Background and Purpose—Uncontrolled studies have shown that statins can improve cerebral vasoreactivity (CVR) in patients with mild small vessel disease. We sought to determine whether high-dose atorvastatin increases CVR compared with placebo in patients with severe small vessel disease.

Methods—Ninety-four adults with recent lacunar stroke were randomly allocated in a double-blind manner to 80 mg of atorvastatin daily or matching placebo after stratification for hypertensive and diabetic status. The primary end point was change in CVR after 3 months of treatment. Secondary outcomes were changes in brachial and carotid artery endothelial-dependent vasodilations.

Results—At baseline, all patients had a severely impaired CVR (mean, 12.1%; 95% CI, 9.5–14.7) and carotid (mean, −0.25%; 95% CI, −1.17–0.67) and brachial artery (mean, 2.72%; 95% CI, 1.39–4.05) endothelial function. Despite reductions of 55% in low-density lipoprotein cholesterol and of 30% in high-sensitivity C-reactive protein in the active arm compared to placebo, atorvastatin 80 mg per day did not improve CVR or endothelial dysfunction of carotid and brachial arteries.

Conclusion—We found no positive effect of 3-month treatment with atorvastatin on severe cerebral microvasculature endothelial dysfunction in patients with lacunar stroke. *Stroke.* 2009;40:1721-1728.

Key Words: atorvastatin ■ cerebral vasoreactivity ■ endothelial dysfunction ■ lacunar stroke

By guest on April 13, 2017

http://stroke.ahajournals.org/ Downloaded from

Placebo-Controlled Trial of High-Dose Atorvastatin in Patients With Severe Cerebral Small Vessel Disease

Philippa C. Lavallée, MD; Julien Labreuche, BS; Fernando Gongora-Rivera, MD; Arturo Jaramillo, MD; David Brenner, MD; Isabelle F Klein, MD, PhD; Pierre-Jean Touboul, MD; Eric Vicaut, MD; Pierre Amarenco, MD; on behalf of the Lacunar-B.I.C.H.A.T. Investigators*

B rain infarction attributable to small vessel disease (SVD) accounts for ≈30% of ischemic strokes (ie, lacunar infarction).¹ In >80% of cases these brain infarcts are associated with multilacunes, leukoaraiosis, dilatation of perivascular spaces, and asymptomatic microbleeds, accounting for a diffused cerebral arteriolopathy.² Pathologically, there is thickening of the media of vessels <300 μm in diameter with invasion of the media by fibrin, lipid deposit, and fibrosis (lipohyalinosis), and presumably endothelial dysfunction. Consequently, intracranial arterial resistance increases with lower diastolic velocities on transcranial Doppler and impaired vasomotor reactivity. Cerebral vasoreactivity (CVR) is the compensatory dilatory capacity of cerebral resistance vessels in response to a stimulus such as carbon dioxide.³ Impaired CVR has been reported in SVD.⁴ ⁷ Impaired vasoregulation of the subcortical microvasculature could be a pathogenic mechanism of SVD and a target for specific treatment. In animal models, statins have been reported to improve endothelial homeostasis by increasing the bioavailability of nitric oxide,⁸ and small uncontrolled studies involving statins showed improvement in CVR in patients with mild SVD.⁹ In addition to the pleiotropic effect of statins, the presence of lipid deposits in the media of lipohyalinotic vessels¹⁰ and high low-density lipoprotein (LDL) cholesterol levels in patients with SVD in observational studies¹¹ forms the rationale for a possible efficacy of statins in patients with SVD. A treatment that improves CVR could potentially improve the outcome of cerebral SVD.

The aim of this study was to investigate the effect of high-dose atorvastatin treatment on CVR in patients with a recent lacunar infarction. The secondary objective was to determine whether atorvastatin can improve brachial and carotid endothelial function in the same population.

Materials and Methods

The study protocol was approved by the local research ethics committee. All patients gave written informed consent before participating in the study. Patients were recruited from 9 neurology departments in French hospitals.

Received October 16, 2008; accepted November 27, 2008.

From INSERM U-698 and Department of Neurology and Stroke Centre (P.C.L., J.L., F.G.-R., A.J., D.B., P.J.T. P.A.), Bichat University Hospital, Denis Diderot University and Medical School, Paris, France; Neuroradiology Unit (I.F.K.), Department of Radiology, Bichat University Hospital, Denis Diderot University and Medical School, Paris, France; Department of Biostatistics and Clinical Research (E.V.), Fernand Widal University Hospital, Denis Diderot University and Medical School, Paris, France. ¹¹ The list of investigators is provided in the appendix.

Trial registration: ClinicalTrials.gov NCT00163150.

Correspondence to Professor Pierre Amarenco, Department of Neurology and Stroke Centre, Assistance Publique-Hôpitaux de Paris, Bichat hospital, Denis Diderot University and Medical School, 46, rue Henri Huchard, 75018 Paris, France. E-mail pierre.amarenco@bch.aphp.fr

© 2009 American Heart Association, Inc.

*Stroke* is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.108.540088

1721
Patient Population
Eligible patients were adult (≥18 years) men and women who had had a lacunar stroke within the previous 3 months. Lacunar stroke was defined according to previously published criteria. Briefly, patients were eligible for inclusion if they had clinical lacunar syndrome—a small, deep infarct (<15 mm on diffusion-weighted imaging corresponding to the symptoms and no other cause of stroke. All patients had standard investigations to exclude a cardiac source of embolism (ie, physical examination, ECG, transesophageal echocardiography), dissection or significant atherosclerosis (ie, cervical duplex ultrasonography, transcranial Doppler, magnetic resonance angiography of extracranial and intracranial vessels). Patients with arterial stenosis ≥50% in the stroke territory were excluded. Other exclusion criteria were women of child-bearing potential, current statin or fibrate treatment, and contraindication to CBFV tests (ie, unstable angina, severe respiratory insufficiency, no temporal bone window).

Vascular risk factors were systematically recorded. Hypertension was defined as a history of treated hypertension or current antihypertensive medication. Smoking history was coded as current smoker, ex-smoker, or nonsmoker. Subjects were classified as having diabetes if they were treated for insulin-dependent or noninsulin-dependent diabetes, and as having hypercholesterolemia if they have been treated with lipid-lowering drugs.

Study Design
Patients were enrolled in this randomized, double-blind, placebo-controlled trial between April 2003 and November 2005 (ClinicalTrials.gov—NCT00163150). Patients were selected in the 48 hours after lacunar stroke as defined. No recommendations were made for secondary stroke prevention except for the exclusion of lipid-lowering treatment. Because uncontrolled hypertension and diabetes decreased CVR, all patients were seen by 1 neurologist (P.L.) at Bichat Hospital 1 month after the stroke event (M-2 visit). If hypertension or diabetes was uncontrolled (blood pressure >140/90 mm Hg or glycosylated hemoglobin >6.2%), treatments were adjusted according to guideline recommendations. Baseline CVR evaluation was performed 3 months after the stroke event (M0, randomization visit). Brachial and carotid endothelium-dependent vasodilation (EDV) and endothelium-independent vasodilation (EIV) were measured at the same time. Patients were stratified according to hypertensive and diabetic status, and were randomly assigned to receive either atorvastatin 80 mg per day or matching placebo. After a 3-month treatment period, CVR and carotid and humeral tests were reassessed (M+3 visit). Systolic blood pressure and diastolic blood pressure and blood tests including lipid profile, glycemia, glycosylated hemoglobin, high-sensitivity C-reactive protein (hsCRP), and homocystinemia were measured at M0 and M3.

Cerebrovascular Reactivity Protocol
All vascular studies were performed in a quiet room in 12-hour fasting patients after 10 minutes of rest in a supine position. Right middle cerebral artery was insonated using transcranial Doppler (DWL Elektronique Systeme GmbH) with a 2-MHz probe placed on the physiological temporal bone window at a depth of 50 to 60 mm. Mean middle cerebral artery blood flow velocities (CBFVm) were calculated from the velocity curve of the velocity spectrum recorded during rest and after 5 minutes of CO2-enriched gas mixture inhalation (15% O2, 5% CO2, and 80% N2; Air Liquide, France). CVR was calculated from the formula: CVR=(CBFVm(CO2)−CBFVm(basal))/CBFVm(basal)×100, where CBFVm(basal) means CBFVm under rest conditions and CBFVm(CO2) means CBFVm after 5 minutes of CO2-enriched gas mixture inhalation.

Assessment of EDV of BA and CCA
Endothelial function of the BA was assessed using the vasodilation response to endothelium-dependent stimuli, as previously reported. Reactive hyperemia was induced by deflating a cuff previously inflated to 200 mm Hg for 4 minutes around the forearm. The diameter of the BA was measured at rest and 60 to 90 seconds after deflation of the cuff.

Assessment of EIV of BA and CCA
After assessment of BA and CCA EDV, 10 minutes were allowed for vessel recovery. Sublingual nitroglycerin spray was then administered (300 μg; Natispray; Proctor and Gamble Pharmaceuticals, France). Measurement of BA and CCA diameters was obtained 3 to 5 minutes after nitroglycerine (NTG) administration.

Calculations
EDV of the BA and CCA was defined as the relative increase in lumen diameter observed under reactive hyperemia and calculated as percent of basal values. EIV of the BA and CCA was defined as the relative increase in lumen diameter observed after NTG administration and was calculated as percent of basal values.

MRI Analysis
Two neurologists (P.L., H.A.) independently reviewed and graded the MRI scans using a standardized form. Any disagreements were resolved by a third neurologist (P.A.). Leukoaraiosis was rated in accordance with the scale of Scheltens et al. Scores depending on the size and number of lesions in the frontal, temporal, parietal, and occipital periventricular and subcortical white matter were summed to give a total score ranging from 0 to 30. Lacunar infarction was defined as an abnormal signal, hypointense on T2-weighted images, and hypointense on T1-weighted images. The size of the infarct had to be <15 mm and the margins had to be irregular. Multilacunar state was defined as number of lacunar infarctions >1. Dilated perivascular spaces, or "état criblé," was defined as hypersignal on T2-weighted images and hyposignal on T1-weighted images with a round shape and smooth margins in the lenticulostriate area and with multiple long, thin (<1 mm) hypesignals in the semiovale area with a comb-like aspect. Microbleeds were defined as small, silent foci of signal loss on T2*-weighted MRI.

Efficacy Outcomes
The primary efficacy outcome was the change in CVR after 3 months. Secondary efficacy outcomes were the change in endothelium-dependent and independent vasodilations of the BA and CCA.

Database
CLINACT, a clinical research organization, performed independent monitoring and data management on behalf of the sponsor. After the end of the follow-up for the last patient enrolled, we performed a blinded review (April 10, 2006). The database was closed on July 18, 2006, and was then transferred to the study biostatistician (J.L.).
Statistical Analyses
The present study was designed to have a statistical power of 80% to detect an absolute difference of 6% in CVR between 2 groups using a 2-sided t test with a significance level of 5% and an estimated standard deviation of 12%. In this case, 64 subjects were needed in each group. Because the analysis of covariance was planned to be used, the test power was expected to be higher even if the exact power could not be assessed because the correlation value between variable and covariable was unknown. Considering that the main objective was to evaluate a pharmacodynamic property of atorvastatin (its potential effect on CVR), primary and secondary end points were analyzed according to randomized patients who completed the treatment as defined in the protocol (per protocol [PP]). Secondary efficacy analysis was performed in all randomized patients (intention-to-treat [ITT]). Differences in primary and secondary efficacy outcomes between treatment groups were calculated as means and 95% CI, and were tested by analysis of covariance with the baseline values of analyzed criterion as covariate. In sensitivity analysis, multiple imputation based on the Markov Chain Monte Carlo method was used for handling missing data.

Exploratory analysis on the PP population was also performed to evaluate the between-group difference in change in biological parameters and blood pressure by analysis of covariance with the baseline value as the covariate; nonparametric analysis was used for skewed variables (triglycerides, homocysteine, and hsCRP). No correction was made for multiple comparisons, and this analysis should be interpreted with caution.

Statistical testing was performed with a 2-tailed α level of 0.05. Data were analyzed using SAS software, version 9.1.3 (SAS Institute Inc).

Role of the Funding Source
The study sponsors had no involvement in the study design, in the collection, analysis, and interpretation of data, in the writing of the report, or in the decision to submit the paper for publication. The investigators managed the database, had full access to the data, and take full responsibility for the accuracy of the report.

Results
The number of eligible individuals screened, randomized, treated, and included in the primary efficacy analysis, along with the main reasons for exclusion, are shown according to treatment group in Figure 1. Because of the strict exclusion criteria (eg, exclusion of patients with coexisting causes even if the clinical and radiological data strongly suggested SVD, and of patients not previously using statin therapy), the trial failed to meet the recruitment rate target (n=128). Of the 117 eligible patients screened, 94 were randomized and 91 patients received at least 1 dose of assigned treatment. These 91 patients had baseline CVR measurements and constitute the ITT population; 69 patients with no major protocol deviations (as defined before the database was closed) constitute the PP population.

Baseline Characteristics
Baseline characteristics of the ITT population, including lipid levels and outcomes, are shown in Table 1. Treatment groups were well-balanced with regard to demographics, vascular risk factors, biological parameters (including levels of lipids, glucose, homocysteine, and hsCRP), blood pressure, and MRI data. All patients had a severely impaired CVR (mean, 12.1%; 95% CI, 9.5–14.7) and carotid (mean, 0.25%; 95% CI, 1.17–0.67) and brachial artery (mean, 2.72%; 95% CI, 1.39–4.05) endothelial function. CVR was slightly higher in the atorvastatin group (mean, 14.3%; 95% CI, 11.1–17.6) compared to the placebo group (mean, 9.9%; 95% CI, 5.8–14.0). Carotid and brachial EDV or EIV were similar in the 2 groups. A total of 47% of patients were identified as having a multilacunar state and 80% as having état criblé.

The median of leukoariosis score was 7 (interquartile range, 4–19), and 41% of the 63 patients with a T2*-MRI had at least 1 microbleed.

Biological Parameters and Blood Pressure
Figure 2 shows changes in lipid profile, hsCRP, homocysteine, and glucose during the trial in the PP population. After
3 months, the mean total cholesterol level decreased to 3.6 mmol/L (140 mg/dL) in the atorvastatin group and remained unchanged in the placebo group at 5.8 mmol/L (226 mg/dL); the resulting difference in total cholesterol was 37% (95% CI, 32–42). LDL cholesterol levels decreased by 55.3% in the atorvastatin group and remained unchanged in the placebo group. The resulting LDL cholesterol between-group difference was 53% (95% CI, 47–59). No significant change in high-density lipoprotein cholesterol levels was found in either treatment group. Triglyceride levels decreased in the atorvastatin group without significant difference with the placebo group. Similar results were observed in the ITT population, with a total and LDL cholesterol reduction of 33% (95% CI, 26–39) and 47% (95% CI, 38–55), respectively, in the atorvastatin group compared to the placebo group. With regard to hsCRP, a large decrease was observed in the atorvastatin group (median change, –30.3%), whereas the level remained unchanged in the placebo group (median change, 3.1%). There was no significant difference in change in glucose and homocysteine levels between the treatment groups.

No significant between-group difference was found for blood pressure changes. In the atorvastatin group, mean absolute systolic blood pressure and diastolic blood pressure changes were −3.9 mmHg (95% CI, −8.2–0.3) and −2.8 mmHg (95% CI, −5.5–−0.1), respectively. In the placebo group, the corresponding changes were −0.8 mmHg (95% CI, −5.2–3.6) and −1.4 mmHg (95% CI, −4.2–1.5).

**Treatment-Related Changes in CVR**

CVR assessment at follow-up was missing for 3 patients because they declined to undergo the CO2 test; none was part of the PP population. No significant change in CVR was found between the treatment groups in the PP or the ITT populations (Table 2). The estimated treatment effect (atorvastatin minus placebo) was −1.2% (95% CI, −7.1–4.7) in the PP population and −2.3% (95% CI, −7.6–2.9) in ITT population (Figure 3).

**Treatment-Related Changes in EDV and EIV of BA and CCA**

Because of missing values at baseline and follow-up visits, the change in carotid vasodilation was available for 70% (EDV) and 61% (EIV) of patients included in the PP population. All missing values were attributable to a computer failure with loss of data from consecutively recruited patients. Carotid EDV and EIV remained unchanged at the end of the trial in both the atorvastatin and placebo groups (Table 2). The estimated treatment-related difference was −0.8% (95% CI, −3.0%–1.4%) for EDV and −0.5% (95% CI, −3.3–2.4) for EIV. The change in brachial vasodilation was available for 67% (EDV) and 59% (EIV) of patients in the PP population. As reported in Table 2 and Figure 3, treatment with atorvastatin did not improve brachial EDV or EIV. Similar results were found in the ITT analysis and in sensitivity analysis using a multiple imputation method to handle missing values.

**Discussion**

Despite average reductions of 55% in LDL cholesterol, 20% in triglycerides, and 30% in hsCRP, this prospective, randomized, double-blinded, placebo-controlled trial showed no evidence that 3-month treatment with atorvastatin 80 mg per day improved severely impaired CVR in patients with lacunar stroke. Two previous studies reported that statin therapy increased CVR in patients with SVD.7,9 One evaluated pravastatin 20 mg per day for 2 months,7 and the other evaluated atorvastatin 40 mg per day for at least 3 months.7

### Table 1. Baseline Characteristics of Patients Randomly Allocated to Atorvastatin or Placebo*

<table>
<thead>
<tr>
<th></th>
<th>Atorvastatin (n=45)</th>
<th>Placebo (n=46)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>61.0±11.8</td>
<td>60.0±9.9</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.8±3.5</td>
<td>26.5±4.5</td>
</tr>
<tr>
<td>Sex, male</td>
<td>(66.7%)</td>
<td>(73.9%)</td>
</tr>
<tr>
<td>Vascular risk factor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>39 (86.7%)</td>
<td>39 (84.8%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>6 (13.3%)</td>
<td>8 (17.4%)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>14 (31.1%)</td>
<td>15 (32.6%)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>15 (33.3%)</td>
<td>23 (50.0%)</td>
</tr>
<tr>
<td><strong>Lipid profile, mmol/L (all median values)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>5.8±0.9</td>
<td>5.7±1.0</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>3.6±0.9</td>
<td>3.6±0.9</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>1.5±0.5</td>
<td>1.4±0.4</td>
</tr>
<tr>
<td>Triglycerides, median (IQR)</td>
<td>1.3 (0.8–1.9)</td>
<td>1.3 (0.9–1.7)</td>
</tr>
<tr>
<td><strong>Other biological variable, median (IQR)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hsCRP, mmol/L</td>
<td>2.5 (1.2–7.0)</td>
<td>3.1 (1.2–6.4)</td>
</tr>
<tr>
<td>Homocystein, mmol/L</td>
<td>11.2 (9.2–13.9)</td>
<td>11.5 (9.6–15.0)</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>5.3 (4.9–5.7)</td>
<td>5.5 (5.0–6.0)</td>
</tr>
<tr>
<td><strong>Vital sign parameter at rest</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>132.7±14.6</td>
<td>133.7±12.8</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>78.0±8.3</td>
<td>78.1±7.7</td>
</tr>
<tr>
<td><strong>MRI variable</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multilacunar state</td>
<td>17 (41.5%)</td>
<td>22 (52.4%)</td>
</tr>
<tr>
<td>Etat criblé</td>
<td>31 (75.6%)</td>
<td>35 (83.3%)</td>
</tr>
<tr>
<td>Leukoaraiosis score, median (IQR)</td>
<td>8 (4–21)</td>
<td>6 (3–18)</td>
</tr>
<tr>
<td>Microbleeds†</td>
<td>16 (48.5%)</td>
<td>10 (33.3%)</td>
</tr>
<tr>
<td><strong>Outcome, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVR</td>
<td>14.3±10.8</td>
<td>9.9±13.9</td>
</tr>
<tr>
<td>Carotid EDV‡</td>
<td>−0.1±4.0</td>
<td>−0.3±3.9</td>
</tr>
<tr>
<td>Brachial EDV‡</td>
<td>−1.0±6.1</td>
<td>0.2±4.9</td>
</tr>
<tr>
<td>Carotid EIV‡</td>
<td>2.2±6.5</td>
<td>3.3±4.2</td>
</tr>
<tr>
<td>Brachial EIV‡</td>
<td>15.4±9.7</td>
<td>17.7±9.2</td>
</tr>
</tbody>
</table>

*ITT population. Values are expressed as mean (±SD) unless otherwise indicated.
†Data among the 63 T2*−weighted MRI.
‡Rates of missing data ranged from 20%–29%.
BP indicates blood pressure; CVR, cerebral vasoreactivity; DBP, diastolic BP; EDV, endothelium-dependent vasodilation; EIV, endothelium-independent vasodilation; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; SBP, systolic BP.
However, because the study designs were very different from the present study, the findings are not directly comparable. The sample sizes were small (16 and 18 patients, respectively), both were open label and nonrandomized, and there was no control group in the pravastatin study. Moreover, in the pravastatin study, the population was heterogeneous, with a broad definition of SVD, including not only patients with an old lacunar stroke on neuroimaging (none was a recent stroke) but also patients with only leukoaraiosis and some cognitive decline or gait instability or an epileptic seizure. As a result, the patients in the pravastatin study had a much less severe cerebral arteriolopathy than the individuals included in our present study. Pretreatment CVR was 41.9±23.7% compared to 12.1±12.6% in our study.

One strength of our study was that all of the patients had SVD and were randomized to 3 months of treatment, 90 days after the qualifying lacunar stroke, which was ascertained by diffusion-weighted imaging; none had ipsilateral stenosis of extracranial or intracranial parental vessels or other cardiac or arteriolar source of embolism that could explain the small deep infarct. We cannot exclude the possibility that the lack of efficacy of high-dose atorvastatin in our trial was partly caused by too severe or advanced SVD. As mentioned, CVR was unexpectedly low in both active and placebo groups, with a slight non significant absolute difference between 2 groups. Because of the severely impaired baseline CVR in both groups, this absolute difference probably did not impact our results.

Cerebral vasoreactivity measured by a CO2 test in healthy adults has been reported to be ~50%. With these baseline conditions, we cannot exclude the possibility that a small positive effect could have been masked by the large variability of CVR, or that the arteriolopathy was too severe to expect a beneficial effect, or that a longer treatment duration may have been necessary to observe a positive effect of treatment. However, it is clear that we did not miss a meaningful effect. We also did not measure end tidal CO2 and cannot exclude that because of variable individual response to inhaled CO2 a slight non significant absolute difference between 2 groups. Because of the severely impaired baseline CVR in both groups, this absolute difference probably did not impact our results.

Cerebral vasoreactivity measured by a CO2 test in healthy adults has been reported to be ~50%. With these baseline conditions, we cannot exclude the possibility that a small positive effect could have been masked by the large variability of CVR, or that the arteriolopathy was too severe to expect a beneficial effect, or that a longer treatment duration may have been necessary to observe a positive effect of treatment. However, it is clear that we did not miss a meaningful effect. We also did not measure end tidal CO2 and cannot exclude that because of variable individual response to inhaled CO2, we have missed a small effect. However, when we measured CVR, we always waited for a stable state. Finally, we cannot exclude lack of power in our study. In fact, the planned sample size was 128 patients and only 94 (69 in the PP population) were randomized. We had a statistical power of 65% to assess our study hypothesis with 94 patients (ITT population), and 53% with 69 patients (PP population). However, our study sample size remained largest than the previous studies reported in the literature and we observed no effect at all. As reported previously, patients with lacunar stroke have severe endothelial dysfunction. The high rate of hypertension (85%), diabetes (15%), hypercholesterolemia (32%), and tobacco use (41%) in our population could explain this result. However, it is possible that cerebral SVD is associated with a more generalized arteriopathy. Further studies are required to address this question. Previous studies have reported conflicting results about restoration of endothelial dysfunction by statins in patients at high vascular risk. Coronary endothelial dysfunction was improved by statins in patients with coronary artery disease in some studies, but this was not confirmed in others. Similarly, statins improved brachial EDV in patients with coronary artery disease but not in patients with very severe endothelial dysfunction. Only 1 study has tested the effect of statin
treatment on endothelial function in stroke patients with multiple lacunes, and it found that 40 mg per day of atorvastatin for at least 3 months restored endothelial function completely. At baseline, brachial flow-mediated dilation was severely impaired (0.06%) and returned to normal level after treatment (7%). However, the study was open-label and not randomized. In our study, atorvastatin did not improve brachial or carotid EDV. One explanation could again be the strong severity of endothelial dysfunction in our patients. We also could not exclude the lack of adequate statistical power because of the presence of missing values. However, as previously reported, the minimal flow-mediated vasodilatation difference that could be detected with 40 to 60 patients in a parallel group study design ranged from 1.5% to 2%. Therefore, even with the loss of patient data because of the computer failure, our power appeared sufficient, retrospectively. The fact that the data lost related to consecutive patients limited any possible bias in treatment–effect estimates.

In this study, a 3-month high-dose atorvastatin regimen decreased hsCRP by 30% (from 3.0 to 1.7 mg/dL), whereas in the placebo group hsCRP increased by 10% (from 3.1 to 3.7 mg/dL). This is an interesting point because in several studies, hsCRP predicted incident strokes independently of LDL cholesterol levels. There have been suggestions that beside the lipid-lowering mechanism, the positive effect of statins observed on recurrent stroke and coronary events (such as the observation in the SPARCL trial) could partly be explained by the antiinflammatory properties of statins. But in the present trial, despite such strong reductions in hsCRP and LDL cholesterol, there was no apparent improvement of endothelial dysfunction.

As reported recently in a meta-analysis, in the present study with high-dose atorvastatin there was a trend for decreased blood pressure compared to the placebo group, despite no change in blood pressure-lowering treatment. Several mechanisms have been proposed whereby statins may affect blood pressure: increased endothelial nitric oxide production, interaction with the renin–angiotensin system, and improvement of large artery compliance.

In conclusion, in patients with a recent lacunar stroke, despite a 30% reduction in hsCRP and a 55% reduction in LDL cholesterol, treatment with atorvastatin 80 mg per day did not improve severe CVR and CCA or BA endothelial dysfunction.

Appendix

Scientific Committee
Pierre Amarenco, MD (Chair), Philippa Lavallée, MD (Principal Investigator), Isabelle Pithois-Merli, MD (sponsor representative), Pierre-Jean Touboul, MD, Eric Vicaut, MD.

Participating Institutions and Investigators
The following institutions and investigators participated in the Lacunar-B.I.C.H.A.T. study (Lacunar-Brain Infarction, Cerebral Hypereactivity, and Atorvastatin Trial). The number of patients enrolled at each institution is included in parentheses.

Paris, Bichat Hospital, Denis Diderot-Paris VII University: (55) Philippa Lavallée, MD, Denise André, Maguy Desmangles, and Annie Adala (study nurses), Homa Madrakian (clinical research assistant).

Paris, Salpêtrière Hospital, Pierre and Marie Curie-Paris VI University: (3) Yves Samson, MD, Sophie Crozier, MD, Anne Léger MD, Michael Obadia, MD.

Meaux, Centre Hospitalier Général: (6) François Chédré, MD, Alain Améri, MD, Frédéric Klapczynski, MD.

Saint-Denis, Centre Hospitalier Général: (6) Thomas Debroucker, MD, Laurent Martinez, MD.

Pontoise, Centre Hospitalier Général: (5) Jérôme Servan, MD, Bobigny, Avicenne Hospital, Paris XIII University: (3) Jeffrey Salama, MD.

Versailles, Mignot Hospital: (1) Fernando Pico, MD, PhD, Marie Laure Chadenat, MD.

Créteil, Henri Mondor Hospital, Paris XII University: (11) Hassan Hosseini, MD.

Foch, Centre Hospitalier Général: (4) Frédéric Bourdain, MD, Central ultrasound examinations, Bichat Stroke Centre: Philippa Lavallée, MD, David Brenner, MD, Fernando Gongora-Rivera, MD, Arturo Jaramillo, MD.

Patient follow-up, Bichat Stroke Centre: Philippa Lavallée, MD.

Central blood sample analysis, DNA, plasma, and serum banking, Laboratoire de Biochimie, Bichat Hospital, Paris: Bernard Grandchamps, PhD, Joelle Benessiano, PhD.

Statistical analyses: Julien Labreuche, BS, Biostatistician, Eric Vicaut, MD.

Figure 3. Estimated treatment effect of atorvastatin minus placebo on cerebral vasoreactivity and carotid and brachial vasodilatations. Mean changes (adjusted on baseline values) during 3 months of treatment and their 95% CI are illustrated by the squares and bars. The dashed lines show the estimates after handling the missing data using multiple imputation method. *P<0.10, **P<0.05, ***P<0.001 for comparison between treatment groups.
Core laboratory for ultrasound reading: brachial, carotid vasoreactivity, and intima-media thickness measurements of the common carotid arteries: Intelligence in Medical Technology. Data monitoring: CLINACT clinical research organization. Coordinating Center, Department of Neurology and Stroke Centre, Bichat Hospital: Philippe Lavalleé, MD, Homa Madrakian (research assistant), Maguy Desangles, Annie Adala, and Denise André (research nurses).

Acknowledgments
Sophie Rushton-Smith provided editorial services.

Sources of Funding
Supported by a grant from Pfizer France and the SOS-Attaque Cerebrale Association. Sophie Rushton-Smith was funded by the SOS-Attaque Cerebrale Association.

Disclosures
Pierre Amarenco received lecture fees from the sponsor and honoraria for participation to advisory boards and steering committee meetings of another trial funded by the same sponsor. Pierre-Jean Touboul received lecture fees from the sponsor and honoraria for participation to advisory boards and steering committee meetings of another trial funded by the same sponsor. Eric Vicaut received lecture fees from the sponsor and honoraria for participation to advisory boards and steering committee meetings of another trial funded by the same sponsor.

References


Placebo-Controlled Trial of High-Dose Atorvastatin in Patients With Severe Cerebral Small Vessel Disease

*Stroke*. 2009;40:1721-1728; originally published online March 12, 2009;
doi: 10.1161/STROKEAHA.108.540088

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/40/5/1721