Atorvastatin Reduces the Risk of Cardiovascular Events in Patients With Carotid Atherosclerosis
A Secondary Analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Trial

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Background and Purpose—The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial found that treatment with atorvastatin 80 mg per day reduced the risk of stroke and cardiovascular events in patients with a recent transient ischemic attack (TIA) or stroke. We hypothesized this benefit would be greatest in the subgroup of patients with carotid stenosis.

Methods—The SPARCL trial randomized patients with TIA or stroke within 1 to 6 months without known coronary heart disease (CHD) and low-density lipoprotein cholesterol 100 to 190 mg/dL to treatment with atorvastatin 80 mg per day or placebo. Investigators identified subjects as having carotid stenosis not requiring revascularization at the time of randomization. Of the total SPARCL population, 1007 were documented as having carotid stenosis at baseline, 3271 did not, and the status of 453 was unknown.

Results—We found no heterogeneity in the treatment effect for the SPARCL primary (fatal and nonfatal stroke) and secondary end points between the group with and without carotid stenosis. The group with carotid artery stenosis had greater benefit when all cerebro- and cardiovascular events were combined. In the group with carotid artery stenosis, treatment with atorvastatin was associated with a 33% reduction in the risk of any stroke (hazard ratio [HR] 0.67, 95% confidence interval [CI] 0.47, 0.94; P=0.02), and a 43% reduction in risk of major coronary events (HR 0.57, 95% CI 0.32, 1.00; P=0.05). Later carotid revascularization was reduced by 56% (HR 0.44, 95% CI 0.24, 0.79; P=0.006) in the group randomized to atorvastatin.

Conclusion—Consistent with the overall results of the SPARCL intention to treat population, intense lipid lowering with atorvastatin reduced the risk of cerebro- and cardiovascular events in patients with and without carotid stenosis. The carotid stenosis group may have greater benefit. (Stroke. 2008;39:3297-3302.)

Key Words: cholesterol-lowering drugs ■ cerebrovascular disease ■ carotid stenosis

Carotid artery atherosclerosis is causally related to stroke in cases of stenosis greater than 50% and is considered the cause of stroke in up to 20% of cases. Systematic screening of stroke patients found 45% had carotid atherosclerosis. It is also a marker for systemic atherosclerosis involving brain as well as coronary arteries and the aorta and its branches. Autopsy examination of patients who died of stroke found that 83% of those with carotid atherosclerosis had coronary plaques, as compared with 55% of those without carotid atherosclerosis. As compared with those transient ischemic attack (TIA) or stroke patients without carotid atherosclerosis, the presence of carotid disease identifies a population at particularly high risk for recurrent events.

Statin trials showed a reduction in stroke in patients with coronary heart disease (CHD) or atherosclerotic risk factors. Because of the association between carotid atherosclerosis and coronary disease, it is possible that targeting this population of stroke patients would show an effect of statins on stroke and CHD end points similar to that observed in early statin trials in patients with coronary atherosclerotic disease (CAD).

The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study showed that intense lipid
lowering with atorvastatin reduced the risk of stroke by 16%, major coronary vascular events by 35%, and any revascularization procedure by 45% in patients with recent TIA or stroke, no known CHD, and a baseline low-density lipoprotein cholesterol (LDL-C) 100–190 mg/dL.¹⁰

We hypothesized that atorvastatin had a greater impact in patients with stroke or TIA and carotid stenosis than in patients without. This analysis investigates the subpopulation of patients within the SPARCL trial who had investigator-identified carotid stenosis at study entry.

**Subjects and Methods**

The methods of the SPARCL study have been described in detail previously. The primary hypothesis of the SPARCL trial was that treatment with 80 mg of atorvastatin per day would reduce the risk of fatal or nonfatal stroke among patients with a history of recent stroke or TIA and no known CHD. Eligible patients were men and women >18 years of age who had had an ischemic or hemorrhagic stroke or a TIA (diagnosed by a neurologist within 30 days after the event) 1 to 6 months before randomization. Patients with hemorrhagic stroke (2% of the study population) were included if they were deemed by the investigator to be at risk for ischemic stroke or CHD. Stroke was defined by focal clinical signs of central nervous system dysfunction of vascular origin that lasted for ≥24 hours; TIA was defined by the loss of cerebral or ocular function for <24 hours. Patients had to be ambulatory, with a modified Rankin score of no more than 3 (scores can range from 0 to 5, with higher scores indicating more severe disability), and to have an LDL-C level ≥100 mg/dL (2.6 mmol/L) and <190 mg/dL (4.9 mmol/L). Excluded patients included those with atrial fibrillation, mechanical prosthetic heart valves, subarachnoid hemorrhage, and carotid revascularization within 30 days. Patients were enrolled between September 1998 and March 2001. The local research ethics committee or institutional review board at each participating study center approved the study protocol (15 of 205 centers excluded otherwise suitable patients with an LDL-C level above 160 mg/dL [4.1 mmol/L], as required by their institutional review boards), and all patients gave written informed consent.

The primary outcome was the time from randomization to a first nonfatal or fatal stroke. There were 7 prespecified secondary composite outcomes: stroke or TIA; major coronary event (cardiac death, nonfatal myocardial infarction [MI], or resuscitated cardiac arrest); major cardiovascular event (stroke plus any major coronary event); acute coronary event (major coronary event or unstable angina); any CHD event (acute coronary event plus coronary revascularization procedure, unstable angina, or angina/ischemia requiring emergent hospitalization); revascularization procedure (coronary, carotid, or peripheral); and any cardiovascular event (any of the former plus clinically significant peripheral vascular disease). An independent committee adjudicated all potential end points without knowledge of the patients’ treatment status or cholesterol levels.

The SPARCL steering committee developed the study protocol with the sponsor and takes responsibility for the data and data analyses. Medpace managed all data. Medpace, Charles River Laboratories Clinical Services, and the sponsor provided site monitoring throughout the study. A data and safety monitoring board with independent statistical support performed interim monitoring analyses for safety and efficacy.

**Subgroup With Carotid Stenosis**

Assessment of carotid stenosis was not required by the SPARCL protocol and was done at investigator discretion. However, in 4278 (90.4%) of the SPARCL subjects, carotid stenosis was identified by the investigators at patient randomization into the study and noted in the Case Report Form (CRF) as present, absent, or unknown. If present, the percent degree of stenosis was to be indicated. The

### Table 1. Baseline Characteristics for Patients With and Without Carotid Stenosis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>With Carotid Stenosis (n = 1007)</th>
<th>Without Carotid Stenosis* (n = 3724)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent carotid stenosis</td>
<td>51%±29% (N = 966)</td>
<td>...</td>
</tr>
<tr>
<td>Age, years</td>
<td>65.1±0.32</td>
<td>62.1±0.19</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>638 (63.4)</td>
<td>2185 (58.7)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>140±0.61</td>
<td>138±0.32</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>81±0.32</td>
<td>82±0.18</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.3±0.14</td>
<td>27.5±0.08</td>
</tr>
<tr>
<td>Creatinine clearance, mL/s/1.73 m²</td>
<td>1.13±0.01</td>
<td>1.12±0.01</td>
</tr>
</tbody>
</table>

| Entry event, n (%)                   |                                  |                                     |
|--------------------------------------|                                  |                                     |
| Stroke                               | 691 (68.6)                       | 2577 (69.2)                         |
| Ischemic                             | 686 (68.1)                       | 2468 (66.3)                         |
| Hemorrhagic                          | 2 (0.2)                          | 91 (2.4)                            |
| Other and unable to determine        | 3 (0.3)                          | 18 (0.5)                            |
| Transient ischemic attack            | 316 (31.4)                       | 1144 (30.7)                         |
| Unknown                              | 0                                | 3 (0.1)                             |
| Time since entry event, days         | 88±1.5                           | 85±0.7                              |

| Risk factors, n (%)                  |                                  |                                     |
|--------------------------------------|                                  |                                     |
| Current smoker                       | 215 (21.4)                       | 693 (18.6)                          |
| Former smoker                        | 430 (42.7)                       | 1451 (39.0)                         |
| Systemic hypertension                | 655 (65.0)                       | 2273 (61.0)                         |
| History of diabetes mellitus         | 197 (19.6)                       | 597 (16.0%)                         |
| Any prior statin therapy, n (%)      | 33 (3.3)                         | 87 (2.3)                            |

| Lipids, mg/dL                        |                                  |                                     |
|--------------------------------------|                                  |                                     |
| Low-density lipoprotein cholesterol  | 134±0.76                         | 133±0.40                            |
| High-density lipoprotein cholesterol | 49±0.41                          | 50±0.23                             |
| Total cholesterol                    | 212±0.94                         | 212±0.48                            |
| Triglycerides                        | 149±3.73                         | 142±1.13                            |
| Apolipoprotein A1                    | 147±0.83                         | 150±0.47                            |
| Apolipoprotein B                     | 135±0.70                         | 133±0.36                            |

| Concomitant therapy, n (%)           |                                  |                                     |
|--------------------------------------|                                  |                                     |
| Aspirin or other antiplatelet drug, excluding heparin | 885 (87.9) | 3245 (87.1) |
| Angiotensin converting enzyme inhibitor | 305 (30.3) | 1045 (28.1) |
| Dihydropyridine derivative           | 168 (16.7)                       | 541 (14.5)                          |
| Beta-blocker                         | 128 (12.7)                       | 529 (14.2)                          |
| Angiotensin II-receptor antagonist    | 54 (5.4)                         | 158 (4.2)                           |
| Vitamin K antagonist, including warfarin | 82 (8.1) | 211 (5.7) |

Mean = SEM. Includes 453 subjects with unknown carotid stenosis status. To convert values for cholesterol to mmol/L, multiply by 0.02586; to convert values for triglycerides to mmol/L, multiply by 0.0113.
In the carotid stenosis group, LDL-C was reduced from 132 mg/dL at baseline to an average of 70 mg/dL during the study.

### Table 2. Primary and Secondary End Points for Patients With and Without Carotid Stenosis (CS) and by Treatment Group

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Atorvastatin Events (%)</th>
<th>Placebo Events (%)</th>
<th>Placebo Group $P$ value*</th>
<th>Adjusted Hazard Ratio (95% CI)</th>
<th>Treatment $P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cerebrovascular end points</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With CS</td>
<td>55 (11.2)</td>
<td>83 (16.1)</td>
<td>0.113</td>
<td>0.67 (0.47, 0.94)</td>
<td>0.0197</td>
</tr>
<tr>
<td>Without CS</td>
<td>210 (11.2)</td>
<td>228 (12.3)</td>
<td>0.90 (0.74, 1.08)</td>
<td></td>
<td>0.2413</td>
</tr>
<tr>
<td>Fatal stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With CS</td>
<td>0</td>
<td>15 (2.9)</td>
<td>0.055</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>Without CS</td>
<td>24 (1.3)</td>
<td>26 (1.4)</td>
<td>0.91 (0.52, 1.59)</td>
<td></td>
<td>0.7385</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With CS</td>
<td>55 (11.2)</td>
<td>72 (14.0)</td>
<td>0.246</td>
<td>0.77 (0.54, 1.10)</td>
<td>0.1449</td>
</tr>
<tr>
<td>Without CS</td>
<td>192 (10.3)</td>
<td>208 (11.2)</td>
<td>0.89 (0.74, 1.09)</td>
<td></td>
<td>0.2654</td>
</tr>
<tr>
<td>Stroke or transient ischemic attack</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With CS</td>
<td>79 (16.0)</td>
<td>118 (23.0)</td>
<td>0.246</td>
<td>0.66 (0.50, 0.89)</td>
<td>0.0053</td>
</tr>
<tr>
<td>Without CS</td>
<td>296 (15.8)</td>
<td>358 (19.3)</td>
<td>0.80 (0.69, 0.94)</td>
<td></td>
<td>0.0049</td>
</tr>
<tr>
<td><strong>Cardiovascular end points</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major coronary event</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With CS</td>
<td>19 (3.9)</td>
<td>33 (6.4)</td>
<td>0.274</td>
<td>0.57 (0.32, 1.00)</td>
<td>0.0503</td>
</tr>
<tr>
<td>Without CS</td>
<td>62 (3.3)</td>
<td>87 (4.7)</td>
<td>0.69 (0.50, 0.96)</td>
<td></td>
<td>0.0257</td>
</tr>
<tr>
<td>Major cardiovascular event</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With CS</td>
<td>70 (14.2)</td>
<td>108 (21.0)</td>
<td>0.090</td>
<td>0.64 (0.47, 0.86)</td>
<td>0.0035</td>
</tr>
<tr>
<td>Without CS</td>
<td>264 (14.1)</td>
<td>299 (16.1)</td>
<td>0.85 (0.72, 1.00)</td>
<td></td>
<td>0.0561</td>
</tr>
<tr>
<td>Carotid revascularization</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With CS</td>
<td>16 (3.2)</td>
<td>37 (7.2)</td>
<td>&lt;0.001</td>
<td>0.44 (0.24, 0.79)</td>
<td>0.0057</td>
</tr>
<tr>
<td>Without CS</td>
<td>13 (0.7)</td>
<td>7 (0.4)</td>
<td>1.83 (0.73, 4.59)</td>
<td></td>
<td>0.1980</td>
</tr>
<tr>
<td>Any coronary event</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With CS</td>
<td>31 (6.3)</td>
<td>59 (11.5)</td>
<td>0.039</td>
<td>0.51 (0.33, 0.80)</td>
<td>0.0028</td>
</tr>
<tr>
<td>Without CS</td>
<td>92 (4.9)</td>
<td>145 (7.8)</td>
<td>0.61 (0.47, 0.80)</td>
<td></td>
<td>0.0002</td>
</tr>
<tr>
<td>Any cardiovascular event</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With CS</td>
<td>119 (24.1)</td>
<td>194 (37.7)</td>
<td>&lt;0.001</td>
<td>0.58 (0.46, 0.73)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Without CS</td>
<td>403 (21.5)</td>
<td>491 (26.5)</td>
<td>0.79 (0.69, 0.90)</td>
<td></td>
<td>0.0004</td>
</tr>
<tr>
<td>Any revascularization</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With CS</td>
<td>38 (7.7)</td>
<td>76 (14.8)</td>
<td>&lt;0.001</td>
<td>0.49 (0.33, 0.73)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Without CS</td>
<td>56 (3.0)</td>
<td>87 (4.7)</td>
<td>0.61 (0.44, 0.86)</td>
<td></td>
<td>0.0049</td>
</tr>
</tbody>
</table>

*Test of hazard ratio for placebo patients with carotid stenosis at baseline relative to placebo patients without carotid stenosis at baseline.

Results

Baseline demographics for patients with and without carotid stenosis are given in Table 1. Of the 4731 SPARCL subjects, 4278 (90.4%) had either reported “yes” or “no” for the presence of carotid stenosis, whereas it was documented as “unknown” in 453 subjects (9.6%). To ensure robustness of the statistical analyses these patients have been added to the “no stenosis” group. Analyzing the groups separately did not alter the results. Patients with carotid stenosis were older and the proportion of men, smokers, and patients with diabetes was higher as compared with the group without carotid stenosis. The average degree of stenosis was 51% (±29%) although only given in 966 of the 1007 (96%) patients.

### Notes

- *P*<0.05 was considered significant.

- Side of the stenosis, method of diagnosis, and validation of the degree of narrowing were not requested and are not available for analysis.

- For this prespecified analysis, Cox proportional hazards models were used to calculate hazard ratios (HRs), 95% confidence intervals (CIs), and probability values and were adjusted for geographic region, entry event (stroke or TIA), time since entry event, sex, and age at baseline in the groups of subjects with or without carotid stenosis, as indicated by the investigators. A test for heterogeneity was performed to compare HRs between the groups of subjects with and without carotid stenosis using the Cox proportional hazards model by including an interaction term for treatment (atorvastatin/placebo) by stenosis (present/absent). Cox proportional hazards models were also used to compare groups of patients according to their average LDL-C reduction over the course of the study (<70 mg/dL, 70 to 100 mg/dL, or >100 mg/dL). All probability values were 2-sided with no adjustment for multiple testing; *P*<0.05 was considered significant.
trial in the atorvastatin group, whereas it changed from 133 mg/dL at baseline to an average of 130 mg/dL in the placebo group. These changes in LDL-C were observed despite drop-in and drop-out rates that were greater in the placebo group. These changes in LDL-C were observed despite any cardiovascular event, all revascularization, and carotid revascularization procedures (Table 2). Treatment with atorvastatin resulted in a net significant risk reductions in the subpopulation with carotid stenosis (CS).

Among the subjects with carotid stenosis, a primary end point (fatal or nonfatal stroke) occurred in 55 patients randomized to treatment with atorvastatin and in 83 of those randomized to placebo. The 5-year difference in the Kaplan–Meier curves was 5% (Table 2; Figure 1). Randomization to treatment with atorvastatin reduced the risk of stroke by 33% (HR 0.67, 95% CI 0.47, 0.94; P=0.02; Figure 1; Table 2) and the risk of TIA or stroke by 34% (HR 0.66, 95% CI 0.50, 0.89; P=0.005).

Cardiovascular end points were also reduced in patients with carotid stenosis (Table 2; Figure 1). The risk of major coronary events (cardiac death, nonfatal myocardial infarction, or resuscitated cardiac arrest) was reduced by 43% (HR 0.58, 95% CI 0.37, 0.83; P=0.0029), the incidence of any cardiovascular event (24.1% in the atorvastatin-treated group and 37.7% in the placebo group) was reduced by 42% (HR 0.58, 95% CI 0.46, 0.73; P<0.0001), the risk of having any revascularization procedure was reduced by 51% (HR 0.49, 95% CI 0.33, 0.73; P=0.0004), and carotid revascularizations by 56% (HR 0.44, 95% CI 0.24, 0.79; P=0.006). Of the 50 carotid revascularizations performed in the carotid stenosis group during the trial, 22 were for symptomatic stenosis (7 in the treatment group and 15 in the placebo arm of the trial). Tests for heterogeneity were only significant when all cerebrovascular and cardiovascular events were considered (ie, any cardiovascular event including carotid revascularization, Figure 1).

The effect of LDL changes on efficacy parameters throughout the trial showed a consistent trend toward better efficacy with greater LDL reduction, irrespective of treatment group (Figure 2). Patients who throughout the trial reached an average LDL <70 mg/dL had less chance of experiencing any of the trial end points as compared with patients with an LDL >100 mg/dL.

Among patients with carotid stenosis, there were slightly more reporting myalgia in the treatment group (n=27; 5.5%) compared with the placebo group (n=19; 3.9%). Myopathy (2 versus 1) and rhabdomyolysis (1 versus 2) were rarely observed in the atorvastatin and placebo groups, respectively. Liver enzyme elevation (>3×the upper limit of normal [ULN]) on 2 consecutive measurements was observed in 3 (0.6%) patients in the treatment group and in 1 (0.2%) among patients taking placebo. Increased levels of creatinine kinase (>10×ULN) on 2 consecutive measurements were observed in 1 patient in the atorvastatin group and no patients in the control group. There were no differences in side effects among patients with or without carotid stenosis.

**Discussion**

Although evaluation for the presence of carotid stenosis in the SPARCL baseline data collection was not required or standardized, in 90.4% of SPARCL subjects it was undertaken and proved to be a marker of a high risk of stroke and other cardiovascular events. Thirty-eight percent of the placebo group experienced an atherosclerotic complication during the trial (7.5% per year). The risks in this subpopulation were numerically higher for each study end point compared with subjects in the SPARCL study without carotid stenosis, although the differences were only statistically significant when analyzing all cardiovascular events, any coronary event, all revascularization, and carotid revascularization procedures (Table 2). Treatment with atorvastatin resulted in significant risk reductions in the subpopulation with carotid stenosis.
stenosis. The National Cholesterol Education Program Adult Treatment Panel III (ATP-III) recommends treatment with statins for patients with TIA or stroke of carotid origin or more than 50% obstruction of a carotid artery as it is considered a CHD risk equivalent. Our results support this recommendation among patients with symptomatic cerebrovascular disease with and without carotid stenosis.

In the group with carotid stenosis, the absolute risk reduction for stroke was 1% per year (number needed-to-treat [NNT]=20 in 5 years), and considering all cardiovascular events, the annual risk reduction exceeded 2.5% per year (NNT=8 in 5 years). Interestingly, although the trial populations are not directly comparable, carotid endarterectomy in symptomatic patients confers the same annual stroke risk reduction (a reduction in absolute risk of 1% per year). However, treatment with atorvastatin additionally reduces the risk of other cardiovascular events, which are known to occur more frequently over time than stroke and TIA both in symptomatic and even in asymptomatic patients with carotid stenosis.

The present analysis showed that treatment with atorvastatin 80 mg per day was efficacious in the subgroup of patients with investigator-identified carotid atherosclerosis at baseline. This substudy was not powered to show a difference on the primary end point between the group with and without carotid stenosis. As previously observed in a post hoc analysis of the SPARCL trial, the treatment effect in relation to level of LDL reduction indicated that the lower the achieved LDL-C levels, the lower the stroke risk.

In addition to the lack of a proscribed assessment for carotid stenosis at baseline, other limitations of our study include the fact that the side of the stenosis was not recorded; thus our data cannot be compared directly with effects of local treatments, (ie, carotid endarterectomy or stenting). Although this secondary analysis was prespecified, randomization was not stratified based on the presence or absence of carotid stenosis, and the sample size was not powered to show a difference on the primary end point between the group with and without carotid stenosis. Although we found no heterogeneity regarding stroke prevention between the groups with and without carotid stenosis, we cannot exclude the possibility that such a difference exists.

In conclusion intense lipid lowering with atorvastatin reduced the risk of cerebro- and cardiovascular events in patients with and without carotid stenosis. The carotid stenosis group may have greater benefit.

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References
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