Effect of Pretreatment With Statins on Ischemic Stroke Outcomes

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Background and Purpose—Statins reduce the risk of stroke in at-risk populations and may improve outcomes in patients taking statins before an ischemic stroke (IS). Our objectives were to examine the effects of pretreatment with statins on poor outcome in IS patients.

Methods—Over a 6-month period all acute IS admissions were prospectively identified in 15 hospitals participating in a statewide acute stroke registry. Poor stroke outcome was defined as modified Rankin score ≥4 at discharge (ie, moderate-severe disability or death). Multivariable logistic regression models and matched propensity score analyses were used to quantify the effect of statin pretreatment on poor outcome.

Results—Of 1360 IS patients, 23% were using statins before their stroke event and 42% had a poor stroke outcome. After multivariable adjustment, pretreatment with statins was associated with lower odds of poor outcome (OR=0.74, 95% CI 0.52, 1.02). A significant interaction (P<0.01) was found between statin use and race. In whites, statins were associated with statistically significantly lower odds of poor outcome (OR=0.61, 95% CI 0.42, 0.86), but in blacks statins were associated with a nonstatistically significant increase in poor outcome (OR=1.82, 95% CI 0.98, 3.39). Matched propensity score analyses were consistent with the multivariable model results.

Conclusions—Pretreatment with statins was associated with better stroke outcomes in whites, but we found no evidence of a beneficial effect of statins in blacks. These findings indicate the need for further studies, including randomized trials, to examine differential effects of statins on ischemic stroke outcomes among whites and blacks. (Stroke. 2008; 39:000-000.)

Key Words: ischemic stroke ▪ statins ▪ outcome

Stroke is the third leading cause of mortality and the leading cause of disability in the United States (US), and minority populations, especially blacks, have greater stroke incidence and mortality when compared to whites. Both observational studies and clinical trials have demonstrated that lowering plasma total cholesterol (TC) decreases the risk of coronary heart disease (CHD). In contrast, the evidence for an effect of lowering plasma TC levels on the incidence of stroke has been less definitive. Results from some epidemiological studies have shown no clear association between TC levels and stroke, whereas meta-analyses of clinical trials have shown relative risk reductions for ischemic stroke (IS) of up to about 20% with the use of statins. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study, a randomized clinical trial of atorvastatin in patients who had recent stroke or transient ischemic attack, reported that statins resulted in a 16% reduction in stroke risk. observational studies have also examined the effect of taking statins before an IS event on stroke-related outcomes. The data show that among IS patients, pretreatment with statins is associated with better functional outcomes, and lower in-hospital mortality. Moreover, the SPARCL study also reports that among the subjects who suffered a stroke event during the trial, 90-day functional outcomes were better among those on statins. It has been hypothesized that the positive benefits of statins on reducing stroke risk and improving stroke outcomes may involve pleiotropic mechanisms separate from their direct cholesterol-reducing effects. These mechanisms may include antiinflammatory, neuroprotective, antithrombotic, direct vascular, and plaque stabilizing effects. Our hypothesis was that patients who were on statins before an IS would have better outcomes at discharge than those not on statins. We chose to examine this relationship in a statewide hospital-based acute stroke registry.

Received August 24, 2007; final revision received November 9, 2007; accepted November 14, 2007.
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Stoke is available at http://stroke.ahajournals.org DOI: 10.1161/STROKEAHA.107.501700
Table 1. Demographic and Clinical Characteristics of Statin Users and Nonusers at Admission (n=1360)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total (n=1360)</th>
<th>Statin (Yes) n (%)</th>
<th>Statin (No) n (%)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
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<tr>
<td>Age, y</td>
<td></td>
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<tr>
<td>18–49</td>
<td>144 (10.6)</td>
<td>16 (11.1)</td>
<td>128 (88.9)</td>
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<tr>
<td>50–59</td>
<td>185 (13.6)</td>
<td>38 (20.5)</td>
<td>147 (79.5)</td>
<td></td>
</tr>
<tr>
<td>60–69</td>
<td>263 (19.3)</td>
<td>75 (28.5)</td>
<td>188 (71.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>70–79</td>
<td>390 (28.7)</td>
<td>116 (29.7)</td>
<td>274 (70.3)</td>
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<tr>
<td>&gt;80</td>
<td>378 (27.8)</td>
<td>64 (16.9)</td>
<td>314 (83.1)</td>
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</tr>
<tr>
<td>Female</td>
<td>717 (52.4)</td>
<td>151 (21.1)</td>
<td>566 (78.9)</td>
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<tr>
<td>Black</td>
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<td>53 (20.0)</td>
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<td>0.24</td>
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<td>Past medical history</td>
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<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>513 (37.7)</td>
<td>147 (28.7)</td>
<td>366 (71.4)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Heart disease</td>
<td>437 (32.1)</td>
<td>158 (36.2)</td>
<td>279 (63.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AF</td>
<td>221 (16.2)</td>
<td>53 (24.0)</td>
<td>168 (76.0)</td>
<td>0.62</td>
</tr>
<tr>
<td>Hypertension</td>
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<td>255 (26.6)</td>
<td>705 (73.4)</td>
<td>&lt;0.0001</td>
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<td>Dyslipidemia</td>
<td>395 (29.0)</td>
<td>240 (60.8)</td>
<td>155 (39.2)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Diabetes</td>
<td>391 (28.8)</td>
<td>128 (32.7)</td>
<td>263 (67.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Smoking</td>
<td>331 (24.3)</td>
<td>67 (20.2)</td>
<td>264 (79.8)</td>
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<td>Ambulatory prestroke</td>
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<td>277 (23.3)</td>
<td>912 (76.7)</td>
<td>0.18</td>
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<td>Nursing home residence</td>
<td>57 (4.2)</td>
<td>6 (10.5)</td>
<td>51 (89.5)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*Wald Chi-square; †Column percentage; ‡Row percentage. AF indicates atrial fibrillation.

Methods

Registry Design and Case Ascertainment

The Michigan Acute Stroke Care Overview & Treatment Surveillance System (MASCOTS) was a statewide, hospital-based, acute stroke registry that was a prototype for the Paul Coverdell National Acute Stroke Registry (PCNASR). Details of the design of the MASCOTS registry have been published previously. A single-stage cluster design that used a modified stratified sampling regime was implemented to obtain a representative statewide sample of 15 hospitals. Between May and November 2002, trained study nurses prospectively ascertained all acute stroke admissions. To be included in the registry each subject had to meet 1 of the 7 acute stroke case definitions.

Exposure and Outcome Measures

The MASCOTS data abstraction tool included information on demographics, past medical history (PMH), ambulatory status pre-stroke, emergency evaluation, in-hospital evaluations, treatments and complications, and discharge treatments. The MASCOTS registry also collected information on medications the patient was using before admission. Prestroke statin use was ascertained by identifying patients on any of the following statin drugs at admission: atorvastatin, cerivastatin, fluvastatin, pravastatin, lovastatin, and simvastatin. We included only white or black subjects because the number of other racial groups was small (ie, n=19 other races, n=94 race not documented). Functional status was determined by the modified Rankin Scale (mRS) recorded at discharge; moderate-severe disability was defined as mRS of 4 or 5. The 76 subjects who died in-hospital (mRS=6) were included in the combined measure of poor stroke outcome (ie, mRS ≥4). After excluding subjects who were missing information on mRS (n=31), there were 1360 subjects available for analysis.

Data Analysis

Statistical analyses were performed using SAS software, Version 9.1.3 (SAS Institute Inc). Descriptive frequency tables and χ² analyses were used to identify characteristics associated with pre-stroke statin use and poor stroke outcome. The effect of statin pretreatment on poor stroke outcome (ie, mRS ≥4) was assessed using 2 strategies: traditional multivariable risk-adjusted logistic regression and a propensity score-matched analysis. For the multivariable risk adjustment model, age, gender, and race were regarded as a priori variables of interest and were retained in all models regardless of statistical significance. All other variables with a bivariate probability value of <0.30 were regarded as potential confounders and included in a larger model. Backwards elimination procedures (with P<0.05 to stay) were then used to identify the final main effects models. Two-way interaction terms involving statin use and the other main effect variables were then tested. To assess model fit, the Hosmer–Lemeshow goodness-of-fit χ² statistic was generated (the results indicated an excellent fit ie, P=0.89). Finally, the multivariable logistic model was then regenerated using a generalized estimating equation (GEE) approach that accounted for the potential clustering of data within hospitals. All results presented are from this final GEE-based logistic model.

For the propensity score analysis, a multivariable logistic regression model that predicted statin use among all subjects with IS was generated. A structured, iterative approach was used to develop this propensity score model, where the primary objective was to maximize the balance in the distribution in possible confounders between statin users and nonusers. A broad range of clinical and demographic variables including health insurance status, PMH, concurrent use of other cardiovascular-related medications, enrollment site, and presence of terminal illness were included. The model was modified with the addition of squared terms or interaction terms if imbalances in important covariates were identified between statin users and nonusers. The predicted probability of statin use (ie, the propensity score) was then calculated for each subject using the final model.

A greedy matching algorithm was then used to match statin users with nonusers within 0.2*SD of the logit of the propensity score. Because a statistically significant interaction between race and statin use was identified in the multivariable risk adjustment model, statin users and nonusers were also matched on race. To increase statistical
power, up to 3 nonstatin users were matched to each statin user. To
determine whether the propensity score approach achieved balance in
potential confounders, we compared the proportions of each covariate considered in the multivariable risk adjustment model
between statin users and nonusers. Evidence of imbalance in potential
confounders was identified by examining the reduction in absolute standardized differences (ASD)—adequate balance was
defined as ASD of $<10\%$.24

Using the final matched dataset, odds ratios (OR) and 95% confidence intervals (CI) for prestroke statin use and poor stroke
outcome were generated using a GEE-based logistic regression model that accounted for the matched-pairs design.24 Overall and
race-specific estimates were generated for all subjects and for whites and blacks separately. Because a central motivation of the propensity
score method is to replicate the design of a randomized trial,25 we
determined the treatment effect of prestroke statins by generating
and were included in the final model along with age, race, and
gender. However, multivariable adjustment did not appreciably alter the effect of prestroke statin use on poor outcome:
statin use was associated with a 26% reduction in the odds of
poor outcome (OR = 0.70). Nursing home residence and ambulatory status prestroke were the only variables found to be significant predictors of poor outcome
and were included in the final model along with age, race, and
gender. However, multivariable adjustment did not apprecia-
ably alter the effect of prestroke statin use on poor outcome:
statin use was associated with a 26% reduction in the odds of
poor outcome (OR = 0.74), although the 95% CI (0.53, 1.02)

**Results**

**Descriptive and Unadjusted Results**

Of the 1360 black and white IS patients, 309 or 22.7% were
taking statins before admission. Table 1 shows the demo-
graphic and clinical characteristics of statin users at admission.
Subjects 60 to 69 and 70 to 79 years of age were more likely to
be on statins at admission, as were subjects with a
PMH of stroke, heart disease, hypertension, dyslipidemia,
and diabetes, while nursing home residents were less likely to
be on statins at admission.

Five hundred seventy-seven subjects or 42.4% had a poor stroke outcome (defined as a mRS $\geq4$). Table 2 shows that
poor stroke outcome was more common among older sub-
jects, females, those with a PMH of stroke, heart disease, AF,
hypertension, or nursing home residence. Poor outcome was
less common in blacks, current smokers, and subjects who
were ambulatory prestroke. Poor stroke outcome was also
less common in subjects taking statins before admission: 111
(35.9%) of 309 subjects on statins had a mRS $\geq4$, compared
to 466 (44.3%) of 1051 subjects not on statins before their IS
event. Seventy six or 5.6% of the IS cases died in-hospital.
In-hospital mortality was also lower among the statin users:
2.3% (n = 7) of the 309 subjects on statins before admission
died in-hospital, compared to 6.6% (n = 69) of the 1051
subjects not on statins.

**Multivariable Risk Adjusted Results**

Results from the multivariable model examining the association between prestroke statin use and poor stroke outcome
are shown in Table 3. The unadjusted OR for the effect of prestroke statin use on poor outcome was 0.70. Nursing home
residence and ambulatory status prestroke were the only variables found to be significant predictors of poor outcome
and were included in the final model along with age, race, and
gender. However, multivariable adjustment did not apprecia-
ably alter the effect of prestroke statin use on poor outcome:
statin use was associated with a 26% reduction in the odds of
a poor outcome (OR = 0.74), although the 95% CI (0.53, 1.02)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total n (%)</th>
<th>mRS $\geq4$ n (%)</th>
<th>mRS $=3$ n (%)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>1360 (100)</td>
<td>577 (42.4)</td>
<td>783 (57.6)</td>
<td>. . .</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–49</td>
<td>144 (10.6)</td>
<td>28 (19.4)</td>
<td>116 (80.6)</td>
<td></td>
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<tr>
<td>50–59</td>
<td>185 (13.6)</td>
<td>43 (23.2)</td>
<td>142 (76.8)</td>
<td></td>
</tr>
<tr>
<td>60–69</td>
<td>263 (19.3)</td>
<td>109 (41.4)</td>
<td>154 (58.6)</td>
<td>$&lt;0.0001$</td>
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<tr>
<td>70–79</td>
<td>390 (28.7)</td>
<td>167 (42.8)</td>
<td>223 (57.2)</td>
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</tr>
<tr>
<td>&gt;80</td>
<td>378 (27.8)</td>
<td>230 (60.9)</td>
<td>148 (39.2)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>717 (52.7)</td>
<td>342 (47.7)</td>
<td>375 (52.3)</td>
<td>$&lt;0.0001$</td>
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<tr>
<td>Black</td>
<td>265 (19.5)</td>
<td>94 (35.5)</td>
<td>171 (64.5)</td>
<td>0.01</td>
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<tr>
<td>Past medical history</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>513 (37.7)</td>
<td>258 (50.3)</td>
<td>255 (49.7)</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Heart disease</td>
<td>437 (31.8)</td>
<td>209 (47.8)</td>
<td>228 (52.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>AF</td>
<td>221 (16.3)</td>
<td>125 (56.6)</td>
<td>96 (43.4)</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Hypertension</td>
<td>960 (70.6)</td>
<td>437 (45.5)</td>
<td>523 (54.5)</td>
<td>0.0003</td>
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<tr>
<td>Dyslipidemia</td>
<td>395 (29.9)</td>
<td>147 (37.2)</td>
<td>248 (62.8)</td>
<td>0.01</td>
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<tr>
<td>Diabetes</td>
<td>391 (28.8)</td>
<td>175 (44.8)</td>
<td>216 (55.2)</td>
<td>0.27</td>
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<tr>
<td>Smoking</td>
<td>331 (25.0)</td>
<td>102 (30.8)</td>
<td>229 (69.2)</td>
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<tr>
<td>Terminal illness</td>
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<td>13 (92.9)</td>
<td>1 (7.1)</td>
<td>0.0001</td>
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<td>Ambulatory prestroke</td>
<td>1189 (87.4)</td>
<td>420 (35.3)</td>
<td>769 (64.7)</td>
<td>$&lt;0.0001$</td>
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<tr>
<td>Nursing home residence</td>
<td>57 (4.2)</td>
<td>47 (82.5)</td>
<td>10 (17.5)</td>
<td>$&lt;0.0001$</td>
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</tbody>
</table>

*Wald Chi-square; †Column percentage; ‡Row percentage. AF indicates atrial fibrillation.
indicated that the estimate was no longer statistically significant. A statistically significant interaction ($P<0.01$) was found between statin use and race. Among blacks, prestroke statin use was associated with a nonstatistically significant increased odds of a poor outcome (OR=1.82), compared to black nonstatin users (Table 3), whereas among whites, prestroke statin use was associated with a statistically significant 39% decrease in the odds of a poor outcome (OR=0.61), compared to white nonstatin users.

**Propensity Modeling**

The final logistic regression model for calculating the propensity score had a c-statistic of 0.78 indicating good discriminant ability. The matching algorithm included 884 matched subjects or 65% of the 1360 total subjects. Eighty-eight percent (n=225) of the 256 white statin users were matched to at least 1 white nonstatin user, and 89% of the 53 black statin users (n=47) were matched to at least 1 black nonstatin user.

After matching, examination of ASD for the combined 884 matched subjects showed that matching had resulted in a dramatically improved balance in the potential confounding variables (Figure), although ASD of $>10\%$ were still evident for 3 variables: CHD, diabetes, and poor prognosis. When the ASD where examined within whites and blacks separately, there were 3 variables among whites that had an ASD of $>10\%$ (sex, CHD, and poor prognosis), whereas among blacks there were 4 variables that showed imbalance (sex, older age, atrial fibrillation, and diabetes).

The matched propensity score analyses were concordant with the results of the multivariable risk adjusted models. The OR for prestroke statin use and poor outcome among all 884

Table 3. Odds Ratio (OR)–Based Estimates of the Effect of Prestroke Statin Use on Poor Outcome (Modified Rankin Scale [mRS] $\geq 4$) Including a Statin by Race Interaction

<table>
<thead>
<tr>
<th>Effect of Statins</th>
<th>OR (95% CI)</th>
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<tr>
<td><strong>Main effects models</strong></td>
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<tr>
<td>Unadjusted</td>
<td>0.70 (0.54, 0.92)</td>
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<tr>
<td>Multivariable adjusted*</td>
<td>0.74 (0.53, 1.02)</td>
</tr>
<tr>
<td>Propensity matched</td>
<td>0.83 (0.61, 1.12)</td>
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<tr>
<td><strong>Interaction models</strong></td>
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<tr>
<td>Multivariable adjusted</td>
<td></td>
</tr>
<tr>
<td>Among whites*</td>
<td>0.61 (0.42, 0.88)</td>
</tr>
<tr>
<td>Among blacks*</td>
<td>1.82 (0.98, 3.39)</td>
</tr>
<tr>
<td>Propensity matched</td>
<td></td>
</tr>
<tr>
<td>Among whites</td>
<td>0.71 (0.50, 0.99)</td>
</tr>
<tr>
<td>Among blacks</td>
<td>1.75 (0.92, 3.32)</td>
</tr>
</tbody>
</table>

*Adjusted for age, race, gender, nursing home residence, ambulatory status prestroke.
The propensity score analyses presented in this study should be viewed as confirmatory in that they provide similar effect estimates as the multivariable model results. Our data clearly show evidence that the effects of pretreatment with statins on stroke outcomes differ by race—we found a robust, statistically significant association between pretreatment statin use and better outcomes in whites, but evidence of a possible association between pretreatment statin use and poorer outcomes in blacks. Several mechanisms have been proposed to account for the well recognized racial disparities in stroke, including racial and ethnic variations in lifestyle, access to healthcare, quality of healthcare, differences in health beliefs, and adherence to prescribed therapy. However, there are several reasons why the results generated among blacks in this study should be regarded with some caution at this time. First, the number of black subjects is relatively small (n = 265) and so the study has limited power to examine statin effects among this group (note that none of the estimates for statin use in blacks reach statistical significance, i.e., P < 0.05). Second, the results could be attributable to residual confounding. After propensity score matching relatively large imbalances remained among 3 variables: compared to black nonusers, black subjects on statins were more likely to be female (68% versus 47%), to have diabetes (57% versus 40%), and to be 70 to 79 years of age (34% versus 22%). To explore whether these factors explained the poorer outcomes in blacks, we added these variables to the multivariable risk adjustment model but found no meaningful change in the OR for pretreatment statins (data not shown). Finally, it is also possible that the interaction stems from unmeasured variables that play a larger role in determining stroke outcomes in blacks than whites—for example, these results could be a reflection of the complex interplay between prescription and adherence patterns for statins. Long term adherence to statin therapy in the elderly has been shown to be especially poor in blacks and other nonwhite groups, thus it could be hypothesized that blacks who remain on statins may represent a highly selected high-risk group.

Of course, it is possible that this interaction represents a true biological difference in the effect of statins on stroke outcomes between whites and blacks. Given the broad pleiotropic effects of statins, which include antiinflammatory, neuroprotective, antithrombotic, and vascular stabilizing effects, it is possible that the propensity score method does a better job of controlling confounding. However, recent work has also shown that propensity score analysis may result in the biased attenuation of ORs toward the null, compared to conventional regression adjustment. Another reason for the difference between traditional risk adjustment and propensity methods is that statin users and nonusers that could not be matched on the basis of their propensity score are discarded from the matched analysis (in this study, 12% of users and 42% of nonusers were eliminated). Thus propensity score results are based on a subset of the total study population.

Discussed
shown that statins have a similar clinical efficacy and safety in terms of reducing cholesterol levels in blacks, whereas others have found that statins are less effective in blacks. Because of the fact that relatively few minority patients have been included in statin therapy trials to date, available clinical data concerning the effects of statins among nonwhite racial groups is very limited. However, it is interesting to note that in the only statin trial that included a large number of minority patients, ALLHAT-LLT, there was evidence of significant statin by race interactions. Pravastatin increased the risk of stroke in blacks (RR = 1.12) but reduced the risk in nonblacks (RR = 0.74), whereas for cardiac events, pravastatin was shown to decrease the risk in blacks (RR = 0.73) but had no effect in nonblacks (RR = 1.02).

The strengths of this study include the fact that it is based on a representative sample of statewide hospitals that used prospective case ascertainment and data collection methods. However, because the primary purpose of the registry was to monitor and improve quality of care, we did not collect all the variables that are associated with poor stroke outcome, such as a comorbidity index and stroke severity. In addition, we did not collect information on the duration or dose of statin therapy. Although we do not know how information on race was recorded by the hospitals, we believe that misclassification of black race is unlikely because an independent interrater reliability study found that information on black race was documented with higher reliability (Kappa 0.97) than that of white race (Kappa 0.55). Finally, all outcomes were collected at the time of hospital discharge and the effects of statins are likely to extend beyond this short time horizon.

In summary, this study found that pretreatment with statins was associated with positive benefits with respect to stroke outcomes in whites; however, these data raise the concern that statins are associated with worse outcomes in blacks. These findings suggest the need for further studies, including randomized trials, to explore the possibility of differential effects of statins among whites and blacks with ischemic stroke.

Acknowledgments

We thank the following participating institutions and providers: Borgess Medical Center–Kalamazoo (Rashmi Kothari, MD; Karen McShane, RN, BSN; Brianna Stokes, RN); Bronson Methodist Hospital–Kalamazoo (Rashmi Kothari, MD; Jennifer Brown, RN, BSN; Denise Robinson, RN, MSN); Detroit Receiving Hospital (Julie Klinker, RN, BSN); Harper University Hospital–Detroit (Julie Klinker, RN, BSN); Ingham Regional Medical Center–Lansing (Sid Shah, MD; Christine Bosnerry, RN); Spectrum Health Systems–Grand Rapids (Herman Sullivan, MD; Wendy Arntz, RN; Carmen Noorman, RN); Sparrow Health Systems–Lansing (Gretchen Birbeck, MD; Mary Lou Mitchell, RN, MSN); St. Mary’s Hospital–Saginaw (Faith Abbott, DO; Richard Herm, BSN; Kristin Leedom, MSN); University of Michigan Hospital–Ann Arbor (Susan Hickenbottom, MD; Kate Maddox, MS, RNC). The authors also thank Dr. Peter Austin, PhD, Institute for Clinical Evaluative Sciences, University of Toronto, for his input regarding the propensity based analyses.

Sources of Funding

This study was supported by US Centers for Disease Control and Prevention Cooperative Agreement No. (U50/CCU520272-01).

Disclosures

None.

References

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Mathew J. Reeves, Julia Warner Gargano, Zhehui Luo, Andrew J. Mullard, Bradley S. Jacobs and Arshad Majid
for the Paul Coverdell National Acute Stroke Registry Michigan Prototype Investigators

*Stroke.* published online March 27, 2008;
*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/early/2008/03/27/STROKEAHA.107.501700.citation