patients at the time of stroke.

The use of 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors, or statins, has dramatically increased during the last decade. Statins are mainly effective in long-term primary and secondary prevention of ischemic stroke [5, 6], but their pleiotropic effects could attenuate the ischemic damage in the acute phase of stroke [7] and promote brain tissue repair [8]. In fact, statin pretreatment (SP) has consistently been reported to have clinical benefits for stroke patients who are not candidates to thrombolysis [9–11]. These benefits might also be expected in patients treated with IV t-PA; however, the suggestion by some studies that statin users could be at an exceeding risk of intracranial haemorrhage [6, 12] raises some concerns in this specific population. There is a potential for a complex balance between favourable and detrimental effects of SP in thrombolysis. Although of great interest, this topic has

been little explored, and the studies show controversial results. One retrospective study concluded that SP was an independent predictor of favourable outcome at 3 months in patients receiving IV t-PA [13], but this beneficial effect was not replicated in later studies [14, 15]. Regarding SICH, a higher incidence in statin-pretreated patients (SPP) has only been reported for intra-arterial procedures [16], with no repercussion on functional outcome.

Against this uncertain background concerning the role of statins on thrombolysis we performed the present study. Our aims were: (1) to analyze the influence of SP on functional outcome, mortality and SICH rates in our series of patients treated with IV t-PA; (2) to review the literature and perform a meta-analysis of related studies.

Methods

Study design

We reviewed prospectively collected data from 210 consecutive acute ischemic stroke patients treated with IV t-PA within the first 3 h of symptoms onset. These patients were admitted to our institution between 2000 and 2008, and were selected for thrombolysis following the criteria of ECASS II [17] (2000–2003 period) and SITS-MOST [4] studies (from 2004 onwards). Twenty-eight patients were excluded from the final analysis because data regarding statin use before stroke and/or outcome were missing.

SP was defined as the regular use of any statin until the day of stroke. These data were reported by patients or their relatives. We recorded demographical data (age and sex); vascular risk factors (smoking, hypertension, diabetes, hypercholesterolemia, obesity, previous coronary disease, previous stroke, atrial fibrillation, alcohol abuse); glucose, blood pressure and National Institutes of Health Stroke Scale (NIHSS) score at baseline; time to thrombolysis; previous use of antiplatelet agents (AA); and TOAST stroke etiological subtype.

All patients had a CT at admission and at 24 h after stroke onset, or sooner if neurological worsening was noted. Cerebral haemorrhagic complications were classified according to the ECASS study on hemorrhagic infarct (HI-1 and HI-2) and parenchymal haemorrhage (PH-1 and PH-2) [18]. Remote parenchymal hematoma (rPH) was defined as any bleeding outside the ischemic lesion on follow-up CT. SICH was defined as a PH-2 or rPH-2 bleeding type associated with an increase of 4 or more points in the NIHSS score, within the first 36 h after t-PA infusion [4].

Clinical evaluation was performed at baseline and at 24 h after symptoms onset using the NIHSS score, and at 3 months using the modified Rankin scale (mRS). Early improvement was defined as a decrease of $\geq$4 points in NIHSS score 24 h after baseline assessment. Favourable long-term outcome was defined as a mRS score $\leq$2 at the 3-month follow-up visit.

Meta-analysis

We performed a systematic search using MEDLINE/PubMed and Embase datasets (from inception to October 2010) following the MOOSE Group statement [19]. Main title terms ("statin", "thrombolysis", "ischemic stroke") were combined with "outcome". Additionally, MeSH terms such as "Hydroxymethylglutaryl-CoA Reductase Inhibitors", "Tissue Plasminogen Activator", "Intracranial Haemorrhage" and "Brain Haemorrhage" were also used. From the studies identified, we selected those that fulfilled the following pre-specified inclusion criteria: (1) clinical study; (2) exclusive focus on patients treated with IV thrombolysis for ischemic stroke; (3) baseline and follow-up comparisons between SPP and NSPP, including functional outcome, hemorrhagic complications and/or mortality; (4) English language. Studies were reviewed by two independent physicians (S.M.R & J.M.F.). Where disagreements occurred in study selection, a consensus approach was used.

Statistics

SP was considered a dichotomic variable (yes/no). Patients were divided into two prognostic groups (favourable and unfavourable) both at 24 h and at 3 months after stroke. A univariate analysis was performed to compare the variables between the two prognostic groups; χ^2 test and contingency tables were used for categorical variables, Student's t test for quantitative continuous variables and the Mann–Whitney's U test for quantitative non-continuous variables (NIHSS). The same type of analysis was planned for patients with and without SICH. Logistic regression models were used to identify independent predictors of good outcome at 3 months and SICH; these models included those variables that showed significance ($p < 0.05$) in univariate analysis and those that did not but were considered clinically relevant. The SPSS 17.0 package was used for this set of analysis.

The meta-analysis was conducted using the Mantel–Haenszel estimate for odds ratio (OR), to determine whether SP predicted clinical outcomes (favourable 3-month outcome, mortality and SICH). The Mantel–Haenszel procedure provides a pooled OR across the strata of four-fold tables. It was performed for both random and fixed-effects. Cochran Q test was used to estimate heterogeneity followed by calculation of $I2$ (percentage of effect size attributable to heterogeneity). Effect size heterogeneity

was considered significant for $I2$ values >20%. Publication bias was quantified by inspection of funnel plots. The level of significance was set at 0.05. We used the Review Manager 5 software.

Results

We included 182 patients. Their mean age was 68.3 ± 11.4 years and 54.3% were men. Thirty patients (16.3%) were previously taking statins; the most frequently reported being simvastatin (66.7%). Table 1 compares SPP and NSPP characteristics. SPP had higher frequencies of hypercholesterolemia and prior coronary disease, and these patients were more frequently on AA (all $p < 0.001$). In contrast, SPP showed a lower prevalence of alcohol abuse ($p = 0.016$). Age and baseline NIHSS score did not differ significantly between groups.

Clinical outcome and mortality

Favourable functional outcome at 3 months was achieved in 57.6% of patients, and overall mortality was 12%. Early improvement was observed in 44.8% of SPP and 56.4% of NSPP ($p = 0.3$). Non-significant differences were also found regarding favourable long-term outcome (53.3 vs. 59.2%, $p = 0.55$). However, SPP showed a trend to a higher mortality at 3 months (23.3 vs. 9.9%, $p = 0.06$).

In the univariate analysis, increasing age was related to a poorer short and long-term outcome, whereas a greater baseline NIHSS score was associated with an unfavourable long-term outcome. SP was not related to clinical status at 24 h or 3 months (Table 2).

A logistic regression model that included age, baseline NIHSS score and SP identified age (OR: 0.938, 95% CI: 0.906–0.972, $p < 0.001$) and baseline NIHSS score (OR: 0.831, 95% CI: 0.773–0.893, $p < 0.001$) as independent predictors of favourable outcome at 3 months.

Haemorrhagic complications

Up to 15.8% of patients presented some type of intracranial bleeding, but SICH was diagnosed in only 2.2%. Table 3 shows the bleeding distribution among SPP and NSPP. No significant differences were observed when comparing haemorrhage subtypes (any bleeding, PH type, PH2/rpH2 types and SICH) between both groups. Since SICH rate was very low, univariate analysis was performed on PH-type haemorrhages as a whole (Table 4). Age and baseline glucose were significantly related to PH-type haemorrhages ($p = 0.03$ and 0.02, respectively), whereas previous use of AA showed a trend towards

Table 1 Comparison of demographical, epidemiological and clinical data between statin-pretreated (SPP) and nonstatin-pretreated patients (NSPP)

	SPP ($n = 30$)	NSPP ($n = 152$)	p
Age (mean ± SD), years	70.8 ± 10.1	67.8 ± 11.5	0.15
Male sex (%)	50	55.9	0.55
Vascular risk factors			
Smoking (%)	13.3	28.3	0.11
Hypertension (%)	63.3	56.6	0.54
Diabetes (%)	23.3	21.7	0.81
Hypercholesterolemia (%)	70	20.4	<0.001
Coronary disease (%)	40	3.3	<0.001
Previous stroke (%)	26.7	17.1	0.3
Atrial fibrillation (%)	26.7	30.9	0.82
Obesity (%)	6.7	10.5	0.74
Alcohol abuse (%)	0	15.8	0.016
Clinical variables at baseline			
Systolic BP (mean ± SD), mmHg	147.8 ± 24.6	148 ± 24.5	0.96
Dyastolic BP (mean ± SD), mmHg	82.3 ± 15.4	85.2 ± 14.5	0.35
Glucose (mean ± SD), mg/dl	126.7 ± 55.9	130.2 ± 51.7	0.76
NIHSS score (median, quartiles 1–3)	16, 9–19	14, 9.2–18	0.42
Time to t-PA (mean ± SD), min	140.3 ± 29	143.7 ± 39.2	0.58
Previous antiplatelet therapy (%)	66.7	22.4	<0.001
TOAST stroke subtype (%)			
Large-vessel aterosclerosis	6.7	17.1	
Cardio-aortic embolism	56.7	41.4	0.55
Cryptogenic	33.3	32.2	

BP blood pressure, *NIHSS* National Institutes of Health Stroke Scale

Table 2 Variables related to clinical outcome at 24 h and 3 months

	24 h			3 months		
	Improvement	No improvement	*p*	Rankin ≤ 2	Rankin > 2	*p*
Age (mean ± SD), years	66.8 ± 12.1	70.3 ± 9.8	0.03	65.4 ± 12.6	72.4 ± 7.8	<0.001
Male sex (%)	52.6	56.8	0.65	54.7	55.3	0.99
Glucose at admission (mean ± SD), mg/dL	129.6 ± 50.8	130.7 ± 55.3	0.89	125.2 ± 54.7	136 ± 48.1	0.16
Time to t-PA (mean ± SD), min	140.8 ± 41.6	146.6 ± 32.3	0.29	141 ± 40.9	146.2 ± 32.5	0.34
Baseline NIHSS (median, quartiles 1–3)	14, 10–17.5	15, 9–18	0.66	12, 8–16	17, 14.2–20	<0.001
Previous antiplatelet therapy (%)	28.9	32.1	0.74	26.4	34.2	0.32
Statin pretreatment (%)	13.4	19.8	0.3	15.1	18.4	0.55

Table 3 Comparison of intracranial bleeding rates in relation to statin pretreatment

PH parenchymal haemorrhage, *SICH* symptomatic intracranial haemorrhage

	SPP ($n = 30$)	NSPP ($n = 152$)	*p*
Any bleeding event, no (%)	6 (20)	23 (15.1)	0.58
All PH types, no (%)	3 (10)	12 (7.9)	0.71
PH2 or rPH2 type, no (%)	1 (3.3)	8 (5.3)	0.99
SICH, no (%)	1 (3.3)	3 (2)	0.51

Table 4 Variables related to PH-type haemorrhage

[a] PH1 + PH2 + rPH2

	PH[a]	No PH	*p*
Age (mean ± SD), years	72.6 ± 7.1	67.9 ± 11.6	0.03
Previous antiplatelet therapy (%)	53.3	27.5	0.07
Glucose at admission (mean ± SD), mg/dL	160.6 ± 75.2	127 ± 49.3	0.02
Systolic BP at admission (mean ± SD), mmHg	144.7 ± 24	148.3 ± 24.5	0.6
Diastolic BP at admission (mean ± SD), mmHg	85.7 ± 16.6	84.6 ± 14.5	0.82
Baseline NIHSS score (median, quartiles 1–3)	17, 12–20	14, 9–18	0.13
Statin pretreatment (%)	20	16.2	0.71

higher PH occurrence ($p = 0.07$). No significant associations were found for SP.

Similarly to functional outcome, a logistic regression analysis was performed for hemorrhagic complications. It included age, glucose at admission, previous use of AA and SP. None of these variables were independent predictors of PH-type events.

Meta-analysis

We identified three studies on consecutive patients with ischemic stroke treated with IV t-PA, in which the SP role was specifically analyzed [13–15]. Table 5 summarizes their main features, along with those from our study. Data about long-term functional outcome and mortality were available in all studies but hemorrhagic complications were analyzed only in two. Short-term outcome (24 h after stroke onset) was not assessed in any of them. The definition of favourable long-term outcome was uniform for all studies (mRS ≤ 2 at 3 months). One study adopted SITS-MOST definition for SICH, whereas the other one used criteria from ECASS studies.

Favourable 3-month outcome was related to SP in only one study [13], in which an independent association was found. In the remaining two, functional independency at 3 months was more frequent among NSPP than in SPP, but differences did not reach significance. Regarding SICH and mortality, none of the studies found any independent relationship with SP.

Previous use of AA was significantly more frequent among SPP than in NSPP in the only study reporting such a specific comparison. AA independently predicted SICH in two studies; one of these reported an independent association with favourable long-term outcome at the same time.

The three studies were added to ours to perform a meta-analysis involving 1,055 patients for 3-month outcome and mortality, and 910 patients for SICH (Fig. 1). Significant low-grade data heterogeneity ($I2 = 30\%$) and moderate funnel plot asymmetry (not shown) were only present in the long-term outcome analysis. SP had no significant effects on long-term outcome (OR: 1.09, 95% CI: 0.73–1.61, $p = 0.68$) or mortality (OR: 1.32, 95% CI: 0.84–2.07, $p = 0.23$); however, it was a risk factor for SICH (OR: 1.99, 95% CI: 1.03–3.84, $p = 0.04$). These OR

Table 5 Comparison of studies included in the meta-analysis

	Alvarez-Sabin (2006)	Uyttenboogaart (2008)	Miedema (2010)	Martinez (2011)
Study design	Retrospective	Retrospective	Retrospective	Retrospective
Sample size (included patients)	145	252	476	182
Statin-pretreated patients (% of total)	11	16	20.6	16.3
Previous use of AA (% of total)	25.5	28	16.6	29.6
Within SP group (%)	n.p.	n.p.	**60***	**66.7***
Within non-SP group (%)	n.p.	n.p.	**19**	**22.4**
Outcome assessment				
Short-term (24 h)	No	No	No	Yes
Long-term (3 months)	Yes	Yes	Yes	Yes
SICH	No	Yes	Yes	Yes
SICH criteria	–	ECASS studies	SITS-MOST	SITS-MOST
Rankin ≤ 2 at 3 months (%)	40	49	45.6	57.6
Mortality (%)	19.3	17.1	9	12
SICH (%)	n.p.	5.1	6	2.2
SP association with outcomes				
SICH	Not assessed	Not found	SP associated with SICH in univariate analysis, but not after adjustment	Not found
Rankin ≤ 2 at 3 months	SP independent predictor of favourable outcome	Not found	Not found	Not found
Mortality	Not found	Not found	Not found	Not found (trend to a higher mortality for SP)
Independent predictors of SICH	–	Triglycerides	Blood glucose levels	None
		NIHSS score	NIHSS score	
		Previous use of AA	Prior use of AA	
			Early ischemic changes on brain CT	
Independent predictors of rankin ≤ 2 at 3 months	SP	Age	Age	Age
	NIHSS score < 15	NIHSS score	NIHSS score	NIHSS score
	Age < 70	Early ischemic changes on brain CT	Early ischemic changes on brain CT	
		Prior use of AA		

AA antiplatelet agents, *n.p.* not provided, *SP* statin pretreatment

* $p < 0.05$

were obtained using the random-effects model, a conservative approach that implies wider confidence intervals and more robust results.

Discussion

This study indicates that SP has no significant immediate or delayed effects on outcome in patients treated with IV t-PA for ischemic stroke. Although SP was not related to intracranial bleeding in our series, the meta-analysis showed that it may be a risk factor for SICH.

To our knowledge, three retrospective English-language studies have previously assessed the influence of SP on the clinical results of IV thrombolysis for patients with ischemic stroke. In the first study, the authors identified SP as a good outcome predictor at 3 months in a logistic regression model [13]. This statin-related benefit was not explained by greater recanalization rates in SPP, and no data about final infarct size were reported. Hence, mechanisms underlying

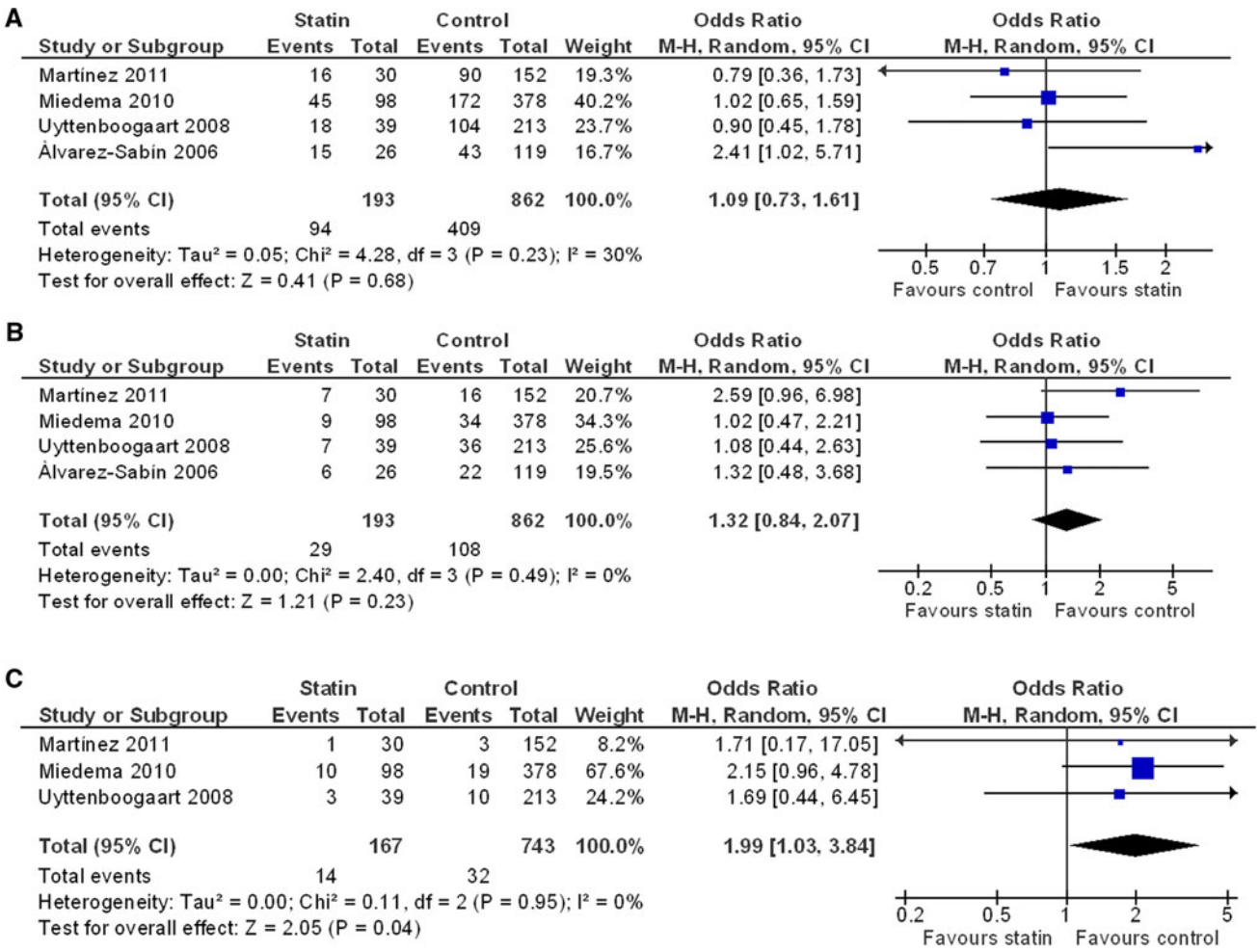

Fig. 1 Meta-analysis. Forest plots **a** Favourable outcome at 3 months (mRS $\leq$ 2), **b** Mortality, **c** Symptomatic intracranial haemorrhage

those possible beneficial effects were speculative and the results required confirmation. However, two subsequent studies found a neutral effect of SP both on the 3-month outcome and mortality [14, 15], even though series were considerably larger. In the present study, SPP and NSPP did not differ in mortality or in functional status at 3 months. Most importantly, no differences were noted in the meta-analysis including all four studies. The analysis of individual series and accumulated data does not currently support a clinical benefit of SP in patients treated with IV t-PA.

When comparing our study to that of Alvarez-Sabin et al. [13], the disagreement in results is difficult to explain. The described methodology was very similar for all studies. Our sample was larger (182 vs. 145) and included a greater proportion of SPP (16.3 vs. 11%). Although not significantly so, the median baseline NIHSS score was slightly higher in SPP than in NSPP in both studies, thus representing a shared unfavourable background to achieve significant associations. There remain two uncertain points: the characteristics of patients excluded from the analysis due to lack of follow-up data, and the time since last statin dose before stroke in SPP. We cannot exclude that differences in these variables could have contributed to the variability of results. However, the funnel plot analysis suggests either a publication bias or an exaggerated effect of SP in Alvarez-Sabin et al.'s study.

Taken together, our findings seem to contradict previous experimental and clinical data suggesting some benefits of SP in ischemic stroke. In animal models, statin treatment has been associated with a smaller area of infarction [7]. Also, several observational studies targeting patients not selected for thrombolysis have reported SP as an independent predictor of good functional outcome at 3 months after stroke [9–11]. Long-term benefits of statins could be explained by immediate effects after stroke (vessel and neuroprotection) and/or delayed effects involving neurogenesis and vasculogenesis [20]. Two major issues need to be considered to understand why SP does not seem to be clinically relevant in the setting of thrombolysis. First, t-PA is a highly effective drug for ischemic stroke which may

mask a more modest effect of statins. We intended to partially avoid this by increasing the number of patients through a meta-analysis. Secondly, no studies on this topic, including ours, have been able to analyze some of the important statin-related actions that may occur after stroke, such as withdrawal or de novo prescription. These actions are known to influence long-term outcome [21]. Therefore, considering that the plasma half-life of statins usually ranges between 2 and 20 h, we included an evaluation of the short-term neurological status. The lack of short-term differences in the NIHSS score further suggests a non-relevant benefit of statins in these patients. This is the first time that the impact of SP has been evaluated as early as 24 h after IV thrombolysis.

The relationship between SP and intracranial haemorrhage (ICH) is another point of interest. Chronic statin therapy has been linked to an increased risk of ICH in some observational studies [12]—allegedly through their cholesterol-lowering action—but not in most clinical trials [5, 22]. The SPARCL trial reported a higher incidence of ICH in the atorvastatin group than in the placebo group [6], though this effect was independent of the LDL-cholesterol levels [23]. When considering acute stroke, the main concern comes from the anti-thrombotic effects of statins [24], which might increase the bleeding risk of t-PA. For patients receiving IV thrombolysis, one study found a significant association between SP and SICH ($p = 0.04$); however, SP was not an independent predictor of SICH after adjustment for blood glucose, baseline NIHSS score, previous antiplatelet treatment and hypodensity area on baseline CT scan [15]. Regarding our series, SICH rates could not be reliably compared between SPP and NSPP, though data were included in the meta-analysis. PH frequencies did not differ significantly between SPP and NSPP. However, the meta-analysis (910 patients) showed that SP was a significant risk factor for SICH, conferring about a twofold increase in risk.

Our meta-analysis showed a significant association between SP and SICH in patients undergoing IV thrombolysis. Interestingly, the increase in SICH risk was not accompanied by an increase in mortality or a poorer functional outcome at long-term. It might be hypothesized that the exceeding risk of bleeding is counterbalanced by an eventual protective effect, thus explaining a neutral effect at 3 months. SP has been associated with better outcomes in patients with primary intracerebral haemorrhage [25], implying protective effects not only related to the ischemic event but also to the hemorrhagic transformation. On the other hand, data from individual studies included in the meta-analysis suggest a potential interaction between statins and AA in terms of SICH risk. First, AA pretreatment is more common among SPP than NSPP, as shown in our series and Miedema et al.'s study. Most importantly, previous AA use appeared as an independent predictor of SICH in two studies. Some studies beyond our scope have also shown an association between AA and a higher risk of SICH after IV thrombolysis, though the prognostic impact is usually neutral [26]. From these considerations, SP could be regarded as a confounding factor for SICH rather than its causal agent. However, this is merely speculative. While the observed influence of SP on SICH could be partially explained by AA, an additive or even synergistic effect between both drugs cannot be ruled out.

In terms of statistical power, this meta-analysis seems adequate to detect the effects of SP. An approximate calculation of the power using both pre-determined data (alpha value, total number of patients) and estimated data (low effect predicted for SP), reported values around 90% for 3-month outcome and mortality and 85% for SICH. The great imbalance between the number of patients in SPP and NSPP groups adds uncertainty to these results. However, as the confidence intervals of OR are considerably narrow—especially for those outcomes not reaching significance—and the heterogeneity values are low, the idea of a well-powered study is reinforced. Even in case the meta-analysis was underpowered, it is the results of functional outcome and mortality analyses that could be questioned (possible false negatives), but the significant association between SP and SICH would remain and even become more robust.

This study has several limitations. The sample of our case–control study was too small to identify SP effects standing out from t-PA. Some relevant data about statin treatment were not collected or not available, including time since last dose before stroke, and prescription and compliance after stroke. Measurements of plasma lipids and coagulation factors were not performed in the acute phase of stroke. With respect to the meta-analysis, it was entirely performed on retrospective data. SICH was not uniformly defined across the studies. We did not look for potential confounding variables, so the high SP-related risk of SICH should be taken with caution and current indications of IV t-PA should not be modified.

In conclusion, our data lend further support to previous studies suggesting SP has no effects on outcome in stroke patients treated with IV t-PA. However, the meta-analysis of published data warns of an increased risk of SICH in SPP. At this point, large, multi-centre prospective studies are needed to fully establish the role of statins in thrombolysis and to clarify safety concerns.

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Conflicts of interest The authors declare that they have no conflict of interest.

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