Coronary Heart Disease Risk in Patients With Stroke or Transient Ischemic Attack and No Known Coronary Heart Disease

Findings From the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Trial

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Background and Purpose—Noncoronary forms of atherosclerosis (including transient ischemic attacks or stroke of carotid origin or ≥50% stenosis of the carotid artery) are associated with a 10-year vascular risk of >20% and are considered as a coronary heart disease (CHD)-risk equivalent from the standpoint of lipid management. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial included patients with stroke or transient ischemic attack and no known CHD regardless of the presence of carotid atherosclerosis. We evaluated the risk of developing clinically recognized CHD in SPARCL patients.

Methods—A total of 4731 patients (mean age, 63 years) was randomized to 80 mg/day atorvastatin placebo. The rates of major coronary event, any CHD event, and any revascularization procedure were evaluated.

Results—After 4.9 years of follow-up, the risks of a major coronary event and of any CHD end point in the placebo group were 5.1% and 8.6%, respectively. The rate of outcome of stroke decreased over time, whereas the major coronary event rate was stable. Relative to those having a large vessel-related stroke at baseline, those having a transient ischemic attack, hemorrhagic stroke, small vessel stroke, or a stroke of unknown cause had similar absolute rates for a first major coronary event and for any CHD event; transient ischemic attack, small vessel, and unknown cause groups had lower absolute revascularization procedure rates. Major coronary event, any CHD event, and any revascularization procedure rates were similarly reduced in all baseline stroke subtypes in the atorvastatin arm compared with placebo with no heterogeneity between groups.

Conclusion—CHD risk can be substantially reduced by atorvastatin therapy in patients with recent stroke or transient ischemic attack regardless of stroke subtype. (Stroke. 2010;41:426-430.)

Key Words: atherosclerosis ■ carotid stenosis ■ cholesterol ■ coronary heart disease ■ lacunar infarcts ■ prevention ■ statin ■ transient ischemic attack

Approximately one fourth of patients with a recent stroke have a history of symptomatic coronary artery disease.1 These patients are prone to recurrent coronary heart disease (CHD) events with a 10-year risk >20%.2,3 Data on the risk of CHD events in patients with stroke with no known coronary heart disease are limited, particularly for those with stroke unrelated to carotid atherosclerosis.4 The National Cholesterol Education Program-III (NCEP-III) guidelines indicate that noncoronary forms of atherosclerosis, including carotid artery disease (transient ischemic attacks [TIAs] or stroke of carotid origin or ≥50% stenosis of the carotid artery) are associated with a 10-year vascular risk of >20% and are considered as CHD-risk equivalents from the standpoint of lipid-lowering therapy.5 Consistent with NCEP-III recommendations, recent autopsy and epidemiological studies show the high frequency of CHD in patients with stroke, including those with no carotid atherosclerosis or history of CHD.6,8–8 The Stroke Prevention by Aggressive Reduction in

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Materials and Methods
The SPARCL methodology has been described in detail previously.5,10 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 low-density lipoprotein cholesterol \(>160\) mg/dL [4.1 mmol/L] as required by their Institutional Review Boards) and patients gave written informed consent.

**Study Hypothesis and Patient Population**

The primary hypothesis of the SPARCL study was that treatment with 80 mg/day atorvastatin would reduce the combined risk of fatal and nonfatal stroke in patients who had a stroke or TIA 1 to 6 months before randomization but no known CHD. The determination of the presence of CHD was based on the investigator’s assessment. The study protocol did not require specific testing to exclude CHD. Eligible patients were men and women \(\geq 18\) years and had a stroke or TIA diagnosed by a neurologist within 30 days of the event. Patients with hemorrhagic stroke were included if they were deemed by the investigator to be at risk for ischemic stroke or CHD. Stroke was defined as focal clinical signs of central nervous system dysfunction of vascular origin lasting \(\geq 24\) hours. TIA was defined as an acute loss of cerebral or ocular function lasting \(< 24\) hours and presumed to be of atherosclerotic origin. Stroke subtypes were classified based on the judgment of the investigators with no independent review. Patients had to be ambulatory (modified Rankin Scale score \(\leq 3\); score can range from 0 to 6 with higher scores indicating more disability or death) and have a low-density lipoprotein cholesterol level \(\geq 100\) and \(\leq 190\) mg/dL (\(\geq 2.6\) and \(\leq 4.9\) mmol/L).4 The exclusion criteria, which have been described in detail previously, included having atrial fibrillation, sinus node dysfunction, mechanical prosthetic heart valves, clinically significant mitral stenosis, CHD, or subarachnoid hemorrhage or stroke resulting from a revascularization procedure or trauma.10 Patients were enrolled between September 1998 and March 2001.

**Study Protocol**

Patients who were taking lipid-altering drugs had to stop these medications 30 days before the screening phase of the study. Within 30 days of the initial screening visit, eligible patients were randomized to double-blind therapy with either 80 mg/day atorvastatin or placebo. All patients were counseled to follow the National Cholesterol Education Program Step 1 (or similar) diet throughout the study.6 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 primary outcome was the time from randomization to the first occurrence of a nonfatal or fatal stroke. There were 7 prespecified secondary composite outcomes: stroke or TIA; major coronary event (cardiac death, nonfatal myocardial infarction, 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).9 Individual components of the composite end points and all-cause mortality were also prespecified secondary outcomes. All primary and secondary end points were adjudicated by an independent adjudication committee.

**Lipid Level Analysis and Safety Assessments**

Full clinical laboratory assessments were performed at each 6-month visit and at study completion with measurement of blood samples in the same central laboratory. Measurements included low-density lipoprotein cholesterol assessment. If low-density lipoprotein cholesterol was \(< 40\) mg/dL, the investigator was informed of the result and could lower the dosage of atorvastatin from 80 to 40 mg per day. A second randomly chosen investigator for a placebo patient was similarly notified, and low-density lipoprotein cholesterol levels were retested for both patients to maintain the blind.

**Statistical Analysis**

To account for baseline factors thought to be related to the risk of events, prespecified Cox proportional hazards models were used to calculate hazard ratios, 95% CIs, and probability values with adjustment for continuous time since entry event, gender, and continuous baseline age. Prespecified tests of heterogeneity were used to assess whether the treatment effect differed in subgroups defined by baseline stroke subtypes. Absolute risk rates were based on the observed proportion of subjects experiencing an event. All probability values are 2-sided with no adjustment for multiple testing. The instantaneous hazard rate in placebo subjects during follow-up was estimated nonparametrically without adjusting for covariates. These estimates were plotted over time to show the evolution of the risk of stroke and major coronary events in the placebo group.

**Results**

Kaplan–Meier curves show survival free of outcome stroke and major coronary event end points (Figure 1) or any CHD end point (Figure 2) in all patients randomized. After 4.9 years of follow-up, the risks of major coronary events and of any CHD end point in the placebo group were 5.1% and 8.6%, respectively.

The Table shows the rates of major coronary events and any CHD end point overall and by baseline stroke subtypes. Relative to large vessel disease, TIA, hemorrhagic stroke, small vessel disease, and unknown cause groups had similar absolute event rates for first major coronary events and for any CHD outcome event; TIA, small vessel disease,
unknown cause groups had lower absolute event rates for revascularization procedures.

Figure 3 shows the evolution of hazard rates for outcome strokes and major coronary events in patients randomized to placebo over the course of the trial. The hazard rates for outcome strokes decreased overtime (0.75 [0.67 to 0.84, \(P<0.001\))] whereas the hazard rates for major coronary events remained stable (1.04 [0.88 to 1.24, \(P=0.644\))].

Major coronary events, any CHD event, and any revascularization procedure were similarly reduced in the atorvastatin compared with placebo-treated subjects in all baseline stroke subtypes with no heterogeneity between groups (Table).

### Discussion

In SPARCL, patients with stroke or TIA having known CHD were excluded. Therefore, patients randomized in SPARCL may be considered as a cohort in prevention of a first CHD event. After a median of 4.9 years of follow-up, the rates of major coronary events, any CHD event, and any revascularization procedure were reduced in the atorvastatin group as compared with the placebo group.\(^9\) It is notable that the relative reduction in the risk of major coronary events in SPARCL patients was double that of stroke events. NCEP-III defines CHD-risk equivalence as a 10-year vascular risk of \(\geq 20\%\), including TIA or stroke of carotid origin.\(^5\) Consistent with NCEP-III recommendations, poststroke 10-year CHD risk in population-based studies was 20%.\(^6\,7\) Patients in the SPARCL trial had a lower projected 10-year risk. The 5-year rates of major coronary event and any CHD event in the SPARCL placebo group were 5.1% and 8.6%, respectively.

### Table. Incidences of CHD Events in SPARCL Trial

<table>
<thead>
<tr>
<th>Event Type</th>
<th>All Patients (N=4726)</th>
<th>Atorvastatin (N=2363)</th>
<th>Placebo (N=2365)</th>
<th>Hazard Ratio (95% CI)</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major coronary event</td>
<td>201 (4.3)</td>
<td>81 (3.4)</td>
<td>120 (5.1)</td>
<td>0.65 (0.49–0.87)</td>
<td>0.0030</td>
</tr>
<tr>
<td>Large vessel</td>
<td>31 (4.1)</td>
<td>11 (3.0)</td>
<td>20 (5.2)</td>
<td>0.60 (0.29–1.25)</td>
<td>0.1690</td>
</tr>
<tr>
<td>TIA</td>
<td>48 (3.3)</td>
<td>20 (2.8)</td>
<td>28 (3.7)</td>
<td>0.70 (0.40–1.25)</td>
<td>0.2317</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>4 (4.3)</td>
<td>2 (4.4)</td>
<td>2 (4.2)</td>
<td>1.09 (0.15–7.93)</td>
<td>0.9324</td>
</tr>
<tr>
<td>Small vessel</td>
<td>72 (5.1)</td>
<td>32 (4.5)</td>
<td>40 (5.7)</td>
<td>0.80 (0.50–1.27)</td>
<td>0.3407</td>
</tr>
<tr>
<td>Unknown</td>
<td>46 (4.5)</td>
<td>16 (3.0)</td>
<td>30 (6.2)</td>
<td>0.43 (0.24–0.80)</td>
<td>0.0071</td>
</tr>
</tbody>
</table>

**Test for homogeneity \(P=0.5873\)**

| Any CHD              | 327 (6.9)             | 123 (5.2)             | 204 (8.6)        | 0.58 (0.46–0.73)      | <0.001      |
| Large vessel         | 58 (7.7)              | 24 (6.5)              | 34 (8.9)         | 0.77 (0.45–1.29)      | 0.3154      |
| TIA                  | 92 (6.3)              | 32 (4.5)              | 60 (8.0)         | 0.53 (0.35–0.81)      | 0.0038      |
| Hemorrhagic          | 7 (7.5)               | 2 (4.4)               | 5 (10.4)         | 0.47 (0.09–2.43)      | 0.3655      |
| Small vessel         | 110 (7.8)             | 42 (5.9)              | 68 (9.7)         | 0.61 (0.41–0.89)      | 0.0113      |
| Unknown              | 60 (5.9)              | 23 (4.3)              | 37 (7.7)         | 0.50 (0.30–0.85)      | 0.0101      |

**Test for homogeneity \(P=0.8027\)**

| Any revascularization | 257 (5.4)             | 94 (4.0)              | 163 (6.9)        | 0.55 (0.43–0.72)      | <0.001      |
| Large vessel          | 65 (8.7)              | 27 (7.4)              | 38 (9.9)         | 0.74 (0.45–1.21)      | 0.2291      |
| TIA                   | 87 (6.0)              | 30 (4.2)              | 57 (7.6)         | 0.52 (0.34–0.81)      | 0.0040      |
| Hemorrhagic           | 5 (5.4)               | 0 (0.0)               | 5 (10.4)         |                      |             |
| Small vessel          | 55 (3.9)              | 19 (2.7)              | 36 (5.1)         | 0.53 (0.30–0.92)      | 0.0245      |
| Unknown               | 45 (4.4)              | 18 (3.4)              | 27 (5.6)         | 0.55 (0.30–1.00)      | 0.0499      |

**Test for homogeneity \(P=0.8647\)**
SPARCL patients, however, received optimal medical therapy for secondary prevention; 68% of patients were treated by antihypertensive agents (ie, nearly all those with hypertension) and 94% received an antithrombotic drug over the course of the trial. Given that optimal preventive treatment in a patient with stroke may be associated with a 50% to 80% risk reduction, these interventions would also be expected to decrease the risk of symptomatic CHD. Despite this, the burden of coronary artery disease is still very high in this group and the 10-year risk would be expected to exceed the 20% vascular risk specified in NCEP-III to qualify as high risk.

**CHD Events in Stroke/TIA of Carotid Origin Compared With Stroke/TIA of Other Origin**

The rates of major coronary event and any CHD events in the SPARCL placebo group were similar across baseline stroke subtypes, indicating that patients with TIA or strokes of noncarotid origin had the same cardiac risk as in those whose strokes were related to carotid disease. Notably, the small vessel disease group had a 5.1% rate of major coronary events and a 7.8% rate of any CHD end point, whereas the corresponding rates in the large vessel disease group were 4.1% and 7.7%, respectively. This similarity between the 2 subgroups was unexpected although consistent with autopsy data showing that patients with small vessel disease (with no history of CHD) had coronary plaque in 79% of cases and coronary stenosis >50% in 37% of cases as compared with 77% and 33% of cases, respectively, in atherosclerotic strokes and no history of symptomatic CHD.6 A systematic review found that the risk of early mortality and stroke recurrence was higher in patients with nonlacunar than lacunar infarction, whereas the long-term risk was similar, including that of fatal or nonfatal myocardial infarction.12 The present data show that patients with small vessel disease had a long-term risk of CHD similar to other ischemic stroke subtypes and therefore should benefit from the same intensive preventive strategies.

**Evolution of CHD Risk in the Placebo Group**

The risk of stroke after the index event decreased over the first 3 years in patients included in the European Carotid Surgery Trial.13 The SPARCL trial extends this observation to all patients with stroke and no known coronary heart disease. In addition, the major coronary event risk in the SPARCL placebo group remained stable over time (Figure 3), consistent with a meta-analysis.7 Observational studies and clinical trials show that the risk of myocardial infarction is far from negligible and eventually equals or exceeds the risk of recurrent stroke.13 Long-term studies powered to detect an effect on coronary events should be considered when designing clinical trials in patients with stroke evaluating new treatment strategies.

These analyses were performed post hoc. The SPARCL trial was not powered to explore the rate of major coronary events in stroke subtypes. Similarly, stroke subtype assignment was based on investigator judgment and was not standardized or adjudicated. We cannot evaluate the impact of treatment on time to an outcome event after the incident stroke or TIA because there was an average of 3 months between the qualifying stroke/TIA and study enrollment. Finally, evaluation for the presence of carotid stenosis in the SPARCL baseline data collection was not required or standardized. Therefore, these analyses should be taken as exploratory.

In conclusion, we found no difference in the risk of outcome CHD events in subjects with TIA or stroke regardless of whether the event was related to carotid disease. Moreover, 80 mg/day atorvastatin was similarly efficacious in reducing outcome CHD events regardless of baseline stroke subtype.

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This study was sponsored by Pfizer Inc, who was involved in the design and conduct of the study; collection, management, and analysis of the data; and review of the manuscript. All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

**Disclosures**

P.A. 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. L.G. has received honoraria from Pfizer during the course of this study. The honoraria did not exceed $10 000/year. H.S. 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. O.B. has received honoraria from Pfizer for the course of this study. The honoraria did not exceed $10 000/year. A.C. has received honoraria from Pfizer in excess of $10 000 during the course of this study. M.H. 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. J.Z. has received honoraria from Pfizer during the course of this study. The honoraria did not exceed $10 000/year. K.M.A.W. has received honoraria from Pfizer during the course of the study in excess of $10 000/year.

**References**

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