Statin treatment withdrawal in ischemic stroke: A controlled randomized study

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ABSTRACT

Background: Pretreatment with statins has been shown to reduce brain injury in cerebral ischemia. In this controlled randomized study, we investigated the influence of statin pretreatment and its withdrawal on the outcome of acute ischemic stroke patients.

Methods: From 215 patients admitted within 24 hours of a hemispheric ischemic stroke, 89 patients on chronic statin treatment were randomly assigned either to statin withdrawal for the first 3 days after admission (n = 46) or to immediately receive atorvastatin 20 mg/day (n = 43). The primary outcome event was death or dependency (modified Rankin Scale [mRS] score > 2) at 3 months. Early neurologic deterioration (END) and infarct volume at days 4 to 7 were secondary outcome variables. In a secondary analysis, outcome variables were compared with the nonrandomized patients without previous statin therapy (n = 126).

Results: Patients with statin withdrawal showed a higher frequency of mRS score > 2 at the end of follow-up (60.0% vs 39.0%; $p = 0.043$), END (65.2% vs 20.9%; $p < 0.0001$), and greater infarct volume (74 [45, 126] vs 26 [12, 70] mL; $p = 0.002$) compared with the non–statin-withdrawal group. Statin withdrawal was associated with a 4.66 (1.46 to 14.91)–fold increase in the risk of death or dependency, a 8.67 (3.05 to 24.63)–fold increase in the risk of END, and an increase in mean infarct volume of 37.63 mL (SE 10.01; $p < 0.001$) after adjusting for age and baseline stroke severity. Compared with patients without previous treatment with statins, statin withdrawal was associated with a 19.01 (1.96 to 184.09)–fold increase in the risk of END and an increase in mean infarct volume of 43.51 mL (SE 21.91; $p = 0.048$).

Conclusion: Statin withdrawal is associated with increased risk of death or dependency at 90 days. Hence, this treatment should be continued in the acute phase of ischemic stroke.
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There is increasing evidence of the role of statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) in the primary and secondary prevention of cardiovascular events.[1,2] In the Stroke Prevention by Aggressive Reduction of Cholesterol Levels (SPARCL) study in subjects without previous history of atrial fibrillation or coronary heart disease who had an ischemic stroke or a TIA 1 to 6 months before enrollment in the trial, atorvastatin 80 mg/day was associated with a significant 16% risk reduction of fatal or nonfatal stroke during a 5-year follow-up.[3]

Besides the effect of statin treatment in stroke prevention, recent open reports suggest that statins may have a neuroprotective effect in the acute phase of stroke.[4,5] In addition to a strong cholesterol-lowering effect, statins have a direct influence on endothelial function, inflammatory activity, oxidative stress, blood coagulation, platelet function, cellular proliferation and differentiation, plaque stability, angiogenesis, and the immune

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system.[6] Recent clinical studies also suggest that the acute withdrawal of statin treatment has deleterious effects on vascular function[7,8] and brain injury.[9]

Discontinuation of oral intake during the first days of an acute stroke, which may include chronic therapy with drugs such as statins, is a practice to avoid the risk of bronchoaspiration, particularly in the most severe strokes; therefore, it is crucial to evaluate the potential harmful effect of this modus operandi. The aim of this open, controlled, randomized study was to investigate the effect on functional outcome of previous statin treatment and its withdrawal after the onset of symptoms in patients with acute ischemic stroke.

METHODS

Study design. This controlled randomized study was conducted from October 2003 to May 2005 at a single center. Consecutive patients with acute hemispheric ischemic stroke admitted within the first 24 hours after onset of symptoms were studied. Reasons for exclusion were chronic inflammatory, infectious, or hematologic diseases; cancer; renal or liver failure; treatment with corticoids or antiinflammatory drugs in the week before stroke; acute treatment with fibrinolytic or investigational drugs; and life expectancy of less than 6 months. The absence of dysphagia was not an exclusion criterion because, when this study was designed, neither statin treatment nor statin withdrawal in the acute phase of stroke had previously shown beneficial or harmful effects in controlled studies. Accordingly, the local ethics committee approved the study, and informed consent was obtained from either the patients or their relatives.

Study intervention. Those patients who were receiving statins before admission were randomly assigned to interrupt this treatment for the first 3 days of hospitalization (statin-withdrawal group) or to immediately receive atorvastatin orally (or through a nasogastric tube) at a dose of 20 mg daily (non–statin-withdrawal group), regardless of the drug and dosage the patient had previously received. Patients were assigned to one group or the other depending on whether their date of admission fell on an odd or an even day. Patients who did not receive statins before admission were followed up as a reference group for secondary analyses. From the fourth day onward, atorvastatin 20 mg daily was also administered in patients who were randomly assigned to statin withdrawal and in those who were not on previous statin treatment. All patients were discharged on treatment with 20 mg of atorvastatin daily. The statin treatment was continued at least 3 months.

Patients were treated in an acute stroke unit following the guidelines of the Study Group for Cerebrovascular Diseases of the Spanish Neurological Society.[10] Transcranial Doppler and carotid ultrasound studies were performed on all patients, whereas echocardiography and magnetic resonance angiography or conventional angiography were performed on selected patients. Stroke subtype was classified as atherothrombotic, cardioembolic, small vessel disease, or cryptogenic.[11]

Clinical and radiologic assessment. The NIH Stroke Scale (NIHSS) score was measured on admission, every 24 hours throughout the period of hospitalization, and at 3 months of follow-up by a certified neurologist. Early neurologic deterioration (END) was defined as an increase of ≥4 points in the NIHSS score between admission and any time during the first 48 hours of hospitalization.

Neuroimaging assessment included a brain MRI with diffusion-weighted imaging, fluid-attenuated inversion recovery, and T2 sequences performed on admission, and a cranial CT performed between the fourth and seventh day after onset of symptoms. Infarct volume was measured on the CT study using a manual tracing method.

The primary outcome event was death or dependency evaluated at 3 months by using the modified Rankin Scale (mRS). Dependency was defined as an mRS score > 2. Secondary outcomes were END and infarct volume. All CT evaluations and mRS score assessments were performed by investigators who were blinded to the randomization and treatment during the acute phase.

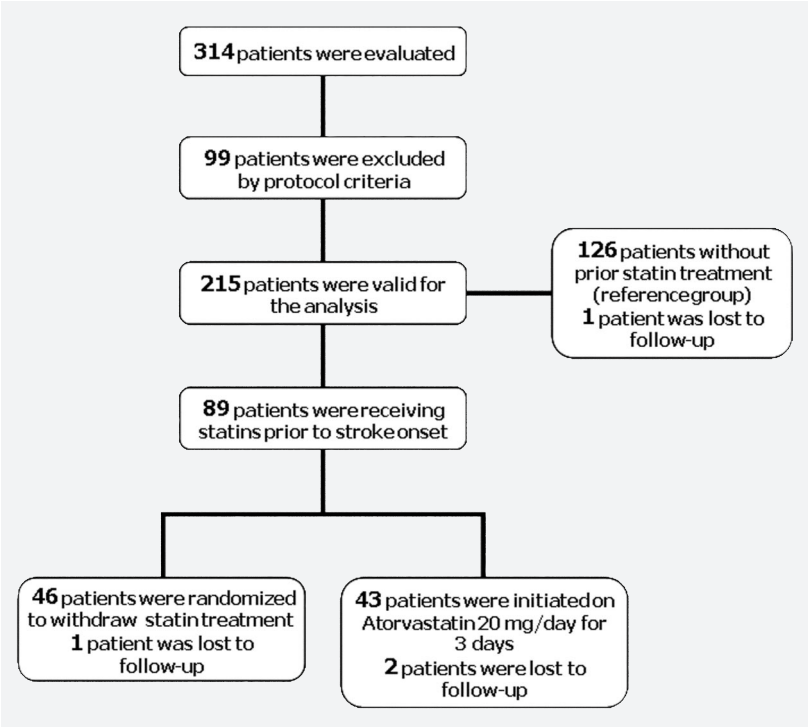
Statistical analysis. The sample size was chosen to provide 90% power and a level of significance of 5% in a unilateral contrast to detect a common odds ratio (OR) for decrease of dependency at 90 days of 4.0, according to the lowest 95% CI observed in a previous retrospective nonrandomized study. Based on these previous data, we assumed a proportion of patients with poor outcome in the non–statin-withdrawal group of 36%.[9]

Results are expressed as percentages for categorical variables and compared using the chi-square test, and as mean (SD), or median [quartiles] for the continuous variables and compared using Student's t test or the Mann–Whitney test, depending on whether they were normally distributed. The influence of statin withdrawal on the primary outcome event and on END was evaluated using logistic regression analysis. The Spearman correlation coefficient was used to analyze the association between infarct volume and baseline continuous variables. Generalized linear models were used to assess the influence of statin withdrawal on infarct volume. For the primary analysis, which was performed comparing the groups of randomized patients, models were adjusted for age and the severity of neurologic deficit on admission. In a secondary analysis, primary and secondary outcome variables in the statin-withdrawal group were compared with those of nonrandomized patients who were not on previous statin therapy ($n = 126$). For the secondary analysis, logistic regression and lineal models were adjusted for age, severity of neurologic deficit at admission, and those variables that were differently distributed between the groups ($p < 0.05$). We fitted the models in a customized way by means of the Enter method. Values of p below 0.05 were considered to be significant in all tests.

RESULTS

Baseline patient characteristics and treatment allocation. Three-hundred fourteen patients were considered for inclusion in the study. Twenty-one patients randomized in clinical trials with drugs under investigation, 27 patients treated with fibrinolysis, 13 patients with chronic inflammatory processes and/or treatment with corticoids or anti-inflammatory drugs in the week before stroke, 31 patients with comorbidity and

Figure 1 Classification of patients included in the study



life expectancy of less than 6 months, and 7 patients in whom the diagnosis of stroke could not be confirmed were excluded; thus, 215 patients [53% men, 68.8 (11.1) years] were valid for the analysis. The median time from the onset of symptoms to inclusion was 6 [3.5, 11.5] hours. Eighty-nine patients who were receiving statins before stroke onset (median duration of chronic statin treatment, 8.7 [2, 34] months) were randomly assigned to withdraw statins (n = 46) or to receive 20 mg/day of atorvastatin for 3 days (n = 43) (figure 1). As expected, the two groups were comparable regarding baseline vascular risk factors, clinical characteristics, and stroke subtype (table 1).

Primary outcome event. Three patients who completed the study during hospitalization were lost to follow-up at 3 months, 1 in the statin-withdrawal group and 2 in the non–statin-withdrawal group. Twenty-seven patients (60%) in the statin-withdrawal group and 16 (39%) in the non–statin-withdrawal group were dead or dependent at the end of the study period (p = 0.043). The adjusted and unadjusted ORs of the effect of statin withdrawal on the primary outcome variable are shown in table 2. Statin with-

Table 1 Baseline vascular risk factors, clinical characteristics, biochemical variables, and stroke subtype in patients with and without statin withdrawal

	Statin-withdrawal group, n = 46	Non–statin-withdrawal group, n = 43	p Value
Age, years	66.5 (11.8)	67.9 (13.1)	0.580
Stroke onset to inclusion, hours	6.5 [3.8, 14.6]	5 [3.5, 10]	0.249
Men, n (%)	22 (47.8)	23 (53.5)	0.673
History of hypertension, n (%)	29 (63.0)	23 (53.8)	0.396
History of diabetes, n (%)	16 (34.8)	16 (37.2)	0.829
History of atrial fibrillation, n (%)	7 (15.2)	5 (11.6)	0.759
History of dyslipemia, n (%)	46 (100)	40 (93)	0.109
Systolic blood pressure, mm Hg	160.9 (34.7)	161.8 (32.2)	0.899
Diastolic blood pressure, mm Hg	89.4 (20.3)	88.6 (20.9)	0.858
Axillary temperature on admission, °C	37.0 (0.7)	37.1 (0.7)	0.680
NIHSS score on admission	12 [8, 18]	14 [10, 18]	0.523
Leukocytes on admission, $\times 10^3$/dL	6.3 (1.9)	6.2 (2.0)	0.832
Blood glucose on admission, mg/dL	156.1 (51.2)	168.5 (83.5)	0.406
Total cholesterol, mg/dL	258.7 (2.3)	261.8 (3.1)	0.674
LDL cholesterol, mg/dL	179.6 (2.1)	182.1 (3.9)	0.706
Etiological diagnosis, n (%)			0.965
Atherothrombotic	27 (58.7)	23 (53.3)	
Cardioembolic	9 (19.6)	10 (23.3)	
Lacunar	8 (17.4)	8 (18.6)	
Cryptogenic	2 (4.3)	2 (4.7)	

NIHSS = NIH Stroke Scale; LDL = low-density lipoprotein.

Table 2 Unadjusted and adjusted ORs of death or dependency and END in patients with and without statin withdrawal

	Statin-withdrawal group, n (%)	Non–statin-withdrawal group, n (%)	OR (95% CI)	Adjusted OR (95% CI)*
Primary outcome event†	27 (60.0)	16 (39.0)	2.39 (1.02, 5.62)	4.66 (1.46, 14.91)
Early neurologic deterioration	30 (65.2)	9 (20.9)	7.08 (2.73, 18.37)	8.67 (3.05, 24.63)

* Adjusted by age and NIH Stroke Scale score at admission
† Death or dependency (modified Rankin Scale score > 2) was evaluated at 3 months in 45 patients of the statin-withdrawal group and in 41 patients of the non–statin-withdrawal group.
OR = odds ratio; END = early neurologic deterioration.

drawal was associated with a significant increase in the risk of death or dependency, which was even higher after adjustment for age and stroke severity at admission (OR 4.66; 95% CI 1.46 to 14.91).

Secondary outcome variables. END was found in 30 patients (65.2%) of the statin-withdrawal group and in 9 patients (20.9%) of the non–statin-withdrawal group ($p < 0.0001$). Statin withdrawal was associated with an increase in the risk of END (unadjusted OR 7.08; 95% CI 2.73 to 18.37; $p < 0.001$), which was not substantially modified after adjustment for age and stroke severity (table 2).

Infarct volume was greater in the group of patients with statin withdrawal compared with the non–statin-withdrawal group (74, 45, 126 vs 26, 12, 70 mL; $p = 0.002$) (figure 2). After adjusting for age and NIHSS score at admission, the withdrawal of statins was found to be associated with greater enlargement of the infarct volume, because this factor yielded an estimated mean increase in infarct volume of 37.63 mL (SE 10.01; $p < 0.001$).

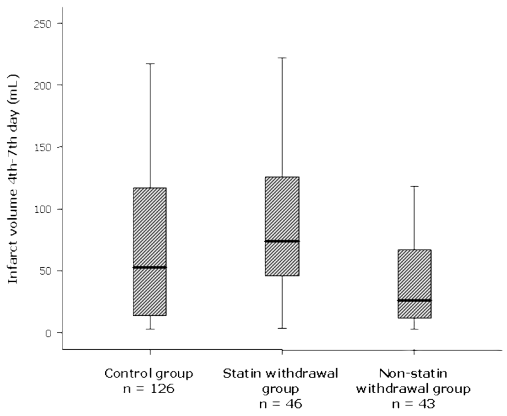
Secondary analysis. Patients of the reference group showed a higher frequency of atrial fibrillation (31% vs 13.1%; $p = 0.003$) and lower frequency of previous history of hypercholesterolemia (2.4% vs 96.6%; $p < 0.0001$) than the randomized patients. No other significant differences were found in the distribution of the baseline characteristics between the groups.

A 2 × 2 secondary post hoc analysis showed no differences in the percentage of patients with the primary outcome event between the statin-withdrawal group and the reference group of patients who had not been on previous treatment with statins (58.7% vs 42.1%; $p = 0.059$), but the statistical power to detect differences was of 26%. The proportion of patients with END was higher in the statin-withdrawal group (65.2% vs 27.8%; $p < 0.0001$). Compared with patients without previous treatment with statins, statin withdrawal was associated with a 19.01 (1.96 to 184.09)–fold increase in the risk of END after adjusting for potential confounders (table 3).

Regarding infarct volume, the 2 × 2 secondary post hoc analysis showed no differences between the group with statin withdrawal and the reference group (74 [45.5, 126.2] vs 53 [14, 117.2] mL; $p = 0.056$). However, statin withdrawal was associated with an estimated mean increase in infarct volume of 43.51 mL (SE 21.91; $p = 0.048$) after adjusting for covariates (table 4).

There was no significant interaction between the effect of statin withdrawal and those factors associated with the outcome variables, indicating that the risk of withdrawing the treatment cannot be attributed to any particular subgroup.

Figure 2 Infarct volume by groups



Box plots show median values (horizontal line inside the box), quartiles (box boundaries), and the largest and smallest observed values (lines drawn from the end of the box) of infarct volume evaluated on days 4 through 7 of evolution.

DISCUSSION The present study shows that the withdrawal of statin therapy immediately after stroke onset is associated with a 4.7-fold increase in the risk of death or dependency at 3 months in comparison with the statin continuation policy. Importantly, the effect on the primary outcome variable is supported by a deleterious effect of statin withdrawal on secondary outcome variables; patients who were allocated to withdrawn statins had an 8.7-fold increase of END and larger infarct volume.

Retrospective studies have shown the benefit

Table 3 Adjusted ORs of END in patients with and without statin withdrawal comparing with the reference group

	OR	95% CI	*p* Value
Age	0.96	(0.93, 0.98)	0.004
NIHSS score at admission	1.09	(1.03, 1.14)	0.001
Previous history of atrial fibrillation	1.18	(0.54, 2.55)	0.676
Previous history of dyslipemia	0.24	(0.03, 2.04)	0.189
Statin administration in the acute phase			
Reference group	1.00		
Statin-withdrawal group	19.01	(1.96, 184.09)	0.011
Non-statin-withdrawal group	1.81	(0.22, 14.66)	0.579

OR = odds ratio; END = early neurologic deterioration; NIHSS = NIH Stroke Scale.

of previous long-term statin treatment in improving the prognosis of ischemic stroke,[4,5,12] and preliminary data from a prospective pilot study have suggested the usefulness of initiating statin treatment within the first 12 hours after ischemic stroke onset.[13] However, cardiologic studies seem to show a greater efficacy in those patients who have been pretreated with statins than in those only receiving statins after the onset of acute myocardial infarction.[14]

Experimental models of focal cerebral ischemia and data from several clinical trials have demonstrated that the neuroprotective effect of statins is related not only to the reduction of plasma cholesterol levels but rather to direct effects on endothelial function as well as antithrombotic and anti-inflammatory effects.[6,15-18] Likely, the pleiotropic effects of statins associated to their neuroprotective actions in the acute phase of stroke are related to the overexpression of the endothelial nitric oxide synthase,[19-20] which results in an improvement of the endothelial function[21-22] as well as in a reduction in thrombogenesis,[23] and an increase in the expression of tissue plasminogen activator.[24] Statins also reduce the levels of proinflammatory cytokines and decrease the expression of adhesion molecules[25]; in fact, in the Cholesterol and Recurrent Events (CARE) study, a reduction in the levels of C-reactive protein has been reported.[26] In this context, and given the greater prominence of cytotoxic effects after cerebral ischemia, it is not surprising that statin withdrawal has a deleterious effect on the prognosis of ischemic stroke patients.

Table 4 Influence of statin administration in the acute phase of stroke on infarct volume in patients with and without statin withdrawal compared with the reference group

	β	SE	*p* Value
Age	−1.16	0.31	<0.001
NIHSS at admission	5.60	0.52	<0.001
Previous history of atrial fibrillation	−12.30	8.19	0.135
Previous history of dyslipemia	30.15	20.66	0.146
Statin administration in the acute phase			
Reference group	1.00		
Statin-withdrawal group	43.51	21.91	0.048
Non-statin-withdrawal group	3.60	20.67	0.862

NIHSS = NIH Stroke Scale.

Indeed, in the past few years, several studies have questioned the withdrawal effect after discontinuation of statin therapy, particularly in increasing the risk of recurrent coronary events,[27,28] although all studies have consistently shown increased in-hospital mortality.[14,27,29,30] It has been demonstrated that discontinuation of statin treatment abrogates stroke protection in animal models of ischemia,[31] and it has been also reported in a clinical retrospective study the association between statin withdrawal, poor functional outcome, and larger brain injury in patients with acute atherothrombotic ischemic stroke.[9] Importantly, the present findings indicate that statin withdrawal not only suppresses brain protection of previous treatment but causes deleterious effects in comparison with the lack of statin-linked protection at stroke onset; the rate of END and infarct volume were greater in the statin-withdrawal group than in the reference group. In this context, there is evidence suggesting that acute withdrawal of statin treatment impairs vascular function and triggers a proinflammatory and prothrombotic response.[32-34] Of note, the suppression of endothelial nitric oxide (NO) production,[31] which is mediated by a negative feedback regulation of Rho guanosine triphosphatase gene

transcription, might account for this deleterious effect.[35] These actions may explain the harmful rebound phenomenon of statin withdrawal.

Our study has a number of limitations. First, cholesterol levels were not repeatedly measured during the acute phase of stroke. Although the statin-related NO generation is independent of the cholesterol levels,[36] other neuroprotective effects may be related to the degree of lipid levels reduction.[37] A controversial aspect may be the dose of atorvastatin administered in this study. A dose of 80 mg daily has recently shown efficacy in stroke prevention[38]; however, doses between 10 and 20 mg of atorvastatin had been associated with a better outcome in retrospective studies of patients with acute stroke.[5] Although the optimal dose for the acute phase protection of stroke is unknown, this effect of statins likely seems to appear with low doses, because neuroprotection has been demonstrated after the administration of a single dose in animal models of cerebral ischemia.[39]

Our findings strongly support that previous statin therapy should not be interrupted during the acute phase of ischemic stroke. The recommendation to start on statin treatment as soon as ischemic stroke occurs needs to be investigated in further randomized clinical trials.

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