Early Outcome of Acute Ischemic Stroke in Hyperlipidemic Patients Under Atorvastatin Versus Simvastatin

Yair Lampl, MD, Mordechai Lorberboym, MD,† Ronit Gilad, MD,* Igor Vysberg, MD,* Adele Tikozky, MD,* Menachem Sadeh, MD,* and Mona Boaz, PhD‡*

Background: Studies designed to evaluate the efficacy of atorvastatin on stroke suggest that, in addition to cholesterol lowering, this drug may play a role in poststroke neuroprotection. The objective of this historical-prospective study was to analyze the efficacy of atorvastatin (40–80 mg) or simvastatin (at an optimal dose) during the first 2 weeks after stroke in hyperlipidemic patients treated with simvastatin before stroke onset.

Methods: Medical records of all adult (aged >18 years) patients diagnosed with acute stroke were reviewed. Subjects were categorized on the basis of poststroke treatment exposure: atorvastatin (40 or 80 mg) or simvastatin (at an optimal dose). Each patient was examined using the National Institutes of Health Stroke Scale (NIHSS) and the modified Rankin Scale (mRS). Blood lipid profile was determined. All tests were performed at baseline and at 4 weeks after stroke.

Results: A total of 371 patients (249 male and 122 female) were included. Subjects who received simvastatin were significantly older than those who received either dose of atorvastatin. Baseline differences in functional scores were not detected across treatment groups. Two weeks after stroke, subjects exposed to simvastatin had significantly poorer NIHSS and mRS scores than did subjects exposed to either atorvastatin dose. Atorvastatin 80 mg was associated with significantly better outcome compared with either of the other treatment groups. These differences persisted even after controlling for age and baseline scores.

Conclusions: Early outcome measured by NIHSS and mRS was better in acute stroke patients treated with atorvastatin than in those treated with simvastatin. These differences may reflect a neuroprotective effect unique to atorvastatin.

Key Words: atorvastatin, simvastatin, statins, acute ischemic stroke

(*Clin Neuropharm* 2010;33: 129–134)

A number of mechanisms have been proposed to explain the neuroprotective effect of statins.[1–3] One hypothesis, supported by in vitro studies exposing embryonic mouse neocortical cultures to *N*-methyl-D-aspartate, proposes that statins preserve *N*-methyl-D-aspartate–expressing cortical neurons and reduce lactate dehydrogenase release. They vary in their ability to protect cultured neurons from neuroexcitatory death; specifically, this capacity is higher in rosuvastatin and simvastatin and lower in atorvastatin and pravastatin.[4,5] Nevertheless, it has been proposed that atorvastatin possesses a pleiotropic effect. Atorvastatin has been shown to up-regulate endothelial nitric oxide synthase (eNOS), inhibit reduction of protease-activated receptor 1, and directly act on metalloproteinases 2 and 9 in the core and boundary of the infarction. These effects were demonstrated after administration of recombinant human plasminogen activator in rat models after inducing embolic stroke, 4 hours after the event.[6] The evidence that atorvastatin protects against stroke by acting on the eNOS and the endogenous plasminogen activator was demonstrated also in the middle cerebral artery embolic ischemic mouse model, 14 days after treatment with atorvastatin. Treatment was associated with an increase in endogenous eNOS expression, but without involvement of plasminogen activator inhibitor 1. Similar findings were observed in the eNOS knockout mice model and were associated with reduction of infarcted tissue volume and better neurological outcome.[7] The effect of atorvastatin on local cerebral blood flow via nitric oxide production and reduction of asymmetric dimethylarginine was confirmed in stroke-prone spontaneously hypertensive rats (SHRPS) after treatment with 2 and 20 mg/kg for 11 weeks.[8] The effect of 40 mg atorvastatin on the cerebral blood flow was also shown in human study of patients after lacunar stroke.[9]

Targets of effect include the increase in interleukin 4 (IL-4), antagonizing the interferon γ effect and increase in microglial activity measured in hippocampal tissue of rats[10] and stabilization of the blood-brain barrier disruption in rats.[11] This effect is supposed to be induced by a direct effect on NADPH oxidase.[12]

In addition, the neuroprotective effect of atorvastatin has been shown in embolic middle cerebral artery occlusion in animal models, in which suppression of early growth response 1, direct modification of vascular endothelial growth factor (VEGF) RNA level, and increase in Brain derived neurotrophic factor and Vascular endothelial growth factor receptor 2 expression have been demonstrated.[13,14]

Atorvastatin has been shown to reduce infarct volume at a dose of 10 mg/kg at 7 and 21 days after stroke[15] and 24 hours after reperfusion.[16] In eNOS knockout mice, the reduction reached values of 38%.[17–19] These observations were attributed to the pleiotropic effect of atorvastatin during acute stroke. To date, studies comparing atorvastatin and simvastatin have not been reported; thus, it cannot be concluded that the neuroprotective effect is specific to one of the statins.

The present historical-prospective study was designed to compare the efficacy of atorvastatin (40 or 80 mg) or simvastatin (at an optimal dose) during the first 2 weeks after stroke in hyperlipidemic patients treated with simvastatin before stroke onset.

PATIENTS AND METHODS

This study, which was approved by the institutional and Ministry of Health ethics committee, was performed retrospectively-prospectively. Medical records for a convenience sample of all patients who fulfilled inclusion criteria were reviewed. The patients were categorized into 3 groups:

1. Patients prescribed the last treatment dose of simvastatin defined as the last dose of medication that resulted in the

Departments of *Neurology, †Nuclear Medicine, and ‡Unit of Epidemiology, Wolfson Medical Center, Holon; and Sackler Faculty of Medicine, Tel Aviv University, Israel.

Address correspondence and reprint requests to Yair Lampl, MD, Department of Neurology, Edith Wolfson Medical Center, Holon 58100, Israel; E-mail: y_lampl@hotmail.com

DOI: 10.1097/WNF.0b013e3181d47863

recommended serum lipid values outlined in the National Cholesterol Education Program Adult Treatment Panel III guidelines,[20] such that prehospitalization hyperlipidemic status was based on general practitioner report. The dose of simvastatin used by the patients ranged between 20 and 80 mg/d.

2. Patients prescribed the last treatment dose of simvastatin before stroke and switched to atorvastatin 40 mg on admission.
3. Patients prescribed the last treatment dose of simvastatin before stroke and switched to atorvastatin 80 mg on admission. Treatment decisions were performed according to the discretion of the attending physician. Approximately 16% of study participants had low-density lipoprotein (LDL) levels greater than 160 mg% before hospitalization. This reflects the fact that, for some of these patients, lipid profiling was performed before the beginning of the statin therapy.

Included were all subjects of both sexes, older than 18 years and presenting with evidence of acute stroke, who arrived at the emergency room of the E. Wolfson Medical Center during the period of 2005 to 2008 and fulfilled the inclusion criteria. Acute ischemic stroke was defined as rapidly developing loss of brain functions persisting at least 24 hours due to disturbance in the blood supply to the brain. Excluded were patients with primary intracranial hemorrhage, previous craniotomy or brain tumor, early epileptic seizure during the acute stroke, thrombolytic therapy (including intravenously administration of tissue plasminogen activator [tPA]), carotid or vertebrobasilar artery dissection, known allergic reaction or prior adverse reaction to one of the statins, elevated serum creatine phosphokinase levels (>190 U/I), myositis, or rhabdomyolysis. All exclusions were in accordance with the nationally accepted consensus guidelines of the American College of Cardiology, the American Heart Association, and the National Heart, Lung and Blood Institute.[21,22]

Only patients with evidence of hyperlipidemia diagnosed at least 1 month before the recent hospitalization were included. The data including lipid values of the last 3 months were obtained immediately and directly from the general physician. The statin drug was administered during the first 2 hours after arrival to the emergency room. Each patient received the best medical treatment according to the American Heart Association guidelines.[23] The relevant medical and demographic data, including risk factors and previous medications, were collected.

TABLE 1. Demographic and Baseline Lipid Profile by Treatment Group

	Group 1	Group 2	Group 3	
	Simvastatin	40 mg Atorvastatin	80 mg Atorvastatin	
	n = 90	n = 185	n = 96	*P*
Age, mean (SD), y	68.86 (12.81)	65.09 (10.51)	63.28 (10.59)	0.002
Sex ratio, no. male/no. female	54/36	126/59	69/27	0.21
Total cholesterol, mean (SD), mg/dL	183.66 (51.48)	181.497 (54.53)	180.24 (55.67)	0.91
Triglycerides, median (minimum-maximum), mg/dL	162 (58–299)	147 (57–299)	162.5 (61–288)	0.84
HDL cholesterol, median (minimum-maximum), mg/dL	39 (27–84)	40 (26–81)	38 (25–80)	0.84
LDL cholesterol, mean (SD), mg/dL	124.91 (30.94)	126.87 (29.68)	128.57 (31.26)	0.71
Comorbidities and risk factors, %				
Hypertension	76.67	76.76	79.17	0.89
Diabetes mellitus	36.67	31.89	39.58	0.41
Present smoker	16.67	23.24	30.21	0.09
Atrial fibrillation	21.11	14.05	9.38	0.08
Congestive heart failure	10.00	7.57	15.63	0.11
Prior myocardial infarction	11.11	7.03	5.21	0.29
CABG	15.56	9.19	18.75	0.06
Prior stroke	20.00	18.38	19.79	0.93
Dyslipidemia	57.78	45.41	48.96	0.16
Obesity	17.78	28.11	29.17	0.13
Medications				
Aspirin	43.3	30.8	38.9	0.11
Clopidogrel	7.8	14.1	22.9	0.01
Coumadin	15.6	7.0	5.2	0.023
Heparin	4.4	0.5	1.0	0.048
Statin drugs	60.0	51.9	46.9	0.19
β-Blockers	44.4	38.9	21.9	0.003
Diuretics	32.2	13.5	20.8	0.001
ACEIs/ARBs	48.9	52.4	47.9	0.73
Calcium-channel blockers	25.6	18.9	36.5	0.006
Oral hypoglycemic agents	22.2	17.3	19.8	0.61
Insulin	2.2	2.7	2.1	0.94

ACEIs/ARBS indicates angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers; CABG, coronary artery bypass graft.

TABLE 2. Baseline and Posttreatment NIHSS and mRS Scores by Treatment Group

	Group 1	Group 2	Group 3	
	Simvastatin	40 mg Atorvastatin	80 mg Atorvastatin	
	n = 90	n = 185	n = 96	*P*
Baseline values				
NIHSS	1 (1–4)	1 (1–5)	1 (1–4)	0.38
mRS	2 (0–5)	2 (0–5)	2 (0–5)	0.17
Posttreatment values				
NIHSS	1 (0–5)	1 (0–5)	1 (0–4)	<0.0001
mRS2	1.5 (0–5)	1 (0–5)	0 (0–5)	<0.0001

Values are median (minimum-maximum).

Neurological deficit was measured using the National Institutes of Health Stroke Scale (NIHSS),[24] whereas disability was assessed using the modified Rankin Scale (mRS).[25] The NIHSS score results were divided into 5 neurological deficit groups based on severity: (1) mild (NIHSS score, 0–5); (2) moderate (NIHSS score, 6–10); (3) severe (NIHSS score, 11–15); (4) highly severe (NIHSS score, >16); and (5) death. Serum lipid levels were examined on day 0 (admission) and on an additional day from days 10 to 14. Type of stroke was classified using the Trial of ORG 10172 in Acute Stroke Treatment classification.[26] Neurological status and disability scoring was performed by the neurologist.

The primary end point of the study was the difference in mRS scores between the day of admission (day 0) and day 30 (delta mRS).

Secondary end points were the differences between NIHSS scores on days 0 and 30 (delta NIHSS), recurrent brain infarction, myocardial infarction, and vascular death after day 30, and recurrent stroke between days 0 and 30. Total cholesterol, triglycerides, high-density lipoprotein (HDL), and LDL levels were examined. The examinations were conducted on admission and on day 30. The 4-week follow-up period was chosen to reflect the idea that any additional neuroprotective effect of atorvastatin may influence outcome at the acute and early subacute phases. The outcome assessments were performed by a blinded evaluator who was not aware of the patients' medications. After 2 weeks, the patient was transferred to a rehabilitation center, or care management was reassigned to a general practitioner, who was requested to continue the statin treatment policy of the study for an additional 2 weeks. The decision to continue statin therapy later was at the physician's discretion.

Blood samples were drawn without anticoagulant, centrifuged at room temperature at 1500*g* for 10 minutes and analyzed on the same day. Concentrations of triglycerides, total cholesterol, and HDL cholesterol in serum were measured using the Olympus AU 2700 analyzer, (Olympus corporation, Tokyo, Japan) using the manufacturer's kits. Low-density lipoprotein cholesterol was calculated using the Friedewald formula.[27]

Statistical Analysis

Analysis of data was carried out using SPSS 10.0 statistical analysis software (SPSS Inc, Chicago, Ill). Distribution of continuous variables was assessed for normality using the Kolmogorov-Smirnov test (cutoff at $P < 0.01$). Normally distributed continuous variables, such as age and serum total cholesterol, were described using mean (SD). Variables such as serum HDL cholesterol, triglycerides, and all scores had distributions significantly deviating from normal so are described using median (minimum-maximum). Categorical variables, such as treatment group, sex, and comorbidities, are described using frequency distributions and are presented as frequency (%). One-way analysis of variance or the Kruskal-Wallis test was used to compare continuous variables across treatment groups. These tests were followed post hoc with Bonferroni test of the Mann-Whitney *U* as appropriate. The χ^2 test (exact as needed) was used to assess associations between treatment group and other categorical variables. Models of posttreatment NIHSS and, separately, mRS scores were developed using general linear modeling with a backward, stepwise approach and included treatment group as a fixed factor in all models. All tests are 2-sided and considered significant at $P < 0.05$.

RESULTS

A total of 371 patients (249 male and 122 female) were included in the present study. Ninety subjects received simvastatin (group 1), 185 received 40 mg atorvastatin (group 2), and 96 were treated with 80 mg atorvastatin (group 3). Demographic, medical, and lipid profile characteristics of the study participants are presented by treatment group in Table 1. As can be seen, subjects in group 1 were significantly older than those in group 2 ($P = 0.03$) or group 3 ($P = 0.002$), but groups 2 and 3 subjects did not significantly differ in terms of age ($P = 0.59$). The proportion of present smokers was lowest in group 1 and highest in group 3; atrial fibrillation was highest in group 1 and lowest in group 3; and the proportion of subjects who had previously undergone coronary artery bypass graft was lowest in group 2; however, none of these observations reached statistical significance across treatment groups. Medications that differed across treatment groups included clopidogrel, which was significantly more frequently prescribed to group 3 than to group 1 ($P = 0.004$) and marginally more than group 2 ($P = 0.06$), but a difference between groups 1 and 2 was not observed ($P = 0.13$). Group 1 subjects received significantly more warfarin than did subjects in group 2 ($P = 0.02$) or group 3 ($P = 0.02$), but no difference between groups 2 and 3 was detected ($P = 0.6$).

TABLE 3. Posttreatment Lipid Profile by Treatment Group

	Group 1	Group 2	Group 3	
	Simvastatin	40 mg Atorvastatin	80 mg Atorvastatin	
	n = 90	n = 185	n = 96	*P*
Total cholesterol, mean (SD), mg/dL	178.59 (52.76)	168.08 (53.33)	160.76 (43.76)	0.06
Triglycerides, median (minimum-maximum), mg/dL	143.5 (60–315)	147 (49–303)	165 (77–317)	0.07
HDL cholesterol, median (minimum-maximum), mg/dL	41 (28–83)	42 (25–77)	40 (30–68)	0.65
LDL cholesterol, mean (SD), mg/dL	118.82 (29.26)	117.09 (28.03)	109.58 (22.39)	0.04

Few subjects received heparin; nevertheless, the 4.4% of subjects in group 1 treated with heparin was significantly more than the proportion in group 2 (0.5%, $P = 0.02$), but other pairwise differences were not noted. Group 3 subjects received significantly fewer β-blockers than did subjects in group 1 ($P = 0.001$) or group 2 ($P = 0.004$), but groups 1 and 2 subjects did not differ ($P = 0.4$). In group 1, significantly more diuretics were prescribed to than in group 2 ($P = 0.0002$) and marginally more in group 3 ($P = 0.08$), but groups 2 and 3 did not differ from one another ($P = 0.11$). Calcium-channel blockers were prescribed significantly more frequently to group 3 subjects than to those in group 2 ($P = 0.001$), but differences between groups 1 and 2 ($P = 0.2$) and groups 1 and 3 ($P = 0.11$) were not observed.

Table 2 depicts baseline and posttreatment NIHSS and mRS scores by treatment group. Neither NIHSS nor mRS values differed across groups at baseline. At the end of the study, both NIHSS and mRS values differed significantly across groups. The NIHSS scores were significantly higher in group 1 than group 2 ($P < 0.0001$) or group 3 ($P < 0.0001$) scores, whereas group 2 scores were marginally higher than those of group 3 ($P = 0.08$). The mRS scores were significantly higher in group 1 than in group 2 ($P = 0.002$) and group 3 ($P < 0.0001$); in addition, group 2 scores were significantly higher than group 3 scores ($P = 0.005$).

At the end of follow-up, serum LDL levels differed significantly across treatment groups, being lowest in subjects in group 3; however, significant post hoc pairwise differences were not detected. Marginal across-group differences were detected for total cholesterol and triglycerides (Table 3).

Tables 4 and 5 present the general linear models for posttreatment NIHSS and mRS scores. These models indicate that even after adjusting for age and baseline scores (and diuretic use in the model of the mRS score), treatment group remained significantly associated with end-of-follow-up scores. Subjects receiving simvastatin had significantly higher posttreatment NIHSS and mRS scores even after adjusting for age and baseline scores.

The distribution of stroke type by treatment group is displayed in Table 6. As can be seen, stroke type was similar across treatment groups ($P = 0.9$).

TABLE 4. General Linear Model of Posttreatment NIHSS Scores

	Type III Sum of Squares	Mean Squares	F	*P*
Source				
Corrected model	286.91	71.73	57.02	0.00
Intercept	10.98	10.98	8.73	0.00
NIHSS at baseline	197.42	197.42	156.95	0.00
Age, y	10.73	10.73	8.53	0.00
Treatment group	56.43	28.17	22.40	0.00
Error	459.13	1.26		
Total	1338.00			
Corrected total	746.04			

$R^2 = 0.385$ (adjusted $R^2 = 0.378$)

Estimated Marginal Means

			95% Confidence Interval	
Treatment Group	**Mean**	**SE**	**Lower**	**Upper**
Group 1	1.96	0.12	1.72	2.19
Group 2	1.09	0.08	0.93	1.26
Group 3	0.95	0.12	0.72	1.17

Evaluated at covariates appearing in the model: baseline NIHSS score = 1.7108, age = 65.5405.

Post hoc analysis indicates that posttreatment NIHSS scores adjusted for baseline NIHSS scores and age were significantly greater in group 1 than in group 2 ($P < 0.0001$) or group 3 ($P < 0.0001$), but a difference between groups 2 and 3 scores was not detected ($P = 0.3$).

TABLE 5. General Linear Model of Posttreatment mRS Scores

	Type III Sum of Squares	Mean Squares	F	*P*
Source				
Corrected model	977.05	195.41	162.15	0.00
Intercept	19.50	19.50	16.18	0.00
mRS at baseline	808.75	808.75	671.09	0.00
Age, y	6.89	6.89	5.72	0.00
Diuretics	7.47	7.47	6.20	0.01
Treatment group	82.14	41.07	34.08	0.00
Error	438.66	1.21		
Total	2428.00			
Corrected total	1415.72			

$R^2 = 0.690$ (adjusted $R^2 = 0.686$)

Estimated Marginal Means

			95% Confidence Interval	
Treatment Group	**Mean**	**SE**	**Lower**	**Upper**
Group 1	2.49	0.12	2.26	2.72
Group 2	1.46	0.08	1.30	1.63
Group 3	1.23	0.11	1.01	1.45

Evaluated at covariates appearing in the model: age = 65.5405, baseline mRS = 2.2270, diuretics = 0.2000.

Post hoc analysis indicates that posttreatment mRS scores were significantly higher in group 1 than in group 2 ($P < 0.0001$) or group 3 ($P < 0.0001$) and marginally higher in group 2 than in group 3 ($P = 0.096$).

DISCUSSION

The objective of the present study was to compare the efficacy of atorvastatin (40 or 80 mg) or simvastatin (at an optimal dose) at 30 days after stroke in hyperlipidemic patients treated with simvastatin before stroke onset. It was assumed that the 30-day follow-up period would reflect the interval during which atorvastatin may confer additional neuroprotective effects. The NIHSS scores suggested an improved neurological outcome among patients receiving atorvastatin therapy after

TABLE 6. Type of Stroke by Treatment Group

Treatment Group	Atheromatotic	Cardiogenic	Lacunar Infarction	Miscellaneous
Group 1	20 (22.2)	16 (16.6)	32 (33.3)	11 (11.5)
Group 2	21 (21.8)	17 (18.8)	30 (33.3)	10 (11.1)
Group 3	40 (21.6)	35 (18.9)	67 (36.2)	25 (13.5)

Values are n (%).

Across comparison groups $P = 0.9$.

stroke. In addition, mRS scores indicated that functioning was marginally better preserved among subjects treated with 80 mg atorvastatin daily. The treatment benefit of atorvastatin was also reflected by a lower mortality rate on atorvastatin-treated patients. This is consistent with the significantly better functional and neurological scores among atorvastatin-treated individuals . The clinical impact of the data is underlined by the fact that the NIHSS score was classified into 5 categories of severity; thus, a 1-point change in score represents an increase or decrease into a higher or a lower severity category.

The more favorable early outcome observed among atorvastatin-treated patients may suggest an additional neuroprotective effect of this drug. Atorvastatin-associated neuroprotection has been consistently demonstrated in a number of animal models.[7,13–16] Mechanisms of action include eNOS expression up-regulation,[17] Akt activation, down-regulation of Erg and VEGF gene expression,[13,14] NADPH oxidase–derived superoxide inhibition,[12,16] increased cerebral blood flow, serum tPA regulation, and stabilization of the disrupted blood-brain barrier.[8,9,11] Improvement in hemorheological parameters and reduced platelet aggregation have been reported after short-term administration of low-dose atorvastatin.[28]

In the present study, a correlation between NIHSS and mRS scores and serum lipids was not detected. This observation implies that neuroprotection, rather than lipid lowering, is associated with better outcome, a finding also described in animal models.[29] Assigning causality of the observed treatment benefit to a pleiotropic effect cannot be made, and such an association remains hypothetical. Because both drugs used in the study affect the geranylgeranyl phosphatase pathway, and because some studies have demonstrated that class effects share some of the pleiotropic effect of statins, it cannot be excluded that other mechanisms are responsible for the clinical difference between groups.[7] It can be explained by differences in potency, pharmacodynamics, distribution, and kinetics. In the FASTER (Fast Assessment of Stroke and Transient Ischemic Attack to Prevent Early Recurrence) study, which compared the efficacy of simvastatin administration within 24 hours of onset of transient ischemic attack or minor stroke, an increase in absolute risk of 3.3% among patients on simvastatin was noted.[30] This suggests that findings of the present study are more consistent with a pleiotropic effect of atorvastatin rather than a class effect of the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors.

Although the present study confirms the neuroprotective effect of atorvastatin therapy, it has several important limitations. First, the 30-day follow-up period may be too short to definitively assess clinical relevance. Nevertheless, our findings support a short-term outcome improvement that can be studied for longer duration in the future. Second, the study was observational, and thus, the postulated presence of additional neuroprotection conferred by atorvastatin has not been demonstrated conclusively. It is also possible that a tolerance to the beneficial effect of all statins develops over time, so that their neuroprotectivity is conferred only in the initial few weeks of usage and then plateaus. Third, the present study compared atorvastatin at 40- and 80-mg doses and simvastatin in optimal prestroke dose. None of these treatments were compared with simvastatin at a higher dose, so comparable or improved poststroke outcomes with high-dose simvastatin cannot be ruled out. Fourth, selection bias for treatment assignment cannot be excluded. For example, simvastatin-treated subjects were significantly older than others, and although this was corrected in statistical analysis, it cannot be ruled out that age difference confounds the association between some unmeasured variable and outcome.

In conclusion, the present study documented better early outcome as measured by NIHSS and mRS in stroke patients treated with atorvastatin than in those treated with simvastatin. This improvement is consistent with a pleiotropic effect of atorvastatin. However, randomized clinical trials with extended follow-up are required to establish treatment guidelines regarding the use of this drug in the immediate poststroke period.

REFERENCES

1. Amarenceo P, Bogousslavsky J, Callahan A 3rd, et al. Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med* 2006;355(6):549–559.
2. Amarenco P, Goldstein LB, Szarek M, et al. SPARCL Investigators. Effects of intense low-density lipoprotein cholesterol reduction in patients with stroke or transient ischemic attack: the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial. *Stroke* 2007;38(12):3198–3204.
3. Goldstein LB, Amarenco P, Lamonte M, et al. SPARCL Investigators. Relative effects of statin therapy on stroke and cardiovascular events in men and women: secondary analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial. *Stroke* 2008;39(9):2444–2448.
4. Zacco A, Togo J, Spence K, et al. 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors protect cortical neurons from excitotoxicity. *J Neurosci* 2003;23(35):11104–11111.
5. Ponce J, de la Ossa NP, Hurtado O, et al. Simvastatin reduces the association of NMDA receptors to lipid rafts: a cholesterol-mediated effect in neuroprotection. *Stroke* 2008;39(4):1269–1275.
6. Liu XS, Zhang ZG, Zhang L, et al. Atorvastatin downregulates tissue plasminogen activator-aggravated genes mediating coagulation and vascular permeability in single cerebral endothelial cells captured by laser microdissection. *J Cereb Blood Flow Metab* 2006; 26(6):787–796.
7. Asahi M, Huang Z, Thomas S, et al. Protective effects of statins involving both eNOS and tPA in focal cerebral ischemia. *J Cereb Blood Flow Metab* 2005;25(6):722–729.
8. Tanaka N, Katayama Y, Katsumata T, et al. Effects of long-term administration of HMG-CoA reductase inhibitor, atorvastatin, on stroke events and local cerebral blood flow in stroke-prone spontaneously hypertensive rats. *Brain Res* 2007;1169:125–132.
9. Pretnar-Obliak J, Sabovic M, Sebestjen M, et al. Influence of atorvastatin treatment on L-arginine cerebrovascular reactivity and flow-mediated dilatation in patients and lacunar infarctions. *Stroke* 2006;37(10):2540–2545.
10. Clarke RM, Lyons A, O'Connell F, et al. A pivotal role for interleukin-4 in atorvastatin-associated neuroprotection in rat brain. *J Biol Chem* 2008;283(4):1808–1817.
11. Kalayci R, Kaya M, Elmas I, et al. Effects of atorvastatin on blood-brain barrier permeability during L-NAME hypertension followed by angiotensin-II in rats. *Brain Res* 2005;1042(2):184–193.
12. Kahles T, Leudike P, Endres M, et al. NADPH oxidase plays a central role in blood-brain barrier damage in experimental stroke. *Stroke* 2007;38(11):3000–3006.
13. Zhang L, Zhang ZG, Liu XS, et al. The PI3K/Akt pathway mediates the neuroprotection effect atorvastatin in extending thrombolytic therapy after embolic stroke in the rat. *Arterioscler Thromb Vasc Biol* 2007;27(11):2470–2475.
14. Chen J, Zhang C, Jiang H, et al. Atorvastatin induction of VEGF and BDNF promotes brain plasticity after stroke in mice. *J Cereb Blood Flow Metab* 2005;25(2):281–290.
15. Yrjanheikki J, Koistinaho J, Kettunen M, et al. Long-term protective

effect of atorvastatin in permanent focal cerebral ischemia. *Brain Res* 2005;1052(2):174–179.

16. Hong H, Zeng JS, Kreulen DL, et al. Atorvastatin protects cerebral infarction via inhibition of NADPH oxidase–derived superoxide in ischemic stroke. *Am J Physiol Heart Circ Physiol* 2006;291(5):H2210–H2215.
17. Laufs U, Gertz K, Huang P, et al. Atorvastatin upregulates type III nitric oxidase synthase in thrombocytes, decreases platelet activation and protects from cerebral ischemia in normocholesterolemic mice. *Stroke* 2000;31(10):2442–2449.
18. Lee SH, Kim YH, Kim YJ, et al. Atorvastatin enhances hypothermia-induced neuroprotection after stroke. *J Neurol Sci* 2008;275(1–2):64–68.
19. Gertz K, Laufs U, Lindauer U, et al. Withdrawal of statin treatment abrogates stroke protection in mice. *Stroke* 2003;34(2):551–557.
20. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *JAMA* 2001;285(19):2486–2497.
21. Smith SC Jr, Allen J, Blair SN, et al. AHA/ACC; National Heart, Lung, and Blood Institute. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. *Circulation* 2006;113(19):2363–2372.
22. Pasternak RC, Smith SC Jr, Bairey-Merz CN, et al. American College of Cardiology, American Heart Association, National Heart, Lung, and Blood Institute. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *Circulation* 2002;106(8):1024–1028.
23. Adams H, Adams R, Del Zoppo G, et al. Stroke Council of the American Heart Association, American Stroke Association. Guideline for the early management of patients with ischemic stroke: 2005 guidelines update a scientific statement from the Stroke Council of the American Heart Association/American Stroke Association. *Stroke* 2005;36(4):916–923.
24. Muir KW, Weir CJ, Murray GD, et al. Comparison of neurological scales and scoring systems for acute stroke prognosis. *Stroke* 1996;27(10):1817–1820.
25. Burn JP. Reliability of the modified Rankin Scale. *Stroke* 1992;23(3):438.
26. Goldstein LB, Jones MR, Matchar DB, et al. Improving the reliability of stroke subgroup classification using the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria. *Stroke* 2001;32(5):1091–1098.
27. Friedewald WT, Levy RT, Fredrickson DS. Estimation of the concentration of low-density lipoprotein-cholesterol without the use of the preparation ultracentrifuge. *Clin Chem* 1972;18:499–502.
28. Szapary L, Horvarth B, Marton Z, et al. Short-term effect of low dose atorvastatin on haemorheological parameters, platelet aggregation and endothelial function in patients with cerebrovascular disease and hyperlipidemia. *CNS Drug* 2004;18(3):165–172.
29. Blanco M, Nombela F, Castellanos M, et al. Statin treatment withdrawal in ischemic stroke: a controlled randomized study. *Neurology* 2007;69(9):904–910.
30. Kennedy J, Hill MD, Ryckborst KJ, et al. FASTER Investigators. Fast Assessment of Stroke and Transient Ischemic Attack to Prevent Early Recurrence (FASTER): a randomized controlled pilot trial. *Lancet Neurol* 2007;6(11):961–969.

