Results of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Trial by Stroke Subtypes

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Background and Purpose—The SPARCL trial showed that atorvastatin 80 mg/d reduces the risk of stroke and other cardiovascular events in patients with recent stroke or transient ischemic attack (TIA). We tested the hypothesis that the benefit of treatment varies according to index event stroke subtype.

Methods—Subjects with stroke or TIA without known coronary heart disease were randomized to atorvastatin 80 mg/d or placebo. The SPARCL primary end point was fatal or nonfatal stroke. Secondary end points included major cardiovascular events (MCVE; stroke plus major coronary events). Cox regression models testing for an interaction with treatment assignment were used to explore potential differences in efficacy based on stroke subtype.

Results—For subjects randomized to atorvastatin versus placebo, a primary end point occurred in 13.1% versus 18.6% of those classified as having large vessel disease (LVD, 15.8% of 4,731 participants), in 13.1% versus 15.5% of those with small vessel disease (SVD, 29.8%), in 11.2% versus 12.7% of those with ischemic stroke of unknown cause (21.5%), in 7.6% versus 8.8% of those with TIA (30.9%), and in 22.2% versus 8.3% of those with hemorrhagic stroke (HS, 2%) at baseline. There was no difference in the efficacy of treatment for either the primary end point (LVD hazard ratio [HR] 0.70, 95% confidence interval [CI] 0.49 to 1.02, TIA HR 0.81, CI 0.57 to 1.17, SVD HR 0.85, CI 0.64 to 1.12, unknown cause HR 0.87, CI 0.61 to 1.24, HS HR 3.24, CI 1.01 to 10.4; P for heterogeneity = 0.421), or MCVEs (P for heterogeneity = 0.360) based on subtype of the index event. As compared to subjects with LVD strokes, those with SVD had similar MCVE rates (19.2% versus 18.5% over the course of the trial), and similar overall reductions in stroke and MCVEs.

Conclusions—Atorvastatin 80 mg/d is similarly efficacious in preventing strokes and other cardiovascular events, irrespective of baseline ischaemic stroke subtype. (Stroke. 2009;40:1405-1409.)

Key Words: stroke ■ transient ischemic attack ■ statins, cholesterol

Stroke is a heterogeneous condition with a number of possible etiologies.1 Whereas myocardial infarction (MI) is almost always attributable to atherothrombotic disease, brain infarction stems from a host of conditions (eg, rheumatic heart disease, arterial dissection, elastic tissue disease, intracranial small vessel disease, atherosclerotic carotid stenosis, etc). Stroke subtyping systems, such as the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification, help classify patients into the most likely cause category.2 Patients with different underlying stroke pathophysologies may variably respond to specific preventive treatment strategies. For example, atherothrombotic stroke is best prevented by antiplatelet agents whereas cardioembolic stroke attributable to atrial fibrillation is best prevented by vitamin K antagonists.3

Statin outcome trials in subjects with established coronary artery disease, hypertension, diabetes, or at high vascular risk have shown a consistent 17% to 21% relative reduction in the risk of incident stroke.4 These trials predominantly included subjects with established atherothrombotic disease or coronary heart disease risk equivalents. It is not known whether the strokes prevented in these trials were mostly of atherothrombotic origin or from other etiologies.

Trials using progression of carotid atherosclerosis as an end point have consistently shown that statins can slow the progression of carotid atherosclerosis with a meta-analysis of these trials indicating that the greater the reduction in low-density lipoprotein cholesterol (LDL-C), the slower the progression.5 It was hypothesized that patients with transient ischemic attack (TIA), ischemic stroke related to atherothrombotic disease, small vessel disease or to undetermined cause, and those with hemorrhagic stroke would benefit from statin therapy similar to those with...
coronary heart disease because of the many risk factors that are shared between these conditions.6,7

The Stroke Prevention by Aggressive Reduction of Cholesterol Levels (SPARCL) trial randomized 4731 subjects with recent stroke or TIA and no known coronary heart disease, and showed that treatment with atorvastatin 80 mg/d reduced the risk of recurrent stroke.8 In a secondary analysis, it was found that the subjects who benefited most had the greatest reductions in LDL-C (ie, >50% LDL-C decrease from baseline).9 The aim of this post hoc analysis of the SPARCL trial was to explore whether the benefit of treatment varied based on the baseline stroke subtype.

Subjects and Methods
The SPARCL methodology has been described in detail previously.7,8 The study was approved by the local research committee or institutional review board at each participating center (15 of 205 centers excluded otherwise suitable subjects with an LDL-C >4.1 mmol/L [160 mg/dL] as required by their institutional review boards) and subjects gave written informed consent.

Study Hypothesis and Patient Population
The primary hypothesis of the SPARCL trial was that treatment with atorvastatin 80 mg/d would reduce the combined risk of fatal and nonfatal stroke in patients with a recent stroke or TIA. Eligible subjects were men and women aged older than 18 years who had an ischemic or hemorrhagic stroke, or TIA (all diagnosed by a neurologist within 30 days of the event) 1 to 6 months before randomization. The protocol did not specifically exclude patients with hemorrhagic stroke. Stroke was defined as focal clinical signs of central nervous system dysfunction of vascular origin lasting ≥24 hours. TIA was defined as an acute loss of cerebral or ocular function lasting <24 hours and presumed to be of atherosclerotic origin. Subjects had to be ambulatory (Modified Rankin score ≤3; score can range from 0 to 6 with higher scores indicating more severe disability or death) and have a LDL-C level ≥2.6 and ≤4.9 mmol/L (≥100 and ≤190 mg/dL).7 Patients were excluded if they had atrial fibrillation, sinus node dysfunction, mechanical prosthetic heart valves, clinically significant mitral stenosis, coronary heart disease, subarachnoid hemorrhage or stroke resulting from revascularization procedure, or trauma.7 Subjects were enrolled between September 1998 and March 2001.

Type of Entry Events
Investigators classified the index event as a TIA or as one of the stroke subtypes based on their clinical judgment without independent adjudication. Strokes were classified as hemorrhagic stroke, small vessel disease stroke, large artery disease stroke, ischemic stroke of unknown cause with more than one cause, unknown cause with complete work-up, or unknown cause with incomplete work-up. For the purposes of this analysis, ischemic stroke of unknown cause was considered as one group.

Study Protocol
Between 1 and 6 months after stroke (within 30 days of the initial screening visit), eligible subjects were randomized to double-blind therapy with either atorvastatin 80 mg/d or placebo. Nonstudy statins were not permitted. Those subjects who began a nonstudy statin or withdrew from randomized treatment were included in the intention to treat analysis.8 All subjects were counseled to follow the National Cholesterol Education Program (NCEP) Step 1 (or similar) diet, throughout the study. Visits were scheduled at 1, 3, and 6 months, and every 6 months thereafter. Surviving patients had last study visits between March and June 2005.

Efficacy Outcomes
The SPARCL primary outcome was the time from randomization to the first occurrence of a nonfatal or fatal stroke. There were 7 prespecified secondary composite outcomes including stroke or TIA; major cardiovascular event (MCVE; stroke, cardiac death, nonfatal MI or resuscitated cardiac arrest); and all-cause mortality.8 End points were adjudicated by an independent committee whose members were unaware of treatment assignment.

Lipid Level Analysis and Safety Assessments
Clinical laboratory assessments were performed at 1, 3, and 6 months, and every 6 months thereafter, with measurement of blood samples in the same central laboratory. Measurements included LDL-C assessment. If LDL-C was <1.0 mmol/L (<40 mg/dL), the investigator was informed of the result and could lower the dosage of study drug from 80 to 40 mg/d. A second randomly chosen investigator for a placebo patient was similarly notified, and LDL-C levels were retested for both patients to maintain the blind. Drug safety was assessed by an evaluation of the type, frequency, severity, and duration of any reported adverse event, and by vital signs, physical examinations, and laboratory tests.

Statistical Analysis
We used the primary end point (fatal and nonfatal stroke) and the MCVE secondary end point for this post hoc analysis. Our main purpose was to search for heterogeneity between entry event subgroups. Potential differences in efficacy based on type of entry event were assessed by testing for an interaction with treatment assignment using Cox regression models. Hazard ratios (HR) relative to large vessel disease group were calculated from Cox regression models adjusted for treatment, time since entry event, sex, and baseline age (prespecified adjustments). A probability value <0.05 was considered significant. SAS software was used for the analyses.

Results
Among 4731 participants, 4728 had information regarding entry event subtype with 15.8% classified as having large vessel disease (n=749), 29.8% small vessel disease (n=1409), 21.5% ischemic stroke of unknown cause (n=1017), 30.9% TIA (n=1460), and 2% hemorrhagic stroke (n=93). Table 1 shows the baseline characteristics by entry event for those randomized to atorvastatin and placebo.

Treatment Effect Across Entry Event Stroke Subtypes
Figure 1 shows that atorvastatin treatment was similarly efficacious in reducing the primary end point (fatal and nonfatal stroke) for all entry event stroke subtypes with no heterogeneity (P for heterogeneity=0.421). Although there was no overall heterogeneity between subtypes, the patients with a baseline hemorrhagic stroke and randomized to atorvastatin were qualitatively different and were more than 3 times more likely to have a recurrent stroke compared with similar patients randomized to placebo. A test for heterogeneity comparing the outcomes of subjects with hemorrhagic and ischemic stroke at baseline was significant (P=0.0482).10 For MCVEs a similar reduction was observed in the atorvastatin compared with the placebo groups for all entry event subgroups with no heterogeneity between groups (P for heterogeneity=0.360).

The rates of adverse events such as liver enzyme elevation 3 times above the upper normal limit, creatine kinase elevation, myalgia, myopathy, or rhabdomyolysis were similar across entry event stroke subtypes in both active and placebo
arms. Only liver enzymes were significantly elevated in the atorvastatin arm compared with placebo.

Risk of Primary and Secondary End Points in Entry Event Stroke Subtypes

Table 2 shows percentages of outcome events according to entry stroke subtype. As shown in Figure 2, relative to the group that had a large vessel disease stroke at baseline, the TIA and unknown cause groups had lower absolute rates of outcome strokes, with the small vessel disease and hemorrhagic stroke groups having similar absolute rates; TIA, hemorrhagic stroke, small vessel disease, and unknown cause groups had similar absolute MCVE rates. Mortality rates were similar across all entry event subgroups. The analyses were also carried out with adjustment for blood pressure, diabetes, and mRS at baseline and the results did not differ substantially (data not shown).

Discussion

We found no heterogeneity in the treatment effect for the primary end point (fatal and nonfatal stroke) across baseline ischemic stroke subtypes. This means that atorvastatin 80 mg/d was similarly efficacious in subjects randomized with a

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Large Vessel</th>
<th>Hemorrhagic</th>
<th>Transient Ischemic Attack</th>
<th>Small Vessel</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62.0 (0.6)</td>
<td>63.3 (0.6)</td>
<td>62.1 (2.0)</td>
<td>63.6 (1.7)</td>
<td>63.5 (0.4)</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>237 (64.6)</td>
<td>242 (63.4)</td>
<td>27 (60.0)</td>
<td>33 (68.8)</td>
<td>403 (56.9)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>138.3 (10.0)</td>
<td>138.8 (0.9)</td>
<td>142.6 (3.5)</td>
<td>140.4 (2.2)</td>
<td>136.7 (0.7)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>81.8 (0.6)</td>
<td>81.1 (0.5)</td>
<td>85.2 (1.9)</td>
<td>85.5 (1.5)</td>
<td>80.8 (0.4)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.3 (0.2)</td>
<td>27.3 (0.2)</td>
<td>26.1 (0.7)</td>
<td>26.8 (0.5)</td>
<td>27.4 (0.2)</td>
</tr>
<tr>
<td>Time since entry event, d</td>
<td>86.9 (2.5)</td>
<td>86.0 (2.5)</td>
<td>95.8 (6.8)</td>
<td>94.7 (7.3)</td>
<td>85.9 (1.8)</td>
</tr>
<tr>
<td>Risk factors, n (%)</td>
<td>Current smoker</td>
<td>70 (19.1)</td>
<td>89 (23.3)</td>
<td>7 (15.6)</td>
<td>5 (10.4)</td>
</tr>
<tr>
<td></td>
<td>Former smoker</td>
<td>164 (44.7)</td>
<td>166 (43.5)</td>
<td>20 (44.4)</td>
<td>21 (43.8)</td>
</tr>
<tr>
<td></td>
<td>Systemic hypertension</td>
<td>227 (61.9)</td>
<td>251 (65.7)</td>
<td>33 (73.3)</td>
<td>39 (81.3)</td>
</tr>
<tr>
<td></td>
<td>History of diabetes mellitus</td>
<td>86 (23.4)</td>
<td>83 (21.7)</td>
<td>3 (6.7)</td>
<td>4 (8.3)</td>
</tr>
<tr>
<td></td>
<td>Any prior statin therapy, n (%)</td>
<td>8 (2.2)</td>
<td>15 (3.9)</td>
<td>1 (2.2)</td>
<td>2 (4.2)</td>
</tr>
</tbody>
</table>

LDL-C indicates low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.
TIA or ischemic stroke, regardless of the ischemic stroke subtype. We also found that atorvastatin treatment similarly reduced MCVE end points in all ischemic stroke subgroups. Therefore, we failed to confirm the hypothesis that the benefit of treatment varies based on the ischemic stroke subtype at baseline. It should be noted that the distribution of stroke subtypes at baseline may not mirror that encountered in clinical practice. This is in part attributable to the SPARCL selection criteria in which subjects with high risk sources of cardiogenic embolism and those with coronary heart disease were excluded. We do not have data to permit us to determine the likely pathophysiologies of TIAs, which were considered as a separate category in the analyses. As we previously reported, we found subjects with a hemorrhagic stroke as the qualifying event had no reduction or an increase in outcome strokes with treatment,10 and in the present analysis, that they had no reduction in MCVEs.

It is notable that the small vessel disease subgroup had an absolute recurrent stroke rate similar to the large vessel disease subgroup (14.3% and 15.9%, respectively). A population-based study has shown that the long-term 5-year recurrent stroke risk was similar across entry stroke subtypes, including patients with lacunar stroke.11 Moreover, small vessel disease entry event group in SPARCL had an 18.5% rate of outcome MCVE, whereas the corresponding rate in the large vessel disease group was 19.2%. This similarity between the 2 subgroups was unexpected, although it is consistent with a recent autopsy study showing that 79% of patients with small vessel disease and no history of coronary heart disease had coronary plaque with 37% having a coronary stenosis >50% (as compared with 77% and 33% of those with atherothrombotic strokes).12 A systematic review showed that the risk of early mortality and stroke recurrence were higher in subjects with nonlacunar than lacunar infarction, whereas the long-term risk was similar, including that of fatal or nonfatal MI.13 The present data clearly show that subjects with small vessel disease had a long-term risk of MCVE similar to other ischemic stroke subtypes, and therefore should benefit from the same intensive preventive strategies, including statin therapy. Indeed, the effect of atorvastatin in reducing MCVEs in SPARCL was similar in those with small vessel and large vessel disease at baseline.

Patients randomized with a TIA had a significantly lower rate of outcome stroke, MCVEs, and deaths as compared to the other

<table>
<thead>
<tr>
<th>Event</th>
<th>Atorvastatin (n=2363)</th>
<th>Placebo (n=2365)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>265 (11.2)</td>
<td>311 (13.2)</td>
</tr>
<tr>
<td>Large vessel</td>
<td>48 (13.1)</td>
<td>71 (18.6)</td>
</tr>
<tr>
<td>TIA</td>
<td>54 (7.6)</td>
<td>66 (8.8)</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>10 (22.2)</td>
<td>4 (8.3)</td>
</tr>
<tr>
<td>Small vessel</td>
<td>93 (13.1)</td>
<td>109 (15.5)</td>
</tr>
<tr>
<td>Unknown</td>
<td>60 (11.2)</td>
<td>61 (12.7)</td>
</tr>
<tr>
<td>All deaths</td>
<td>375 (15.9)</td>
<td>476 (20.1)</td>
</tr>
<tr>
<td>Major cardiovascular event</td>
<td>334 (14.1)</td>
<td>407 (17.2)</td>
</tr>
<tr>
<td>Large vessel</td>
<td>58 (15.8)</td>
<td>86 (22.5)</td>
</tr>
<tr>
<td>TIA</td>
<td>71 (10.0)</td>
<td>93 (12.4)</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>11 (24.4)</td>
<td>7 (14.6)</td>
</tr>
<tr>
<td>Small vessel</td>
<td>120 (16.9)</td>
<td>141 (20.1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>74 (13.8)</td>
<td>81 (16.8)</td>
</tr>
<tr>
<td>All deaths</td>
<td>215 (9.1)</td>
<td>211 (8.9)</td>
</tr>
<tr>
<td>Large vessel</td>
<td>31 (8.4)</td>
<td>44 (11.5)</td>
</tr>
<tr>
<td>TIA</td>
<td>53 (7.5)</td>
<td>53 (7.0)</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>7 (15.6)</td>
<td>5 (10.4)</td>
</tr>
<tr>
<td>Small vessel</td>
<td>77 (10.9)</td>
<td>64 (9.1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>47 (8.8)</td>
<td>45 (9.3)</td>
</tr>
</tbody>
</table>

Values in bold are total No. of patients (%) in each treatment group and overall experiencing each end-point. Values not in bold give corresponding values for each entry event subgroup.

TIA indicates transient ischemic attack.

Table 2. Primary and Secondary Efficacy Event Counts by Entry Events

![Figure 2. Treatment effect by entry event stroke subtypes: primary end point (fatal or nonfatal stroke) and secondary end points. HR indicates hazard ratio; CI, confidence interval; TIA, transient ischemic attack.](http://stroke.ahajournals.org/DownloadedFrom)
subgroups. The 5-year stroke event rate was 8.2% in the group randomized after a TIA versus 15.9% in those with a large vessel disease stroke. The observed event rate in subjects with TIA was even lower than the 3-month event rate that has been reported in patients with a TIA and no predefined therapeutic intervention.14 The low event rate observed in patients randomized with a TIA in SPARCL is likely due to the fact that patients were enrolled a mean of 3 months after the TIA event (ie, after the highest period for stroke risk), to the exclusion of patients with atrial fibrillation or with an indication for carotid endarterectomy and to an early and continued risk factor control, even prior randomization, which has been reported to result in an 80% reduction in the 3-month stroke event rate.15,16 SPARCL subjects, randomized after a TIA, however, still had a beneficial effect of atorvastatin therapy for both stroke and MCVEs similar to subjects who had an ischemic stroke.

This analysis is limited by its post hoc design and the SPARCL trial was not powered for subgroup analyses. We calculated a power of 51% to detect the risk reduction of 16% that was observed for the primary SPARCL end point between all entry event subtypes. The power to detect a risk reduction of 16% was reduced to 20% for the SVD group and to only 6% for the hemorrhagic stroke group. Therefore, we cannot exclude the possibility that a larger study might find a significant difference among ischemic stroke subtypes. Stroke subtype assignment was based on investigator judgment and was not standardized or adjudicated. Neuroimaging data to verify cerebral abnormalities (eg, extent of white matter abnormalities, cerebral microbleeds, or multiple lacunes) which might have confounded or explained some of the associations that we found were not recorded. As a result, this analysis should be viewed as exploratory. With these caveats, the analyses show that atorvastatin 80 mg/d is similarly efficacious in preventing strokes and other MCVEs, regardless of baseline ischemic stroke subtype.

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Disclosures
This study was sponsored by Pfizer Inc, who were involved in the design and conduct of the study; collection, management, and analysis of the data; and review of the manuscript. Pierre Amarenco has received grants from Pfizer for other research or activities not reported in this research exceeding $10,000/year and honoraria from Pfizer in excess of $10,000/year during the course of this study. Oscar Benavente has received honoraria from Pfizer during the course of this study. The honoraria did not exceed $10,000/year. Larry Goldstein has received honoraria from Pfizer during the course of this study. The honoraria did not exceed $10,000/year. Alfred Callahan has received honoraria from Pfizer in excess of $10,000 during the course of this study. Henrik Sillesen has received grants from Pfizer for other research or activities not reported in this research/article in excess of $10,000/year and honoraria exceeding $10,000/year during the course of this study. Michael Hennerici has received grants from Pfizer for other research or activities not reported in this research/article and honoraria from Pfizer during the course of the study. Neither the grants nor the honoraria exceeded $10,000/year. Steve Gilbert is employed by Rho Inc, a company that provides statistical consultation for Pfizer. Amy Rudolph and Lisa Simunovic are employees of Pfizer and have an equity or ownership interest in the sponsor of the study. Justin Zivin has received honoraria from Pfizer during the course of this study. The honoraria did not exceed $10,000/year. K. Michael Welch has received honoraria from Pfizer during the course of the study in excess of $10,000/year. Statistical analysis was performed by Steve Gilbert (employed by Rho Inc, a company that provides statistical consultation for Pfizer).

References

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on behalf of the SPARCL Investigators

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