Statin Use and Sex-Specific Stroke Outcomes in Patients With Vascular Disease

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Background and Purpose—Although statins reduce the risk of stroke in patients with coronary heart disease, possible differing effects of statins on stroke outcomes based on sex remain uncertain. We investigated the relationships between statin use and sex-specific stroke incidence, severity, and mortality.

Methods—Data from 3 trials of oral glycoprotein IIb/IIIa inhibitors (first and second Sibrafiban versus aspirin to Yield Maximum Protection from ischemic Heart events postacute cOronary sYndromes [SYMPHONY] and Blockade of the glycoprotein IIb/IIIa Receptor to Avoid Vascular Occlusion [BRAVO]) were pooled and stroke outcomes compared among 8191 baseline statin users versus 14 752 nonusers. Time-to-event data were modeled with proportional hazards regression. Stroke severity was assessed retrospectively with the Canadian Neurological Scale (CNS) based on records with scoreable neurological examinations.

Results—A total of 217 subjects had strokes (0.95%). Statin users had a lower risk of stroke in unadjusted (hazard ratio [HR], 0.69; 95% CI, 0.51 to 0.92) and risk-adjusted models (HR, 0.72; 95% CI, 0.53 to 0.97). There was no difference in stroke mortality with statin use ($P=0.8$). CNS scores could be assigned to 106 of the subjects, with no difference in severity among statin users and nonusers (median CNS = 10.5 in users versus CNS = 9.75 in nonusers; $P=0.14$). Women had more severe strokes than men (median CNS = 10.5 in men versus 9.5 in women; Poisson regression $P=0.035$). Women had more severe strokes after adjustment for stroke use ($P=0.03$) and the combination of statin use, atrial fibrillation, and age ($P=0.03$).

Conclusions—In patients included in these clinical trials of oral glycoprotein IIb/IIIa inhibitors, statin use is associated with a reduced risk of stroke but not severity or mortality. Women had more severe strokes than men, a difference that was not explained by baseline characteristics or statin use. (Stroke. 2006;37:1427-1431.)

Key Words: stroke assessment ■ stroke outcome

Hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) lower the risk of stroke in patients with coronary heart disease (CHD).1–5 Statins may also improve stroke outcomes through neuroprotective actions or effects on the recovery process.6–8 Studies evaluating the effects of statins on stroke severity and functional outcome in humans have had inconsistent results. One study found that there was no difference in initial stroke severity between statin users and nonusers.9 A second study also found no difference in initial stroke severity, but patients taking lipid-lowering agents (91% of which were statins) were less likely to have worsening of stroke symptoms during hospitalization.10 With the exception of the Cholesterol And Recurrent Events (CARE) trial,11 secondary CHD prevention trials have failed to find a reduction in stroke in women treated with statins.12–15 However, women have a higher stroke-related case fatality rate and poorer outcomes than men.16–19 We hypothesized that statins would reduce stroke severity and mortality in patients with CHD but that the effect might be modified based on sex. The aim of the study was to determine
whether there were sex-specific differences in stroke incidence, severity, and mortality associated with statin use in subjects enrolled in 3 trials of oral glycoprotein IIb/IIIa inhibitors for CHD.

Materials and Methods
Data Sources and Patient Population
Data from 22,943 stable patients randomized in 3 intermediate- to long-term secondary prevention trials of oral glycoprotein IIb/IIIa inhibitors in patients with CHD (first and second SYMPHONY) or vascular disease (BRAVO) were pooled for this analysis. Trial designs and main results have been published.20-23 Briefly, SYMPHONY randomized 9233 patients, stabilized for ≥12 hours and within 7 days after an acute coronary syndrome, to receive either 80 mg aspirin twice daily or 1 of 2 dose regimens (low or high) of sibrafiban twice daily for 90 days. In the second SYMPHONY trial, 6671 patients meeting similar inclusion criteria were randomly assigned to receive 80 mg aspirin, low-dose sibrafiban plus 80 mg aspirin, or high-dose sibrafiban alone twice daily. In the BRAVO trial, patients with vascular disease were randomized to 30 or 50 mg lortafiban twice daily in addition to aspirin (75 to 325 mg per day).

For the purposes of this analysis, patients who reported using statins at enrollment were categorized as statin users. Information about continuation of statin use during the trials was not available. Stroke was a primary end point in BRAVO and a secondary end point in SYMPHONY and second SYMPHONY. All 3 trials used similar approaches to identify all suspected strokes, which were then adjudicated by committees of cardiologists and neurologists who were masked to treatment assignment but not statin use. These committees reviewed the case report form data and key portions of the medical record, including the discharge summary or death note, progress notes around the time of stroke, the treating neurologist’s clinical documentation or autopsy report (if available), and imaging reports or scans (computed tomography or MRI), to verify whether a stroke occurred and to assess the type of stroke.23,24 Fatal stroke was defined as death occurring within 30 days of stroke. Because the present study reflects a post hoc secondary analysis, the knowledge of the adjudication committee of the subjects’ use of statins would not affect the results.

Assessment of Stroke Severity
Hospital records that included neurological examinations of subjects with stroke were reviewed retrospectively to assign stroke severity scores with the Canadian Neurological Scale (CNS). The CNS assesses level of consciousness, orientation, speech, and weakness of the face, arm, and leg on a scale from 11.5 (no deficit) to 0 (most severe deficit).25 The CNS has been validated and is reliable as a retrospective assessment of ischemic stroke severity.26 To avoid confounding from pre-existing neurological deficits, patients with a previous history of stroke were excluded from the stroke severity analyses. Also, patients with spontaneous hemorrhagic strokes (but not ischemic strokes with hemorrhagic transformation) were excluded from the severity analysis because the level of consciousness skewed the scores toward 0 (most severe). Two neurologists experienced in CNS scoring (C.D.B. and L.B.G.) and who were masked to statin use assigned scores independently. When there was disagreement, a consensus score was reached.

Statistical Analysis
Continuous variables are expressed as medians (25th and 75th percentiles) and categorical variables as percentages. Stroke incidence (ischemic and hemorrhagic) was compared among baseline statin users versus nonusers using the $\chi^2$ test. The incidence of fatal strokes between statin users and nonusers and between men and women was compared using Fisher exact tests.

The unadjusted associations between sex and stroke as well as statin use and stroke were tested with a log-rank test. Multivariable Cox proportional hazards modeling was used to account for sex and treatment biases. Potential covariates included: age, race, or region of the world; treatment with $\beta$- blockers, digitals, diuretics, or thrombolytics; history of congestive heart failure, hypertension, diabetes, smoking, myocardial infarction, cardiac arrhythmias, or stroke; procedures such as percutaneous coronary intervention or coronary artery bypass grafting; and other clinical and test measurements such as ECG parameters, creatinine clearance, pulse and systolic blood pressure. The proportional hazards assumption was evaluated after a final model was developed. Factors not meeting that assumption were incorporated in the models as strata rather than covariates. Both stepwise and backward variable selection techniques were used with variables entered and retained at the $P=0.05$ level.

Relationships between CNS scores, statin use, and sex were evaluated using Poisson regression and unadjusted and adjusted for factors commonly associated with stroke severity, such as age and atrial fibrillation. All analyses were performed using SAS V.8.2 statistical software.

Results
Patient Population
Among the 22,943 subjects of the 3 trials, 8191 used statins at baseline, and 14,752 were nonusers. Baseline characteristics of statin users and nonusers are given in the supplemental Table I, available online at http://stroke.ahajournals.org. Statin users were more likely to be men, younger, previous smokers, and to have hypertension, diabetes, hypercholesterolemia, a history of angina or myocardial infarction, previous percutaneous intervention or coronary artery bypass grafting, and a history of peripheral vascular disease. Statin nonusers were more likely to be current smokers and have atrial fibrillation and a history of stroke.

There were more statin users in BRAVO (48.2%) than in first SYMPHONY (27%) or second SYMPHONY (39.8%), but there were no significant differences in use between men and women among the trials. There was an increase in statin use over the time period (1997 to 2000) of the trials ($P<0.001$).

Stroke Characteristics by Trial
Among the 3 trials, 217 (0.95%) subjects had strokes (73 of 9233 [0.79%] in first SYMPHONY; 46 of 6671 [0.69%] in second SYMPHONY; and 98 of 7039 [1.4%] in BRAVO). Because first SYMPHONY followed outcomes only through 90 days, an analysis was done to determine differences in 90-day stroke incidence among the trials. There was no difference in stroke rates at 90 days ($P=0.810$) and no interaction between trial and statin use ($P=0.301$) or trial and sex ($P=0.450$).

Thirty-three percent of the stroke patients were women (23 statin users and 48 nonusers), and 67% were men (40 statin users and 106 nonusers). There were 178 (84%) ischemic strokes (5 of which underwent hemorrhagic conversion), 18 (8.5%) primary hemorrhagic strokes, and 15 (7%) of unknown type. Analyses to evaluate differences in stroke subtypes after stratifying by sex and statin use (limited to ischemic versus primary hemorrhagic stroke subtypes only) showed that women had a higher proportion of hemorrhagic strokes compared with men (16.7% versus 5.6%; $\chi^2$ $P=0.013$), but there was no difference based on statin use (7.8% versus no statin use 10.2%; $P=0.588$).
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Table 1. Unadjusted and Adjusted 90-Day Stroke Event Rates and HRs in Men and Women, With and Without Statin Use

<table>
<thead>
<tr>
<th>Statin Use</th>
<th>90-Day Event Rate Kaplan–Meier</th>
<th>90-Day Event Rate Kaplan–Meier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>Unadjusted</td>
<td>Adjusted</td>
</tr>
<tr>
<td>(+) Statin</td>
<td>0.99%</td>
<td>0.79%</td>
</tr>
<tr>
<td>(−) Statin</td>
<td>0.96%</td>
<td>0.83%</td>
</tr>
<tr>
<td>Women</td>
<td>Unadjusted</td>
<td>Adjusted</td>
</tr>
<tr>
<td>(+) Statin</td>
<td>0.51%</td>
<td>0.51%</td>
</tr>
<tr>
<td>(−) Statin</td>
<td>0.75%</td>
<td>0.82%</td>
</tr>
</tbody>
</table>

Table 2. Stroke Severity and Mortality Stratified by Sex and Statin Use

<table>
<thead>
<tr>
<th></th>
<th>Fatal Strokes (n=217)</th>
<th>Wilcoxon P Value</th>
<th>Median CNS (25th, 75th %; n=106)</th>
<th>Wilcoxon P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Women 12 (16.9%)</td>
<td>0.16</td>
<td>9.5 (6.0, 11.0)</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>Men 15 (10.3%)</td>
<td></td>
<td>10.5 (9.0, 11.5)</td>
<td></td>
</tr>
<tr>
<td>Statin use</td>
<td>Yes 8 (11.8%)</td>
<td>0.84</td>
<td>10.5 (9.5, 11.0)</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td>No 19 (12.8%)</td>
<td></td>
<td>9.8 (6.8, 10.5)</td>
<td></td>
</tr>
</tbody>
</table>

Statin Use, Sex, and Stroke Incidence

Statin users had a lower risk of stroke than nonusers in both the unadjusted (hazard ratio [HR], 0.69; 95% CI, 0.51 to 0.92) and risk-adjusted models (HR, 0.72; 95% CI, 0.53 to 0.97). Independent predictors for increased stroke risk included age, diabetes, history of stroke, atrial fibrillation/flutter, baseline β-blocker use, and transient ischemic attack at entry. Eastern European residence was associated with a lower risk of stroke. Men using statins appeared to have a lower 90-day stroke event rate than women using statins (Table 1); however, the 95% CIs overlap, and there was no interaction between sex and statin use.

Statin Use, Sex, and Stroke Mortality

Case fatality rates appeared to be higher in women (16.9%) than men (10.3%), but the difference was not significant (P=0.165). The risk of fatal stroke was similar in statin users (11.8%) and nonusers (12.8%; P=0.8; Table 2).

Statin Use, Sex, and Stroke Severity

Data were available to assign CNS scores to 106 patients. These patients were more likely to have previous coronary artery bypass grafting (P=0.009), lower diastolic blood pressure (P=0.007), and tended to have lower mortality (P=0.08) compared with the stroke patients for whom these data were not available (data not shown). Stroke severity was similar with or without statin use (Tables 2 and 3).

Women had increased stroke severity compared with men (P=0.035; Tables 2 and 3). Female sex was associated with increased stroke severity after adjustment for age, atrial fibrillation, and statin use in the Poisson regression models (P=0.034; Table 3). There was not a significant relationship between CNS scores and stroke severity after adjustment for female sex (P=0.096; Table 3) and no significant interaction between statin use and female sex (P=0.32; Table 3).

Further subgroup analyses of men and women who did or did not use statins are given in the Figure. Both men and women who had been taking statins had higher CNS scores, consistent with the lack of interaction between sex and statin use. Women who did not use statins had the lowest median CNS score (median CNS=9; interquartile range 4.5 to 11).

Discussion

Consistent with previous analyses showing that statins lower the risk of stroke in patients with heart disease, we found that statin use was associated with a 28% (HR, 0.72; 95% CI, 0.53 to 0.97) reduction in the risk of stroke. However, unlike studies in experimental animals, and similar to previous clinical studies,9,27 we found that there was no overall effect of statin use on initial stroke severity or mortality. We did

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find that women had more severe strokes than men. These results are similar to those of the Northern Manhattan Study, in which there was no difference in stroke severity based on the use of lipid-lowering agents at the time of stroke, with women again having more severe strokes than men. In our study, the sex difference in stroke severity was not explained by baseline characteristics such as age or statin use. Although we did not find a statistical interaction between sex and stroke severity, this analysis may have been underpowered.

In our analysis, there was no statistical interaction between the effects of sex and statin use on the risk of stroke, although the reduction in stroke in women was not significant. A secondary analysis of the Heart and Estrogen-Progestin Replacement Study data also found that baseline statin use was not associated with a reduction in stroke in women. Consistent with these results, 3 completed prospective randomized trials of statin therapy providing subgroup analyses of stroke outcomes stratified by sex have not shown reductions in stroke in women. The Heart Protection Study reported a nonsignificant 17% (95% CI, −10% to 36%) reduction, and the CARE study showed a nonsignificant 35% reduction (95% CI, −25% to 66%) of stroke in women. The Long-Term Intervention With Pravastatin in Ischemic Disease study found that women in the statin group had strokes (4.4%) than in the placebo group (3.6%), whereas the opposite result was found in men (placebo 4.7% versus statin 3.6%), but with no significant interaction between sex and statin treatment ($P = 0.09$). The lack of demonstrated efficacy of statins for stroke prevention in women in these trials might be the result of a lack of adequate statistical power because of the small numbers of strokes. As in our study, the 95% CIs for men and women overlap in each of these studies (ie, there is no clear difference in benefit for men compared with women).

As in our analysis, previous studies have shown that women have poorer stroke outcomes than men, even after adjustment for age. In Sweden, women with strokes had more comorbidities, were more likely to be institutionalized at 3 months, and had greater physical and mental impairments after stroke than men, even after adjustment for age and other prognostic factors. A large European registry reported that female sex was independently associated with disability and handicap after adjustment for age, prestroke disability, and stroke deficits. Women with stroke also had a higher 28-day case fatality rate, in-hospital mortality rate, and longer hospital stay than men. Data from the Registry of the Canadian Stroke Network also showed that women with stroke were more likely to be discharged to a long-term care facility and have greater disability than men 6 months after stroke.

The reasons for these differences between men and women are not clear. One possible explanation could be that women with CHD have greater stroke severity than men with CHD. Support for this notion comes from data showing that women with CHD have a higher stroke severity than women without CHD. About two thirds (62%; $n = 4376$) of the women in our pooled analysis had CHD, based on the enrollment criteria for the 2 SYMPHONY trials (acute coronary syndromes). Because of the high prevalence of CHD, the women in these trials might have been predisposed to have relatively more severe strokes. These analyses are exploratory, and prospective trials of CHD patients including equal numbers of men and women, as well as careful documentation of stroke severity, will be needed to further investigate this association.

There are several limitations to our analysis. First, this was an unplanned post hoc analysis of 3 randomized controlled trials of glycoprotein IIb/IIIa inhibitors. Statin use was not randomly assigned, raising the possibility of a treatment or healthy user effect bias. Statin doses and duration of therapy were not known in all patients. We were able to retrospectively measure stroke severity in only 50% of patients because of a lack of adequate documentation. However, there were only minor differences in clinical factors and outcomes between the stroke patients who were scored and those who were not. The limited number of stroke patients with scores also reduced the statistical power to detect differences in stroke severity between statin users and nonusers. For example, 242 patients would be required to detect a 1-point difference in the CNS between statin users versus nonusers with 80% power.

The limitations in current knowledge highlighted by this analysis point to questions that need to be addressed in future studies of statins and stroke. Prospective statin trials should measure initial stroke severity to determine whether these drugs have a neuroprotective effect. Future studies must also include an adequate sample of women to permit evaluation of possible differences in statin responses by sex. An ongoing randomized trial of secondary stroke prevention in patients without known heart disease, the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study, may provide data to address these questions.

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References


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