Relative and Cumulative Effects of Lipid and Blood Pressure Control in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels Trial

Pierre Amarenco, MD; Larry B. Goldstein, MD; Michael Messig, MD; Blair J. O’Neill, MD; Alfred Callahan, III, MD; Henrik Sillesen, MD; Michael G. Hennerici, MD; Justin A. Zivin, MD; K.M.A. Welch, MD; on behalf of the SPARCL Investigators

Background and Purpose—The relative contributions of on-treatment low- and high-density lipoprotein cholesterol (LDL-C, HDL-C), triglycerides, and blood pressure (BP) control on the risk of recurrent stroke or major cardiovascular events in patients with stroke is not well defined.

Methods—We randomized 4731 patients with recent stroke or transient ischemic attack and no known coronary heart disease to atorvastatin 80 mg per day or placebo.

Results—After 4.9 years, at each level of LDL-C reduction, subjects with HDL-C value above the median or systolic BP below the median had greater reductions in stroke and major cardiovascular events and those with a reduction in triglycerides above the median or diastolic BP below the median showed similar trends. There were no statistical interactions between on-treatment LDL-C, HDL-C, triglycerides, and BP values. In a further exploratory analysis, optimal control was defined as LDL-C <70 mg per deciliter, HDL-C >50 mg per deciliter, triglycerides <150 mg per deciliter, and SBP/DBP <120/80 mm Hg. The risk of stroke decreased with as the level of control increased (hazard ratio [95% confidence interval] 0.98 [0.76 to 1.27], 0.78 [0.61 to 0.99], 0.62 [0.46 to 0.84], and 0.35 [0.13 to 0.96]) for those achieving optimal control of 1, 2, 3, or 4 factors as compared to none, respectively. Results were similar for major cardiovascular events.

Conclusions—We found a cumulative effect of achieving optimal levels of LDL-C, HDL-C, triglycerides, and BP on the risk of recurrent stroke and major cardiovascular events. The protective effect of having a higher HDL-C was maintained at low levels of LDL-C. (Stroke. 2009;40:2486-2492.)

Key Words: stroke ■ TIA ■ LDL-C ■ HDL-C ■ triglyceride ■ statin

The SPARCL trial randomized 4731 patients with recent stroke or TIA and no known coronary heart disease to treatment with atorvastatin 80 mg per day or placebo, and found a significant reduction in stroke and major cardiovascular events (stroke, cardiac death, nonfatal myocardial infarction, or resuscitated cardiac arrest).1 A post hoc analysis found that the subjects with more than a 50% reduction in LDL-C from baseline had greater benefit than in those for whom there was no change or an increase in LDL-C.2 Baseline values of HDL-C and triglycerides were predictive of outcome stroke and major cardiovascular events.3 Blood pressure reduction after stroke has also been shown to reduce the risk of both recurrent stroke and major cardiovascular events.4 In this exploratory analysis of the SPARCL data, we assessed the relative contributions of reductions in LDL-C and triglycerides, levels of HDL-C, and BP control.

Methods

The SPARCL methodology has been described in detail previously.1,5 The study was approved by the local research committee or institutional review board at each participating center (15 of 205 centers excluded otherwise suitable patients with an LDL-C >4.1 millimoles per liter [160 mg per deciliter] as required by their institutional review boards) and patients gave their written informed consent.

Study Hypothesis and Patient Population

The primary hypothesis of the SPARCL trial was that treatment with atorvastatin 80 mg per day would reduce the combined risk of fatal and nonfatal stroke in patients with a recent stroke or TIA. Eligible patients were men and women aged older than 18 years who had an ischemic or hemorrhagic stroke or TIA (diagnosed by a neurologist within 30 days of the event) 1 to 6 months before randomization. Patients with a prior hemorrhagic stroke could be included if they were deemed by the investigator to be at risk for ischemic stroke or coronary heart disease. Stroke was defined as focal clinical signs of central nervous system dysfunction of vascular origin, lasting ≥24 hours.

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hours. TIA was defined as an acute loss of cerebral or ocular function lasting <24 hours and presumed to be of atherosclerotic origin. Patients had to be ambulatory (Modified Rankin score \( \leq 3 \); score can range from 0 to 6 with higher scores indicating more severe disability or death) and have LDL-C \( \geq 2.6 \) and \( \leq 4.9 \) millimoles per liter (\( \geq 100 \) and \( \leq 190 \) mg per deciliter). LDL-C level was calculated using the Friedewald formula. Exclusion criteria included having atrial fibrillation, mechanical prosthetic heart valves, severe mitral valve stenosis, subarachnoid hemorrhage, or coronary heart disease. Patients were enrolled between September 1998 and March 2001.

**Study Protocol**

Between 1 and 6 months after stroke (within 30 days of the initial screening visit), eligible patients were randomized to double-blind therapy with either atorvastatin 80 mg per day or placebo. Nonstudy statins were not permitted. Those patients who began a nonstudy statin or withdrew from randomized treatment were included in the intention-to-treat analysis. All patients 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. Prespecified secondary outcomes included the occurrence of major cardiovascular
events (stroke, cardiac death, nonfatal myocardial infarction, or resuscitated cardiac arrest). Stroke and cardiovascular events were adjudicated by independent committees.

Baseline Assessments
LDL-C, HDL-C, and triglyceride levels were obtained at baseline, before beginning randomized treatment, and were analyzed by a central laboratory. Systolic and diastolic blood pressure were measured with the patient in a sitting position at the time of the baseline evaluation, but were not obtained according to a specific protocol.

Statistical Analysis
In this exploratory analysis, the impact of on-treatment lipid and BP reduction on the effect of treatment with atorvastatin 80 mg per day were analyzed using Cox regression models. In a first analysis, we determined the median percent changes in LDL-C and triglyceride levels between baseline and the Month-1 visit and then compared outcome event rates between subjects having changes above and below the median. The median level of HDL-C at Month 1 was used for the comparison because there was no change in HDL-C between baseline and Month 1. Month 6 was arbitrarily chosen for assessment of the level of BP control values as it was likely optimal at that time of the trial. We tested for heterogeneity in treatment effects between these factors. In a further exploratory analysis, we defined optimal control of LDL-C as <70 mg per deciliter (according to NCEP-III for patients at high cardiac risk), triglycerides <150 mg per deciliter (normal ATP-III levels), BP <120/80 mm Hg (according to JNC-7), and HDL-C >50 mg per deciliter (above the observed median). A probability value at the 0.05 level was considered significant. SAS software was used for the analyses.

Results
Figures 1 and 2 show the levels of LDL-C, HDL-C, triglyceride, and systolic and diastolic BP values at each study visit. Compared with baseline, there was a 16% median reduction in LDL-C and a 15% median reduction in triglycerides at 1 month, across all patients in both treatment groups. The median HDL-C was 47 mg per deciliter. The median BP at the 6-month visit was 138/80 mm Hg.

Table 1 shows that subjects with a reduction in LDL-C above the median (ie, more than 16%) had a reduction in stroke and major cardiovascular events as compared to those with less than a 16% LDL-C reduction. Figure 3 and Table 2 show that, at each level of LDL-C reduction, subjects with a 1-month HDL-C value above the median (47 mg per deciliter) had a reduction in the risk of stroke and major cardiovascular events. There was no interaction between LDL-C and HDL-C on the effect of atorvastatin treatment (probability values, for interaction, 0.814 for stroke and 0.646 for major cardiovascular events).

Table 3 shows only a nonsignificant trend for an additive effect of triglycerides lowering above as compared with below the median for each stratum of LDL-C reduction, and

| Table 1. Risk of Stroke and Major Cardiovascular Events According to Change in LDL-C |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Events          | LDL-C Category  | No. of Subjects | No. of Events (%) | Hazard Ratio (95% CI) | P Value |
| Stroke          | Change <16%     | 2342            | 313 (13.4)        | 1.000             | 0.792 | 0.671, 0.935 | 0.0058 |
|                 | Change >16%     | 2341            | 257 (11.0)        | 0.761             | 0.657, 0.881 | 0.0003 |
| Major cardiovascular events | Change <16% | 2342       | 406 (17.3)        | 1.000             | 0.761 | 0.657, 0.881 | 0.0003 |
|                 | Change >16%     | 2341            | 325 (13.9)        | 0.792             | 0.671, 0.935 | 0.0058 |

*LDL-C categories are below and above the median change in LDL-C at 1-month visit compared with baseline (median change of 16%).
with no interaction between LDL-C and triglycerides on the effect of atorvastatin treatment.

Table 4 shows that, at each level of LDL-C reduction below or above the median, there was a reduction in stroke and major cardiovascular events for subjects with a systolic BP below the median (138 mm Hg) compared to those above the median, with no significant interaction between LDL-C and systolic BP on the atorvastatin treatment effect (proba-
Table 3. Effect of Triglyceride Reduction in Each LDL-C Reduction Categories on Risk of Stroke and Major Cardiovascular Event

<table>
<thead>
<tr>
<th>Events</th>
<th>LDL-C Category*</th>
<th>Triglycerides Category†</th>
<th>No. of Subjects (%)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
<th>P Value for Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>Change &lt;16%</td>
<td>Change &lt;15%</td>
<td>1648 (14.2)</td>
<td>1.000</td>
<td>0.9145</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Change &gt;15%</td>
<td>Change &lt;15%</td>
<td>692 (11.4)</td>
<td>0.823</td>
<td>0.6383, 1.063</td>
<td>0.1363</td>
</tr>
<tr>
<td></td>
<td>Change &gt;15%</td>
<td>Change &lt;15%</td>
<td>693 (12.4)</td>
<td>1.000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major cardiovascular event</td>
<td>Change &lt;16%</td>
<td>Change &lt;15%</td>
<td>1647 (10.4)</td>
<td>0.807</td>
<td>0.622, 1.046</td>
<td>0.1057</td>
</tr>
<tr>
<td></td>
<td>Change &gt;15%</td>
<td>Change &lt;15%</td>
<td>692 (16.6)</td>
<td>0.977</td>
<td>0.787, 1.213</td>
<td>0.8314</td>
</tr>
<tr>
<td></td>
<td>Change &gt;15%</td>
<td>Change &lt;15%</td>
<td>693 (15.2)</td>
<td>1.000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*LDL-C categories are below and above the median change in LDL-C at 1-month visit compared with baseline (median change of 16%).
†Triglycerides categories are below and above the median change in triglycerides at 1-month visit compared with baseline (median change of 15%).

Figure 4 shows that optimal control of LDL-C (<70 mg per deciliter), triglycerides (<150 mg per deciliter), BP (<120/80 mm Hg), and having an HDL-C value above 50 mg per deciliter had a cumulative effect on reducing stroke and major cardiovascular events, with hazard ratios decreasing as optimal levels of 1, 2, 3, or 4 of these factors were achieved (P=0.0012 for stroke and P<0.0001 for major cardiovascular events).

Discussion

In this exploratory analysis, we found that SPARCL subjects with a 1-month reduction in LDL-C above the median had greater reductions in stroke and major cardiovascular events than those with smaller LDL-C reductions. At each level of LDL-C reduction, subjects with a 1-month HDL-C value above the median had greater reductions in stroke and major cardiovascular events. There was no significant additive effect of above the median triglyceride lowering compared with below the median lowering for each strata of LDL-C reduction. At each level of LDL-C reduction, there was a reduction in stroke and major cardiovascular events for subjects with a 6-month systolic BP below the median compared with those above the median, but no significant effect of diastolic BP. In a further exploratory analysis, we also found a cumulative effect of lowering LDL-C, triglycerides, and BP and of higher HDL-C in reducing the risk of stroke and major cardiovascular events.

The observation that those having a 1-month HDL-C above the median (>47 mg per deciliter) and a 6-month systolic BP below the median (<138 mm Hg) significantly reduced the risk of stroke and major cardiovascular events, without

Table 4. Effect of Systolic Blood Pressure (SBP) Then Diastolic BP (DBP) in Each LDL-C Reduction Category on Risk of Stroke and Major Cardiovascular Events

<table>
<thead>
<tr>
<th>Events</th>
<th>LDL-C Category*</th>
<th>SBP–DBP Category†</th>
<th>No. of Subjects (%)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
<th>P Value for Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>Change &lt;16%</td>
<td>&gt;138 mm Hg</td>
<td>1203 (16.0)</td>
<td>1.000</td>
<td>0.5135</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Change &lt;16%</td>
<td>&lt;138 mm Hg</td>
<td>1139 (10.5)</td>
<td>0.704</td>
<td>0.558, 0.887</td>
<td>0.0029</td>
</tr>
<tr>
<td></td>
<td>Change &gt;16%</td>
<td>&gt;138 mm Hg</td>
<td>1172 (13.8)</td>
<td>1.000</td>
<td>0.486, 0.811</td>
<td>0.0004</td>
</tr>
<tr>
<td></td>
<td>Change &gt;16%</td>
<td>&lt;138 mm Hg</td>
<td>1169 (8.1)</td>
<td>0.628</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major cardiovascular events</td>
<td>Change &lt;16%</td>
<td>&gt;138 mm Hg</td>
<td>1203 (20.8)</td>
<td>1.000</td>
<td>0.589, 0.884</td>
<td>0.0016</td>
</tr>
<tr>
<td></td>
<td>Change &gt;16%</td>
<td>&gt;138 mm Hg</td>
<td>1172 (15.3)</td>
<td>1.000</td>
<td>0.526, 0.829</td>
<td>0.0003</td>
</tr>
<tr>
<td></td>
<td>Change &gt;16%</td>
<td>&lt;138 mm Hg</td>
<td>1169 (10.5)</td>
<td>0.660</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>Change &lt;16%</td>
<td>&gt;80 mm Hg</td>
<td>1033 (14.2)</td>
<td>1.000</td>
<td>0.5804</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Change &gt;16%</td>
<td>&gt;80 mm Hg</td>
<td>1309 (12.7)</td>
<td>0.815</td>
<td>0.650, 1.021</td>
<td>0.0753</td>
</tr>
<tr>
<td></td>
<td>Change &gt;16%</td>
<td>&lt;80 mm Hg</td>
<td>956 (11.4)</td>
<td>1.000</td>
<td>0.697, 1.149</td>
<td>0.3849</td>
</tr>
<tr>
<td>Major cardiovascular events</td>
<td>Change &lt;16%</td>
<td>&gt;80 mm Hg</td>
<td>1033 (18.8)</td>
<td>1.000</td>
<td>0.2706</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Change &gt;16%</td>
<td>&gt;80 mm Hg</td>
<td>1309 (16.2)</td>
<td>0.779</td>
<td>0.639, 0.949</td>
<td>0.0132</td>
</tr>
<tr>
<td></td>
<td>Change &gt;16%</td>
<td>&lt;80 mm Hg</td>
<td>956 (14.1)</td>
<td>1.000</td>
<td>0.735, 1.149</td>
<td>0.4572</td>
</tr>
</tbody>
</table>

*LDL-C categories are below and above the median change in LDL-C at 1-month visit compared with baseline (median change of 16%).
†SBP categories are below and above the median (138 mm Hg), and DBP categories are below and above the median (80 mm Hg).
significant interactions between these 2 variables, and the level of LDL-C reduction suggests that the benefit of modifying these risk factors is additive rather than multiplicative. This has also been observed for HDL-C in the Treating to New Target (TNT) trial, and for BP in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT). As observed in the TNT trial in patients with stable coronary heart disease, we found that the protective effect of HDL-C above 47 mg per deciliter seems maintained at low levels of LDL-C in patients with cerebrovascular disease (Table 2). In ASCOT, a potential synergistic effect of LDL-C and BP was found for coronary heart disease reduction ($P$=0.025 for heterogeneity), but LDL-C and BP-lowering therapies had an additive effect for stroke risk reduction with no significant interaction.

Our findings confirm that BP is a major predictor of stroke and major cardiovascular risks after a stroke or a TIA, but suggest that HDL-C is also important. This observation suggests that there may be a role for HDL-modifying agents in secondary stroke prevention. Although there was a trend, median triglyceride lowering of more than 15% from baseline had no additive effect in subjects who had a median LDL-C reduction more than 16% from baseline. Triglycerides $\leq 150$ mg per deciliter was independently associated with lower risk of coronary heart disease events beyond the effect of having a low LDL-C in patients after acute coronary syndrome in the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction (PROVE IT-TIMI) 22 trial. Because the median reduction in triglycerides levels in SPARCL was only 15%, it is possible that agents that lower triglycerides further might have a greater impact in the reduction of recurrent stroke and major cardiovascular events.

The observation that there was an incremental impact of achieving optimal levels of 1, 2, 3, or 4 of these factors (Figure 4) reinforces the need for developing strategies to optimize long-term compliance with secondary prevention interventions, such as with dedicated stroke prevention clinics.

Our study was limited by its exploratory nature. The SPARCL trial was not designed and powered for these analyses. Therefore, these results should be interpreted as hypothesis generating and with appropriate caution.

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Disclosures
Dr Amarenco reports having received consulting fees from AstraZeneca, Bristol-Myers Squibb, Daiichi, Eli Lilly, GlaxoSmithKline, Guerbet, Negma, Novartis, Pfizer, Sankyo, Sanofi-Aventis, and Servier; lecture fees from AstraZeneca, Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Merck, Otsuka Pharmaceutical, Pfizer, Sanofi-Aventis, and Servier; and grant support from Boehringer-Ingelheim, Bristol-Myers Squibb, Eisai, Pfizer, and Sanofi-Aventis. Dr Goldstein has received consulting fees from Pfizer, Bayer, AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb/ Sanofi, Merck Research Laboratories, Curagen Corporation, Johnson & Johnson Cordis, AGA Medical, and Organon. Dr Messig is an employee of Pfizer and owns stock in the company. Dr O’Neill has received consulting fees and unrestricted independent investigator grant support from Pfizer, Astra-Zeneca, Bristol-Myers Squibb, and Merck Pharmaceuticals. Dr Callahan reports having received consulting fees from Pfizer and lecture fees from Bristol-Myers Squibb and Sanofi-Aventis. Dr Sillesen has received consulting fees from Pfizer and Sanofi-Aventis; lecture fees from AstraZeneca, Bristol-Myers Squibb, Merck, and Sanofi-Aventis. Dr Zivin has received consulting fees from Ambit, AstraZeneca, CytRx, Merck Research Laboratories, Johnson & Johnson, PhotoThera, PhRMA, Pfizer, and Remedy Pharmaceutical. Dr Welch has received consulting fees from Eisai, GlaxoSmithKline, Medpointe/AstraZeneca NMT Med, Ortho-McNeil; lecture fees from GlaxoSmithKline; and grant support from Pfizer.
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