Randomized Trial of the Effects of Simvastatin on Cognitive Functioning in Hypercholesterolemic Adults

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PURPOSE: In our initial study of the potential effects of cholesterol-lowering interventions on cognitive functioning, treatment with lovastatin as compared with placebo caused performance decrements on several neuropsychological tests, whereas scores on other tests were unaffected. The current study was designed to confirm and extend those findings.

METHODS: The study comprised 308 hypercholesterolemic adults between 35 and 70 years of age. Employing a randomized double-blind design, we assigned participants to daily treatment with placebo, 10 mg of simvastatin, or 40 mg of simvastatin for 6 months. A neuropsychological test battery was administered to assess cognitive functioning at baseline and at the end of the treatment period.

RESULTS: A total of 283 subjects completed the study: 94 subjects on placebo, 96 taking 10 mg of simvastatin, and 93 taking 40 mg of simvastatin. Compared with placebo, decremental effects of simvastatin treatment were found on tests previously observed to be sensitive to statins (P = 0.008; difference in summary z scores = 0.18; 95% confidence interval [CI]: 0.07 to 0.29) and on tests not previously administered (P = 0.04; difference in summary z scores = 0.17; 95% CI: 0.05 to 0.29), but not on tests previously observed to be insensitive to statins (P = 0.84; difference in summary z scores = 0.02; 95% CI: -0.07 to 0.10). For the three tests specifically affected by simvastatin, effects on cognitive performance were small, manifest only as failure to improve during the 6 months of treatment (compared with placebo), and were confounded by baseline differences on one test.

CONCLUSION: This study provides partial support for minor decrements in cognitive functioning with statins. Whether such effects have any long-term sequelae or occur with other cholesterol-lowering interventions is not known. Am J Med. 2004;117:823–829. ©2004 by Elsevier Inc.

High serum cholesterol level is a widely recognized risk factor for coronary artery disease, the leading cause of death in western industrialized countries. For most patients attempting to lower their serum cholesterol levels, the primary medical intervention is daily, long-term use of a statin.

Initial studies of the adverse effects of statins have been reassuring, although these agents can cause liver injury, myopathy, and peripheral neuropathy (1,2). There also has been recent interest in their potential effects on brain function. It has been suggested that statin therapy reduces the risk of Alzheimer disease (3), but recent clinical trials have found no treatment effect on dementia (4,5). In fact, one review of 60 cases of statin-associated memory loss, along with other reports of depression, sleep disorders, and global amnesia, raise questions about possible adverse effects on the brain (6).

In 2000, we reported the results of our initial study of central nervous system effects of statins (7). The investigation employed a double-blind, randomized, placebo-controlled design to evaluate the effects of lovastatin on cognitive functioning and mood among 209 middle-aged adults with hypercholesterolemia. Compared with masked placebo, 20 mg of lovastatin taken daily for 6 months had detrimental effects on cognitive performance on four neuropsychological tests assessing attention, working memory, and overall mental efficiency. Performance on other cognitive tests and mood were not affected substantially. The observed treatment effects were quantitatively small and were primarily manifest not as an absolute decline in performance but as a failure to improve upon repeat post-treatment testing. Learning or practice effects occur commonly upon readministration of many neuropsychological tests, even though equivalent, alternative versions of the tests are frequently employed to minimize such learning effects. The current trial was undertaken to confirm and extend the observations made in our initial investigation.

METHODS

Subjects were generally healthy men and women between 35 and 70 years of age with mild-to-moderate hypercho-
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Flow diagram of progression of subjects through the phases of the study.

Cognitive performance among high-functioning persons was chosen because of their sensitivity to small differences in specificity of statin effects; and new tests, including the six tests from our initial investigation that had not detected drug effects, readministered to verify the drug effects in our initial investigation; statin-insensitive tests, comprising the four tests revealing logical assessment battery was administered, and four individual tests showed statistically significant effects of statin treatment: Digit Vigilance, Recurrent Words, Elithorn Mazes, and Grooved Pegboard. In the current trial, we assembled a neuropsychological test battery containing statin-sensitive tests, comprising the four tests revealing drug effects in our initial investigation; statin-insensitive tests, including six tests from our initial investigation that had not detected drug effects, readministered to verify the specificity of statin effects; and new tests, including the Mirror Tracer and 4-Word Short-Term Memory tests, chosen because of their sensitivity to small differences in cognitive performance among high-functioning persons.

In our initial investigation (7), a broad neuropsychological assessment battery was administered, and four individual tests showed statistically significant effects of statin treatment: Digit Vigilance, Recurrent Words, Elithorn Mazes, and Grooved Pegboard. In the current trial, we assembled a neuropsychological test battery containing statin-sensitive tests, comprising the four tests revealing drug effects in our initial investigation; statin-insensitive tests, including six tests from our initial investigation that had not detected drug effects, readministered to verify the specificity of statin effects; and new tests, including the Mirror Tracer and 4-Word Short-Term Memory tests, chosen because of their sensitivity to small differences in cognitive performance among high-functioning persons (Appendix).
Testing sessions were conducted at baseline and at the end of treatment. Alternative forms of the tests, where available, were used in randomized order at the baseline and post-treatment assessments. Prior to baseline testing, subjects attended a practice session to familiarize themselves with test materials and instructions. To examine treatment effects on health-related quality of life, participants completed the Medical Outcomes Study Short Form General Health Survey (21).

**Statistical Analysis**

In several instances, continuous variables were subjected to transformation to ensure normality of distribution. Baseline characteristics were compared using analysis of variance, the Kruskal-Wallis test, or the chi-squared test, as appropriate. The effects of treatment on serum lipid concentrations and quality of life were examined with repeated-measures analysis of variance. Where necessary, scores were multiplied by -1 so that higher scores always indicated better performance. Summary scores for the three test categories were constructed by averaging the \( z \) scores of the constituent tests. Change in cognitive performance was calculated by subtracting the summary \( z \) scores at baseline from the summary \( z \) scores post-treatment. A \( t \) test for each of the test categories was conducted to examine the effects of treatment assignment on change in cognitive performance. These analytic procedures were those employed in our initial investigation (7) and are in accord with multivariate statistical analyses used in other studies examining change in cognitive performance based on multiple neuropsychological tests (22). Analyses were performed using SPSS, version 11 (Chicago, Illinois).

**RESULTS**

The subjects were generally middle-aged with moderate hypercholesterolemia (Table 1). Most had attended some college, and scores on tests of vocabulary and problem-solving abilities generally were above average. Comparison of the treatment groups with respect to the 13 demographic and clinical variables and the 12 neuropsychological test scores at baseline indicated that the groups were similar except on the Recurrent Words test (placebo vs. treatment groups: 79.6% vs. 84.0%, \( P = 0.04 \)).
Median treatment adherence based on pill counts during the 6 months of treatment was 95% and did not differ among the treatment groups. Serum lipid concentrations changed little in the placebo-treated subjects during the treatment period. Subjects assigned to 10 mg of simvastatin experienced an average decline in total cholesterol level of 54 mg/dL (95% confidence interval [CI]: 49 to 60 mg/dL), about 21% as compared with baseline, whereas the total cholesterol level of participants receiving 40 mg of simvastatin fell by 80 mg/dL (95% CI: 75 to 85 mg/dL), or about 31%.

In multivariate repeated-measures analysis of variance of the statin-sensitive neuropsychological tests, simvastatin altered cognitive performance compared with placebo ($P = 0.008$). A similar result was noted when the data were analyzed using the difference in change in summary $z$ scores ($score = 0.18; 95% CI: 0.07 to 0.29; P = 0.002$). Examination of the $z$ scores indicated that on statin-sensitive tests subjects receiving placebo improved between baseline and post-treatment visits, whereas those assigned to simvastatin did not (Table 2).

In analyses of the statin-insensitive tests, performance scores were unaffected by treatment (multivariate $P = 0.84$; summary $z$ score = 0.02; 95% CI: -0.07 to 0.10). There was an effect of treatment on the new neuropsychological tests, based on either multivariate analysis ($P = 0.04$) or t test of summary $z$ scores ($score = 0.17; 95% CI: 0.05 to 0.29; P = 0.007$). Cognitive performance on the new tests improved more from baseline to post-treatment in subjects taking placebo than in those receiving simvastatin (Table 2).

In analyses of the mean scores on the individual neuropsychological tests comprising the statin-sensitive and new categories (Table 3), statistically significant treatment effects were observed on scores on Elithorn Mazes ($P = 0.02$) and Recurrent Words ($P = 0.04$) tests in the statin-sensitive category, whereas performance on the Grooved Pegboard ($P = 0.09$) and Digit Vigilance ($P = 0.84$) tests was not significantly affected. Performance improved on the Recurrent Words and Elithorn Mazes tests in placebo-treated subjects but not in those receiving simvastatin. The groups, however, differed at baseline on the Recurrent Words test. On the two new tests, decremental effects of simvastatin reached statistical significance on the 4-Word Memory test ($P = 0.05$) but not on the Mirror tracing test ($P = 0.09$). Again, subjects receiv-

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**Table 2. Summary Z Scores* of Cognitive Function at Baseline and after 6 Months of Treatment**

<table>
<thead>
<tr>
<th>Neuropsychological Test Category</th>
<th>Placebo Group (n = 94)</th>
<th>Simvastatin Group (n = 189)</th>
<th>Group Difference in Change</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Post-Treatment</td>
<td>Baseline</td>
<td>Post-Treatment</td>
</tr>
<tr>
<td>Statin-sensitive tests</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statin-insensitive tests</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New tests</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

* Higher scores indicate better performance.

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**Table 3. Performance on Individual Tests of Cognitive Function at Baseline and after 6 Months of Treatment**

<table>
<thead>
<tr>
<th>Test*</th>
<th>Placebo Group (n = 94)</th>
<th>Simvastatin Group (n = 189)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Post-Treatment</td>
</tr>
<tr>
<td>Mean (95% Confidence Interval)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statin-sensitive tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit Vigilance (errors)†</td>
<td>6.2 (4.7–7.6)</td>
<td>5.7 (4.4–7.0)</td>
</tr>
<tr>
<td>Recurrent Words (% correct)</td>
<td>80 (76–83)</td>
<td>83 (80–86)</td>
</tr>
<tr>
<td>Elithorn Mazes (seconds)†</td>
<td>172 (160–184)</td>
<td>144 (133–155)</td>
</tr>
<tr>
<td>Grooved Pegboard (seconds)†</td>
<td>144 (139–149)</td>
<td>144 (138–150)</td>
</tr>
<tr>
<td>New tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mirror Tracing (errors)†</td>
<td>48 (40–56)</td>
<td>40 (32–48)</td>
</tr>
<tr>
<td>4-Word Memory (no. correct)</td>
<td>18.9 (17.4–20.4)</td>
<td>20.8 (19.1–22.4)</td>
</tr>
</tbody>
</table>

* Descriptions of individual tests are provided in the Appendix.
† Higher scores indicate worse performance.
ing placebo improved in performance whereas those receiving simvastatin did not.

When the two active treatment groups (10 mg and 40 mg) were compared to test for the presence of a dose-response relation, we found that the 40-mg dose of simvastatin did not have greater effects on cognitive performance than the 10-mg dose \( (P > 0.15) \). In addition, neither overall quality of life nor the mental component scale scores differed in placebo and simvastatin-treated participants \( (P > 0.15) \).

**DISCUSSION**

In our re-examination of the effects of statins on cognitive functioning, we found that treatment adversely affected performance on neuropsychological tests that were sensitive to lovastatin in our initial investigation. Performance on new tests was also negatively affected by simvastatin, as compared with placebo. However, these effects were rather circumscribed; statistically significant treatment effects were observed on just three of six tests when analyzed individually, and baseline differences confounded interpretation of one of these measures. The cognitive decrements with the 40-mg dose of simvastatin were no greater than those observed with the 10-mg dose, suggesting a threshold effect. As in our initial investigation, the treatment effects were small and were manifest not as an absolute decline in performance but as a lack of improvement between baseline and post-treatment assessments. Indeed, learning or practice effects are observed upon readministration of most neuropsychological tests; neither study used measures that we have found to be sensitive or to lovastatin in our initial trial. Given the limitations of the current study is warranted because of both the extremely widespread use of these drugs and the decline in cognitive function that accompanies aging. Further study is warranted because of both the extremely widespread use of these drugs and the decline in cognitive function that accompanies aging. Treatment effects may differ by patient group or with nonstatin cholesterol-lowering interventions, and may either amplify or resolve (via development of tolerance) with long-term treatment. In any case, this research challenges the current orthodoxy that cholesterol is of importance only as a risk factor for atherosclerosis.
REFERENCES


Appendix. Neuropsychological Test Battery

**Statin-Insensitive Tests**

- **Elithorn Mazes**
  Planning and drawing time to complete complex lattice-type perceptual mazes (10).

- **Digit Vigilance**
  Number of target stimuli (the number “6”) missed when required to scan two pages of numbers (11).

- **Recurring Words**
  Percentage of words identified correctly as either “new” or “repeated” when words are read using a continuous recognition test format (12).

- **Grooved Pegboard**
  Time required to insert 25 grooved pegs into slotted holes (13).

**Statin-Insensitive Tests**

- **Digit Symbol**
  Time required to recode numbers into symbols using a key that pairs each of nine digits with a meaningless shape. Time converted to scaled, normalized score (14).

- **Stroop Interference**
  Viewing a list of color words printed in an incongruous ink color, participants say each ink color as quickly as possible (seeing “red” printed in blue ink, they respond “blue”). Number correct is converted to a scaled, normalized score (15).

- **Trail Making B**
  Time required to draw a line connecting alternating numbers and letters (e.g., 1-A-2-B) that are arrayed on a piece of paper (16).

- **Digit Span**
  Longest span of digits correctly recalled forwards and longest span recalled backwards. Sum of spans is converted into scaled, normalized score (14).

- **Complex Figure**
  Score on the reproduction of the Rey or Taylor figure, drawn from memory 30 minutes after having copied the figure (17).

- **Letter Rotation**
  Number of stimuli (the letters F, L, or R rotated 0°, 30°, 60°, 90°, 120°, 150°, or 180°) misidentified as being either oriented normally or reversed (18).

**New Tests**

- **Mirror Tracing**
  Number of errors made when tracing over a star pattern that can be seen only in mirror-reversed view (19).

- **4-Word Short-Term Memory**
  Across several trials, the number of words correctly recalled after intervening distraction consisting of serial subtraction arithmetic for 15 or 30 seconds (20).

* Tests on which two alternative forms were used.