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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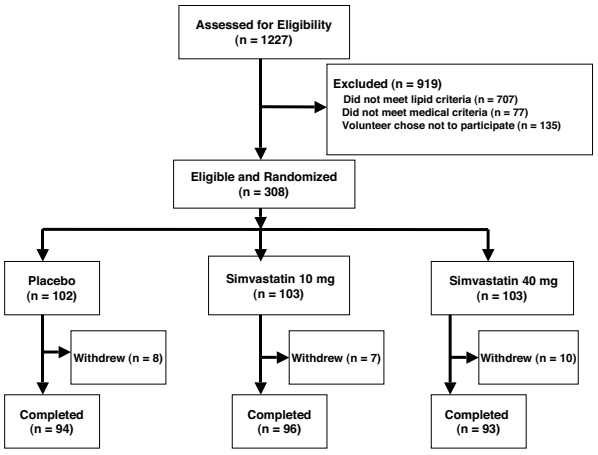

Figure. Flow diagram of progression of subjects through the phases of the study.

lesterolemia, defined as a low-density lipoprotein (LDL) cholesterol level between 160 and 220 mg/dL. Participants were recruited from Allegheny County in southwestern Pennsylvania by mass mailings of the study brochure and placement of media advertisements. The study protocol was approved by the University of Pittsburgh Institutional Review Board, and informed consent was obtained from all subjects.

Exclusion criteria included the following medical conditions: secondary hyperlipidemia (lipid disorders attributable to chronic hepatitis, renal failure, or untreated hypothyroidism), severe hypertriglyceridemia (fasting serum triglyceride level >350 mg/dL), coronary artery disease, stroke, diabetes, untreated hypertension (diastolic blood pressure >95 mm Hg), cancer, and major neuropsychiatric conditions (e.g., schizophrenia, seizures, dementia). Subjects were also excluded if they reported current treatment with any lipid-lowering medication or supplement, psychotropic medication, glucocorticoid, or opiate analgesic. Sexually active premenopausal women were excluded unless they were using birth control.

Sample size calculations indicated that 100 subjects per condition (n = 300 total) would provide at least 80% power to detect an effect size of $f = 0.25$ between placebo and 10 mg of simvastatin, and between 10 and 40 mg of simvastatin from baseline to post-treatment (i.e., group by time interaction) when using a two-tailed F-test from a repeated-measures analysis of variance with a significance level of 0.01. The effect size measure (f) is the standard deviation of the standardized means; from a behavioral science perspective, an effect size of 0.25 would translate into a medium-sized effect (8).

A total of 1227 subjects attended at least one screening visit, of whom 443 (36%) met all eligibility criteria (Figure). Of these 443 volunteers, 308 (70%) completed the screening procedures. Following stratification by race (black vs. other), age (≤50 vs. >50 years), and sex, each participant was assigned randomly to daily treatment with placebo,10 mg of simvastatin, or 40 mg of simvastatin. Permuted block randomization within strata for each combination of the three factors was used to generate the treatment assignment lists. All three treatments were encapsulated and identical in appearance to preserve blinding of subjects and research staff. The treatment period was 6 months.

Two hundred and eighty-three of the randomized participants (92%) completed the investigation. The number of withdrawals did not differ by treatment condition, although the reasons varied. Withdrawals due to suspected adverse treatment reactions included 4 among subjects receiving 40 mg of simvastatin and 3 among those receiving 10 mg of simvastatin; none in the placebo group had adverse reactions. Withdrawal due to a serious adverse event occurred in only 1 subject who suffered a stroke while taking 40 mg of simvastatin. Compliance was monitored by pill counts at interim follow-up appointments (weeks 8 and 16) and at the final visit (month 6). Compliance averaged 95% over the treatment period and did not differ by condition.

Measurements

Fasting blood samples for serum lipid determinations were drawn twice during screening (separated by 1 to 3 weeks), after 2 and 4 months, and twice during the last month of treatment. The two baseline lipid measurements were averaged, and the two post-treatment measurements were averaged. Determinations of serum total cholesterol, high-density lipoprotein cholesterol, and triglyceride levels were performed by the Heinz Nutrition Laboratory, Department of Epidemiology, University of Pittsburgh Graduate School of Public Health, which has met the criteria of the Centers for Disease Control and Prevention–National Heart, Lung, and Blood Institute Lipid Standardization Program since 1982. LDL cholesterol level was calculated using the Friedewald equation (9).

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).

Table 1. Baseline Characteristics of Subjects by Treatment Group*

Characteristic	Placebo (n = 94)	Simvastatin 10 mg (n = 96)	Simvastatin 40 mg (n = 93)
	Number (%) or Mean ± SD		
Age (years)	54.1 ± 8.7	53.0 ± 9.9	54.2 ± 8.7
Female sex	50 (53)	51 (53)	46 (50)
White	84 (89)	82 (85)	78 (84)
Weight (kg)	81.7 ± 13.6	82.8 ± 13.2	84.0 ± 15.4
Blood pressure (mm Hg)	125/80 ± 12/8	125/81 ± 14/9	125/82 ± 13/8
Education (years)	14.8 ± 3.2	15.0 ± 3.7	14.7 ± 3.3
Alcohol (drinks per week)	2.4 ± 1.2	2.6 ± 2.2	2.3 ± 1.3
Total cholesterol (mg/dL)	261 ± 20	261 ± 21	266 ± 22
LDL cholesterol (mg/dL)	180 ± 16	180 ± 15	183 ± 15
HDL cholesterol (mg/dL)	51 ± 11	50 ± 12	53 ± 18
Triglycerides (mg/dL)	150 ± 69	152 ± 62	152 ± 60
Vocabulary (NAART errors)	24 ± 10	24 ± 13	24 ± 12
Fluid intelligence (Block Design scaled score)	8.7 ± 2.2	8.7 ± 2.9	8.7 ± 2.6

* The treatment groups did not differ on any listed characteristic.
HDL = high-density lipoprotein; LDL = low-density lipoprotein; NAART = North American Adult Reading Test.

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.

To limit experiment-wise error, the neuropsychological data were grouped into the following categories: statin-sensitive tests, statin-insensitive tests, and new tests. Repeated-measures multivariate analysis of variance was utilized to analyze the multiple test scores in each category simultaneously. Treatment type and test form were between-subjects factors and visit (baseline and post-treatment) was the within-subjects factor. The two levels of active treatment (10 and 40 mg of simvastatin) were collapsed in the initial analyses, and then separated in subsequent analyses to test for a dose-response relation. Effects of drug treatment were indicated in the omnibus F statistic for the interaction of treatment type with visit. Significant treatment effects observed in multivariate analyses were followed by univariate analyses to identify on which neuropsychological test or tests performance differed by treatment assignment. All analyses utilized two-tailed P values, with $P \leq 0.05$ indicating statistical significance.

In a second parallel set of analyses conducted to estimate effect sizes, we computed standardized z scores (individual test score minus mean test score divided by the standard deviation) at baseline and post-treatment using the mean and standard deviation of the baseline tests. 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%, $P = 0.04$).

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

Neuropsychological Test Category	Placebo Group (n = 94)		Simvastatin Group (n = 189)		Group Difference in Change	*P* Value
	Baseline	Post-Treatment	Baseline	Post-Treatment		
	Mean ± SD				Mean (95% Confidence Interval)	
Statin-sensitive tests	−0.05 ± 0.61	0.15 ± 0.56	0.02 ± 0.61	0.04 ± 0.59	0.18 (0.07 to 0.29)	0.002
Statin-insensitive tests	0.00 ± 0.60	0.09 ± 0.54	0.00 ± 0.63	0.08 ± 0.65	0.02 (−0.07 to 0.10)	0.72
New tests	−0.07 ± 0.81	0.19 ± 0.84	0.03 ± 0.76	0.13 ± 0.80	0.17 (0.05 to 0.29)	0.007

* Higher scores indicate better performance.

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-

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

Test*	Placebo Group (n = 94)		Simvastatin Group (n = 189)	
	Baseline	Post-Treatment	Baseline	Post-Treatment
	Mean (95% Confidence Interval)			
Statin-sensitive tests				
Digit Vigilance (errors)†	6.2 (4.7–7.6)	5.7 (4.4–7.0)	6.9 (6.0–7.9)	6.2 (5.1–7.3)
Recurrent Words (% correct)	80 (76–83)	83 (80–86)	84 (82–86)	85 (83–86)
Elithorn Mazes (seconds)†	172 (160–184)	144 (133–155)	162 (154–170)	160 (152–168)
Grooved Pegboard (seconds)†	144 (139–149)	144 (138–150)	147 (142–152)	150 (145–154)
New tests				
Mirror Tracing (errors)†	48 (40–56)	40 (32–48)	43 (38–48)	41 (35–46)
4-Word Memory (no. correct)	18.9 (17.4–20.4)	20.8 (19.1–22.4)	19.4 (18.3–20.4)	20.0 (18.9–21.1)

* 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 confound 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 within 1 year (22,23) and can obscure small or modest drug effects.

Cognitive function is often divided into domains or skill areas, such as memory, psychomotor speed, attention, and mental flexibility. In our studies, the neuropsychological tests on which performance was affected by statins tap a variety of skills, and therefore our findings indicate that such cognitive effects are not specific to one or two domains of function. Tests found to be sensitive to the effects of statins tended to have relatively large learning or practice effects, as evidenced by the improvement seen in placebo-treated participants. This suggests that the effects of statins on cognition may affect patients' abilities to benefit from prior experience or devise performance-enhancing strategies.

Even though the brain contains five to 10 times as much cholesterol as other organs, and most of its dry weight is lipid (24,25), few studies have examined the effects of variation in serum cholesterol level or cholesterol reduction on the brain. Familial hypobetalipoproteinemia, a genetic disorder resulting in hypocholesterolemia, is associated with spinocerebellar degeneration and dementia (26). Inhibition of hydroxymethylglutaryl coenzyme A reductase with statins impairs learning processes in rodents (27,28), and large doses of statins have neurotoxic effects in dogs (29,30). In cross-sectional studies, low (untreated) serum cholesterol concentration has been associated with relatively poor performance on some cognitive tests (31,32). Conversely, age-related cognitive decline has been associated with either low (33,34) or high (35,36) serum cholesterol level.

Few randomized clinical trials have been reported. Wardle and colleagues assigned 176 hypercholesterolemic volunteers to either of two cholesterol-lowering diets or a waiting-list control condition (37). Scores on three cognitive tests were unaffected by treatment, but performance on a test measuring sustained attention was poorer in both diet groups compared with controls, and performance decrement correlated with the decline in serum cholesterol level. A small industry-sponsored study of statin therapy found deleterious effects of lovastatin on tests measuring vigilance and divided attention, whereas two other similar studies reported no effects on cognitive performance (38–40). Cognitive assessments were unaffected in the elderly in two placebo-controlled trials of statin treatment conducted for other purposes (4,41). However, one study administered only one neuropsychological test and the other study administered only three tests; neither study used measures that we have found to be sensitive to statin treatment. As noted earlier, observational studies have suggested that statin use may decrease the risk of Alzheimer disease (3), but recent clinical trials have not reported any treatment effects on the incidence of dementia (4,5).

The mechanism by which statins may affect cognitive function is not known, but given the broad effects of these drugs on cellular metabolism, there are several possibilities (42,43). For example, statins might alter neuronal function through effects on brain cholesterol metabolism (44–46), ubiquinone, protein prenylation (47), vitamin E (48–50), or omega-3 fatty acids (51,52). We recently observed that simvastatin increases the preponderance of omega-6 over omega-3 fatty acids (53).

The results of this investigation stand as a partial replication of our earlier trial. Given the limitations of the findings, the evidence of decremental effects of statins on cognitive functioning remains preliminary. 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.

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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.