A randomized, double-blind, placebo-controlled trial of simvastatin to treat Alzheimer disease

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ABSTRACT

Background: Lowering cholesterol is associated with reduced CNS amyloid deposition and increased dietary cholesterol increases amyloid accumulation in animal studies. Epidemiologic data suggest that use of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) may decrease the risk of Alzheimer disease (AD) and a single-site trial suggested possible benefit in cognition with statin treatment in AD, supporting the hypothesis that statin therapy is useful in the treatment of AD.

Objective: To determine if the lipid-lowering agent simvastatin slows the progression of symptoms in AD.

Methods: This randomized, double-blind, placebo-controlled trial of simvastatin was conducted in individuals with mild to moderate AD and normal lipid levels. Participants were randomly assigned to receive simvastatin, 20 mg/day, for 6 weeks then 40 mg per day for the remainder of 18 months or identical placebo. The primary outcome was the rate of change in the Alzheimer's Disease Assessment Scale–cognitive portion (ADAS-Cog). Secondary outcomes measured clinical global change, cognition, function, and behavior.

Results: A total of 406 individuals were randomized: 204 to simvastatin and 202 to placebo. Simvastatin lowered lipid levels but had no effect on change in ADAS-Cog score or the secondary outcome measures. There was no evidence of increased adverse events with simvastatin treatment.

Conclusion: Simvastatin had no benefit on the progression of symptoms in individuals with mild to moderate AD despite significant lowering of cholesterol.

Classification of evidence: This study provides Class I evidence that simvastatin 40 mg/day does not slow decline on the ADAS-Cog. *Neurology*® 2011;77:556–563

GLOSSARY

Aβ = amyloid β peptide; **AChE** = acetylcholinesterase; **AD** = Alzheimer disease; **ADAS-Cog** = Alzheimer's Disease Assessment Scale–cognitive portion; **ADCS** = Alzheimer's Disease Cooperative Study; **ADCS-ADL** = Alzheimer's Disease Cooperative Study Activities of Daily Living; **ADCS-CGIC** = Alzheimer's Disease Cooperative Study Clinical Global Impression of Change; **ADCS-RUI** = Alzheimer's Disease Cooperative Study Resource Use Instrument; **ALT** = alanine aminotransferase; **AST** = aspartate aminotransferase; **ATP** = Adult Treatment Panel; **CRP** = C-reactive protein; **GEE** = generalized estimating equation; **HDL** = high-density lipoprotein; **HMG-CoA** = 3-hydroxy-3-methylglutaryl coenzyme A; **ITT** = intent-to-treat; **LDL** = low-density lipoprotein; **MMSE** = Mini-Mental State Examination; **NPI** = Neuropsychiatric Inventory; **QOL** = quality of life.

Substantial evidence from laboratory research in animal model and cell culture systems,[1] some[2–5] but not all[6] observational epidemiologic studies, and some small clinical trials[7,8] suggest that lowering cholesterol may favorably influence the pathology of Alzheimer disease (AD) and thereby slow the clinical progression.

The gene for apoE, a cholesterol transporter, is an important determinant of risk of sporadic AD[9] and cholesterol may be involved in the accumulation of amyloid in the brain. Animal studies have demonstrated that a high-cholesterol diet can increase levels of the amyloid β peptide (Aβ), the primary constituent of amyloid plaques,[10,11] and conversely, statins may

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Study funding: Funding information is provided at the end of the article.
Disclosure: Author disclosures are provided at the end of the article.

reduce Aβ levels in these animal models.[12] Additionally, neurofibrillary tangles may be reduced by statins.[13]

C-reactive protein (CRP), a plasma inflammatory marker, elevated in association with cardiovascular risks, and in the presence of dementia, including AD,[14] is lowered by statins.[15,16] Taken together, these studies suggest that cholesterol may influence AD via multiple pathways.

Simvastatin, a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, penetrates the CNS and has been shown to reduce the risk of cardiovascular disease and death. It was selected for use in this randomized clinical trial to test the hypothesis that lipid lowering could reduce the clinical progression in subjects with AD who have cholesterol levels not otherwise requiring treatment.

METHODS

Study design. The primary study objective was to determine if simvastatin slows the progression of symptoms in AD. It was designed to provide Class I evidence that treatment with simvastatin would slow the decline on the cognitive portion of the Alzheimer's Disease Assessment Scale (ADAS).

The trial was conducted by the Alzheimer's Disease Cooperative Study (ADCS), a consortium of US centers funded by the National Institute on Aging. It used a placebo-controlled, parallel design study with 2 groups.

Standard protocol approvals, registration, and patient consent. Forty-five sites participated in this trial after obtaining approval from their local Institutional Review Boards. Informed consent was obtained from subjects or legally authorized representatives, according to local guidelines. Of note, 13 sites participated in a substudy to examine the views of patients with AD and their study partners on the ethics of proxy consent for clinical research[17] and to assess the ability of a standardized capacity assessment procedure to identify persons who are capable of giving their own informed consent.[18] The trial was registered as follows: clinicaltrials.gov Identifier: NCT00053599.

Subjects. Individuals with probable AD,[19] recruited from local clinic populations and via locally approved advertisements, were eligible if they were medically stable. Inclusion criteria included age older than 50 years and a Mini-Mental State Examination (MMSE)[20] score within the range of 12 to 26. Individuals were excluded if they had other neurologic or psychiatric diagnosis that could interfere with cognitive function. They were also excluded if they were taking lipid-lowering drugs, or if they had conditions requiring cholesterol lowering treatment as defined by the Adult Treatment Panel (ATP III) guidelines[21] which were current during the period of study. They were also excluded if they had low-density lipoprotein (LDL) cholesterol below 80 mg/dL or triglycerides >500 mg/dL. Individuals were also excluded if they had recently taken drugs with significant central anticholinergic effects, sedatives, antiparkinsonian medications, or any investigational treatment for AD. Other excluded medications were those that are specifically contraindicated with simvastatin as well as those that could interact with CYP 3A4 to either increase or decrease the level of simvastatin. Stable use (for at least 3 months) of cholinesterase inhibitors and memantine was allowed.

Randomization and masking. The randomization sequence was generated with equal probability of assignment to drug and placebo using a random permuted block treatment assignment, stratified by site. The randomization sequence was generated by the ADCS data center. "Scratch-off" codebreakers were used so that instances of unblinding would be documented; all codebreakers were collected at the end of the trial. Adequacy of the blind was assessed by questionnaires completed by participants, caregivers, psychometrists, and site investigators.

Study medication. The dose of simvastatin was based on known lipid-lowering capacity in those with hypercholesterolemia. The initiation dose of 20 mg per day on average reduces total cholesterol by 28%, LDL cholesterol by 34%, and increases high-density lipoprotein (HDL) by 8%. The dose of 40 mg per day, which was used after the first 6 weeks, typically reduces total cholesterol by 25% to 31%, LDL cholesterol by 41%, and increases HDL by 9% to 13% in patients with hypercholesterolemia. Study medication administration used this single dose escalation with all subjects receiving one tablet per day in the evening. For the first 6 weeks, each contained active drug (simvastatin 20 mg) or identical placebo. The dose was increased to 40 mg of simvastatin for the active drug or identical placebo for the remainder of the 18-month study. Study medication was packaged and dispensed in 6-week supplies for 2 intervals followed by a 3-month supply and 2 6-month supplies, and was dispensed at each visit.

Outcome measures. The primary outcome measure was the rate of change on the cognitive portion of the ADAS (ADAS-Cog) score,[22] a psychometric instrument that evaluates memory, attention, reasoning, language, orientation, and praxis. The score ranges from 0 to 70 and a higher score indicates more impairment. A positive change score indicates cognitive worsening.

Secondary outcome measures included the ADCS Clinical Global Impression of Change (ADCS-CGIC),[23] the MMSE, the Dependence Scale,[24] the ADCS Activities of Daily Living (ADCS-ADL), Neuropsychiatric Inventory (NPI),[25] and 3 supplemental cognitive tests from the ADCS instrument protocol, including Maze A2, a measure of executive function; Number Cancellation, a measure of visual attention; and Delayed Word Recall.[26] Quality of life (QOL) was measured with is a 13-item scale which ranges from 0 to 52, with a higher score indicative of a better QOL.[27] QOL is rated by both the subject and the informant. The ADCS Resource Use Instrument (ADCS-RUI) was used to measure the number of hours per day of assistance from primary and secondary caregivers.[28] Raters for all outcomes were trained at an investigator meeting and certified through online assessments and remained constant throughout the trial whenever possible. Primary and secondary outcomes were measured at 3, 6, 12, and 18 months after baseline.

Safety measures included standard reporting of any adverse events, laboratory abnormality, or endorsement of items from a "symptom checklist" which directly inquired about known side effects of the drug with specific queries for muscle pain, tenderness, or weakness.

Laboratory evaluations. *APOE* genotyping was carried out on all subjects who consented to be used as a predictor of clinical change over time. Routine laboratory studies included lipids levels (which were blind to the investigative staff) and liver function

tests at follow-up visits. CRP was collected at baseline and at 18 months. Special attention was given to serum transaminases and aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevations greater than or equal to 3 times the upper limit of normal, which required discontinuation of study drug.

Statistical analysis. The primary analysis used the generalized estimating equations (GEE) method to assess group differences (simvastatin vs placebo) in rate of change on the ADAS-Cog score. The power calculations were based on GEE analysis of repeated ADAS-Cog score data from a previous trial with similar subjects which identified visit-to-visit correlation, of 0.853, an ADAS-Cog score SD of 11.5, and an annual change among the placebo of 6.3 points. With a dropout rate estimated at 30%, α set at 0.05, and a sample of 400, there was 80% power to see a 20% difference in drug vs placebo rate of change.

The primary analysis was an intent-to-treat (ITT) analysis. All available ADAS-Cog assessments were used in the analysis for subjects who discontinued medication but agreed to be followed. A list of covariates anticipated to be associated with rate of change in ADAS-Cog over 18 months included *APOE* ε4 allele count, baseline lipid level, demographic variables (age, education, gender, race/ethnicity), and clinical variables (i.e., duration of disease, baseline measures of ADAS-Cog, ADCS-ADL, and NPI). A data analysis plan, finalized prior to breaking the blind, added the MMSE to the covariates described above. These variables were to be included as covariates in secondary analyses of the primary outcome using the GEE analysis model only if found to be moderately associated both with treatment group ($p < 0.1$) and with response ($p < 0.15$). In addition to the ITT analysis, both a completers (those who completed the protocol) and compliers (those who ingested ≥80% of the prescribed medication based on return pill count) analyses were conducted. Further, as a confirmatory analysis, and to allow comparison with other rate of change AD trials, a set (ITT, completers, compliers) of change score analyses were performed with 18-month values imputed using the multiple imputation method.[29]

The statistical software for the primary hypothesis analysis was *R* (version 2.6.2, 2/8/2008).[30]

RESULTS **Study participants and follow-up.** The flow of participants though the study is summarized in figure 1. Recruitment continued from December 11, 2002, to January 11, 2006, and study completion (last subject assessed) was September 19, 2007. A total of 685 participants were screened and 406 met criteria and were randomized with 204 in the simvastatin group and 202 in the placebo group.

Discontinuation rates in the active treatment group and placebo group were similar (40/202 in the placebo arm vs 43/204 in treatment arm; $p = 0.766$). Predominant reasons for early discontinuation were side effect (16 in placebo arm vs 13 in treatment arm) and study partner's unwillingness or inability to continue (7 in the placebo arm vs 22 in the treatment arm). The median length of follow-up was 17.9 months and this was comparable between arms. There were no statistically significant differences in baseline characteristics between participants who discontinued early and study completers (data available by request from authors).

Table 1 lists the baseline demographic and clinical features and other covariates. The placebo group had significantly more Hispanics ($p = 0.012$) and slightly higher ADCS-ADL scores ($p = 0.041$) than the simvastatin group. Differences in the MMSE and LDL levels between the 2 groups also met criteria ($p < 0.10$) for consideration for inclusion in the GEE model depending on their relationship to the outcome.

There was no difference in the use of approved antidementia medications during the study. A total of 94.3% of participants were taking a cholinesterase inhibitor (placebo arm: 94.06; treatment arm: 96.61%). Memantine was taken by 54.19% (placebo arm: 53.96%; treatment arm: 54.41%). Both agents were used by 51.72% of the cohort (placebo arm: 50.5%; treatment arm: 52.94%). Compliance was comparable between groups (90.54% in the placebo group and 91.67% in the treatment group; $p = 0.841$).

Total cholesterol and LDL levels were significantly reduced by the treatment compared to placebo ($p < 0.001$); the reduction was 23% in total cholesterol and 37% in LDL. HDL levels were also increased with treatment by 2% ($p = 0.02$).

Primary outcome. Ethnicity and baseline MMSE, ADCS-ADL, and LDL levels met criteria for consideration as confounders in outcome analyses. Presence

Figure 1 **Flow of participants**

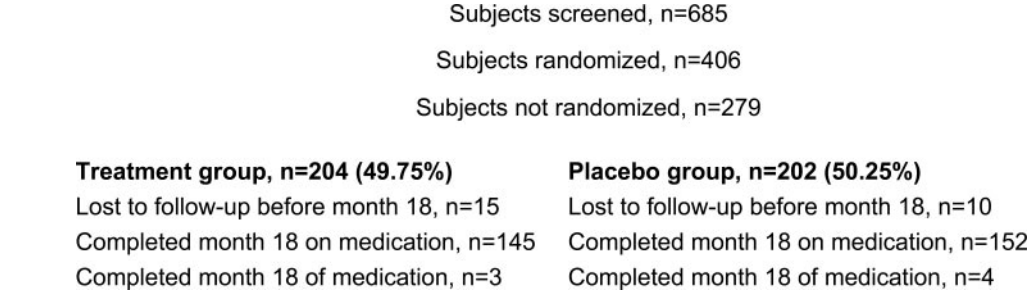


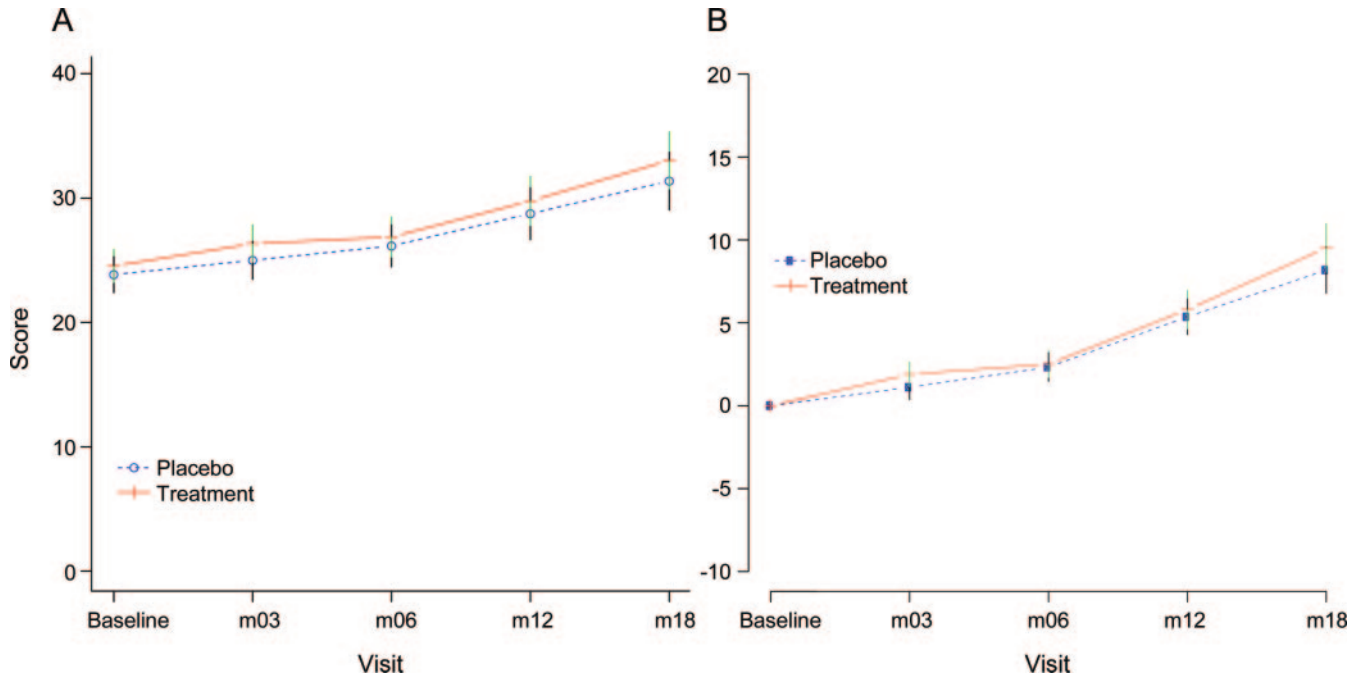
Table 1 Baseline characteristics of the subjects

Variable	Placebo group (n = 202)	Simvastatin group (n = 204)	All subjects (n = 406)	Placebo/simvastatin difference p value
Age, y, mean ± SD	75.1 ± 9.0	74.0 ± 9.6	74.6 ± 9.3	0.2931
Female sex, n (%)	121 (59.9)	120 (58.8)	241 (59.4)	0.8404
Education, y, mean ± SD	14.2 ± 3.3	14.3 ± 3.2	14.3 ± 3.2	0.9273
Duration of disease, y	4.23 (2.63)	4.03 (2.58)	4.13 (2.61)	0.3922
Caucasian, n (%)	188 (93.1)	181 (88.7)	369 (90.9)	0.1672
Hispanic/Latino, n (%)	18 (9.0)	6 (3.0)	24 (6.0)	0.0188
APOE ϵ4 carrier, n (%)	100 (55.3)	108 (61.0)	208 (58.1)	0.2853
Total cholesterol, mean ± SD	208.8 ± 28.6	215.0 ± 32.5	211.9 ± 30.8	0.1153
Low-density lipoprotein	123.2 ± 24.4	128.9 ± 26.4	126.0 ± 25.1	0.0529
High-density lipoprotein	61.1 ± 16.7	60.7 ± 16.2	60.9 ± 16.4	0.6945
ADAS-Cog score, mean ± SD	23.9 ± 10.5	24.5 ± 9.7	24.2 ± 10.1	0.2647
MMSE score, mean ± SD	20.7 ± 4.9	20.0 ± 4.5	20.4 ± 4.7	0.0895
ADCS-ADL, mean ± SD	68.6 ± 10.4	67.2 ± 10.0	67.9 ± 10.2	0.0414
Dependence scale, mean ± SD	4.9 ± 2.3	5.2 ± 2.3	5.1 ± 2.3	0.2432
Neuropsychiatric Inventory, mean ± SD	7.8 ± 8.3	9.2 ± 10.5	8.5 ± 9.5	0.6246

Abbreviations: ADAS-Cog = Alzheimer's Disease Assessment Scale–cognitive portion; ADCS-ADL = Alzheimer's Disease Cooperative Study Activities of Daily Living; MMSE = Mini-Mental State Examination.

of the *APOE*4 allele was not different in the 2 groups and not associated with the rate of change in the ADAS-Cog score and therefore not included in the analysis. The effect of treatment on the primary outcome measure is shown in figure 2 and table 2. In the primary GEE analysis the rate of change in ADAS-Cog score did not differ between treatment groups ($p = 0.25$; 95% CI −0.0462 to 0.1680). The annual point change was 5.52 points for the placebo group and 6.28 points for the treatment group. Further, using a median split we examined those of low and high age and low and high baseline MMSE score and

Figure 2 Effect of treatment on the primary outcome measures



Mean of ADAS-Cog = Alzheimer's Disease Assessment Scale–cognitive portion total score (A) and change score (B) by treatment and visit. Presented with 95% confidence intervals.

Table 2 Changes from baseline in cognitive and functional measures

Test and cognitive and functional measures	Change in score from baseline			
	3 mo	6 mo	12 mo	18 mo
ADAS-Cog				
Placebo	1.11 ± 5.32	2.32 ± 5.90	5.36 ± 6.95	8.18 ± 8.70
Simvastatin	1.89 ± 5.35	2.51 ± 5.61	5.79 ± 7.76	9.51 ± 9.48
MMSE				
Placebo	−0.10 ± 3.10	−0.89 ± 3.23	−2.28 ± 4.08	−3.75 ± 4.38
Simvastatin	−0.52 ± 2.74	−0.72 ± 3.26	−2.47 ± 3.80	−4.23 ± 4.77
Dependence scale				
Placebo	−0.15 ± 0.87	−0.21 ± 0.83	−0.36 ± 0.96	−0.53 ± 1.10
Simvastatin	−0.04 ± 0.85	−0.10 ± 1.04	−0.26 ± 1.02	−0.48 ± 1.09
Activities of daily living scale				
Placebo	−1.20 ± 6.09	−3.95 ± 8.42	−6.21 ± 10.94	−9.62 ± 13.86
Simvastatin	−1.54 ± 7.44	−3.66 ± 8.18	−7.45 ± 10.18	−10.47 ± 13.37
Neuropsychiatric Inventory				
Placebo	0.21 ± 8.02	1.26 ± 9.16	3.60 ± 10.38	3.78 ± 10.73
Simvastatin	−0.64 ± 8.61	−0.09 ± 9.61	1.95 ± 10.64	3.21 ± 12.71

Abbreviations: ADAS-Cog = Alzheimer's Disease Assessment Scale–cognitive portion; MMSE = Mini-Mental State Examination.

found no difference in rate of ADAS-Cog change between the simvastatin vs placebo groups in any of the subgroups.

Secondary outcomes. There were no significant differences between groups in the secondary outcomes (MMSE, Dependence Scale, ADCS-ADL, and NPI or the additional cognitive measures) (table 2) or the CGIC (data available upon request). There were no significant differences between groups in QOL as measured by informant or subject. Caregiving hours at baseline were comparable between groups (placebo: 2.03 ± 4.1 vs treatment: 2.44 ± 5.0) and did not change throughout the trial.

CRP. At baseline, CRP values were equivalent between groups. There was a significant reduction in CRP in the treatment group compared to the placebo group (−0.017 ± 1.56 in the placebo group vs −0.031 ± 0.77 in the treatment group; $p < 0.005$).

Effects of antidementia drug use. Cholinesterase inhibitor medication (acetylcholinesterase [AChE]) exposure was reported at some point during the trial in 383/406 (94%) and 220 (54%) reported use of memantine at some point during the trial, respectively. Of those exposed to memantine, 210 (95%) were also exposed to AChE, resulting in 210 (52%) with reported exposure to both drugs. There were no differences in rate of exposure by treatment arm. The use of antidementia drugs alone or in combination did not change the primary results. That is, even in the presence of antidementia drugs, there was no benefit in the rate of decline on the ADAS-Cog in the simvastatin group compared to the placebo groups.

Blindness evaluation. There was no difference in perceived assignment in the treatment vs placebo group for participants, informants, study coordinators, and study physicians.

Safety data. The number of subjects with one or more adverse events in the placebo group, 181/202 (89.6%), and treatment group, 189/204 (92.7%), did not differ ($p = 0.30$). Similarly, the groups did not differ in the number of subjects with serious adverse events (placebo group: 54/202 [26.7%]; treatment group: 56/204 [27.5%]; $p = 0.91$), the number of subjects with serious adverse events requiring hospitalization (placebo group: 46/202 [22.7%], active treatment group: 53/204 [25.9%]; $p = 0.52$), and the number of deaths (placebo group: 9/202 [4.5%], active group: 5/204 [2.5%]; $p = 0.0.29$).

Liver enzyme elevations (defined as 3 times the upper limit of normal for γ-glutamyl transpeptidase, ALT, or AST) were noted in 2% of treatment and 4% placebo group. There were no elevations in creatine phosphokinase.

Treatment-emergent adverse events were grouped into categories for analysis. The most commonly occurring adverse events were falls, agitation, and anxiety. However, there was no significant difference between drug and placebo in any category. Those events that occurred in at least 5% of either group are reported in table 3.

Table 3 No. (%) of individuals in each group experiencing an adverse event[a]

Symptom	Placebo group (n = 202)	Treatment group (n = 204)
Abdominal discomfort	11 (5.4)	13 (6.4)
Nausea	11 (5.4)	23 (11.3)
Diarrhea	28 (13.9)	40 (19.6)
Asthenia	43 (21.3)	43 (21.1)
Urinary tract infection	12 (5.9)	14 (6.9)
Fall	63 (31.2)	57 (27.9)
Arthralgia	24 (11.9)	25 (12.2)
Myalgia	10 (4.9)	11 (5.4)
Back pain	19 (9.4)	21 (10.3)
Joint swelling	10 (4.9)	13 (6.4)
Headache	13 (6.4)	19 (9.3)
Dizziness	29 (14.4)	18 (8.8)
Anxiety	34 (16.8)	48 (23.5)
Restlessness	12 (5.9)	24 (11.8)
Agitation	47 (23.3)	50 (24.5)
Depression	11 (5.4)	14 (6.9)
Somnolence	29 (14.4)	34 (16.7)
Depressed mood	28 (13.9)	31 (15.2)
Insomnia	18 (8.9)	19 (9.3)
Crying	26 (12.9)	26 (12.7)
Pollakiuria	21 (10.4)	29 (14.2)
Cough	24 (11.9)	26 (12.7)
Dyspnea	15 (7.4)	6 (2.9)
Rash	15 (7.4)	19 (9.3)

[a] Events reported for those symptoms occurring in 5% of either group.

DISCUSSION Simvastatin treatment for 18 months had no effect on the progression of symptoms in individuals with mild to moderate AD. No drug–placebo differences were observed on the change in ADAS-Cog score or on the secondary outcome measures. Although this study examined individuals with normal lipid levels (i.e., levels that do not require lipid-lowering therapy to prevent cardiovascular disease), the treatment regimen significantly reduced both total cholesterol and LDL levels, marginally raised HDL levels, and reduced CRP. Of note was the relatively benign side effect profile of simvastatin in this frail elderly population. There were no treatment differences in liver enzyme elevations, reports of muscle pain, complaints of change in consciousness, or confusion.

Despite the fact that simvastatin penetrates the CNS, the results are consistent with those for the nonpenetrating atorvastatin, which was assessed in a trial of comparable design.[31] It remains unknown whether statin therapy has a favorable impact on individuals with AD and elevated cholesterol levels; such individuals should receive lipid-lowering therapy for cardiovascular health, so a placebo-controlled statin trial may be unethical. However, such a benefit would seem unlikely, given the results of 2 large randomized clinical trials of primary prevention of cardiovascular outcomes among individuals without AD and elevated cholesterol levels.[32,33] These trials assessed cognition and incident dementia as secondary measures and found no benefit of statin use, despite significant benefit on cardiovascular outcomes. Also unaddressed by the present study is the utility of statin therapy in individuals who do not otherwise require lipid lowering, at predementia stages, mild cognitive impairment, or presymptomatic AD.

Recent reports have suggested that the use of antidementia drugs may reduce the sensitivity of outcome measures such as the ADAS-Cog and the CGIC to capture treatment effects.[34] However, this and other trials have demonstrated that these outcomes are reasonably efficient in measuring change in clinical trials of 18 months—even in the presence of stable doses of antidementia drugs.[35,36] Also, some have reported an enhancement of benefit in those using cholinesterase inhibitors and statins in post hoc analysis.[37] We found no evidence of enhancement of benefit in the combined use of statins and cholinesterase inhibitors. These results suggest that permitting background use of standard medications does not affect the ability to observe decline in trials of this length.

Mechanistically, it remains unclear whether the regimen of simvastatin used in this trial influenced pathogenic mechanisms of AD in the brain or affected biomarkers of amyloid, tau, or other neuropathology. Comparable doses of simvastatin in hypercholesterolemic subjects without dementia have been found to reduce CSF levels of phospho-tau-181 but not total tau, amyloid markers, or isoprostanes.[38] However, in a small randomized clinical trial in patients with AD, higher doses (80 mg daily) for 26 weeks did not significantly alter CSF levels of Aβ40 and Aβ42, although in a post hoc analysis, of a subgroup with mild AD, simvastatin significantly decreased Aβ40 levels compared to placebo.[8]

A large body of evidence from randomized clinical trials using statins consistently reports no benefit in cognition[32,33] or dementia prevention,[32] calling into question the relevance of preclinical and epidemiologic findings.

These results do not support the use of simvastatin for the treatment of AD. Further exploration of

cholesterol-lowering therapy for treatment or prevention of AD should be weighed against other treatment approaches with plausible rationales.

AUTHOR CONTRIBUTIONS

Dr. Sano: drafting/revising the manuscript, study concept or design, analysis or interpretation of data. Dr. Bell: drafting/revising the manuscript, study concept or design, acquisition of data, study supervision. Dr. Galasko: drafting/revising the manuscript, study concept or design. Dr. Galvin: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data. Dr. Thomas: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, statistical analysis, study supervision. Dr. van Dyck: drafting/revising the manuscript, acquisition of data. Dr. Aisen: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, study supervision.

STUDY FUNDING

This work was supported by NIA grant U01AG10483. The ADCS received an unrestricted educational grant from Merck who also supplied drug and placebo. Merck did not participate in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation of the manuscript. Authors had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

ACKNOWLEDGMENT

The authors thank the following, who participated in the trial: Oregon Health and Science University, PI Jeff Kaye; University of Southern California, PI Lon Schneider; University of California, San Diego, PI Adam Fleisher; University of Michigan, Ann Arbor, Raymond Scott Turner; Mayo Clinic, Rochester, PI Ron Petersen; University of Washington (SIBCR), PI Murray Raskind; Baylor College of Medicine, PI Rachelle Doody; Columbia University, PI Karen Bell; University of Alabama, Birmingham, PI Ed Zamrini; Mount Sinai School of Medicine, PI Mary Sano; Rush University Medical Center, PI David Bennett; Wien Center for Clinical Research, PI Raj Duara; Washington University, St. Louis, PI James Galvin; New York University Medical Center, PI Steve Ferris; Duke University Medical Center, PI Murali Doraiswamy; University of Pennsylvania, PI Chris Clark; University of Kentucky, PI Greg Jicha; University of Pittsburgh, PI Steve DeKosky; University of Rochester Medical Center, PI Pierre Tariot; University of California, Irvine, PI Carl Cotman; University of Texas, Southwestern MC, PI Ramon Diaz-Arrastia; Emory University, PI Allan Levey; University of California, Los Angeles, PI Jeff Cummings; Mayo Clinic, Jacksonville, PI Neil Graff-Radford; Indiana University, PI Martin Farlow; Memorial Hospital Rhode Island, Brown University, PI Brian Ott; Yale University, PI Chris Van Dyck; University of California, Davis, PI Charles DeCarli; SUNY Stony Brook, PI Mark Sedler; Arizona Health Sciences Center, PI Geoffrey Ahern; The Memory Clinic at Southwestern Vermont Medical Center, PI Paul Soloman; Barrow Neurology; PI Jiong Shi; Northwestern University, PI Marek-Marsel Mesulam; Medical University of South Carolina, PI Jocobo Mintzer; Premiere Research Institute, PI Carl Sadowsky; Georgetown University, PI Paul Aisen; Brigham and Women's Hospital, PI Reisa Sperling; Boston University, PI Robert Green; Howard University, PI Thomas Obisesan; Case Western Reserve University, PI Alex Auchus; Neurological Care of CNY, PI Smita Kittur; MD Clinical, PI Kerri Wilks; Stanford, PI Jerome Yesavage; SUNY Downstate, PI Howard Crystal.

DISCLOSURE

Dr. Sano serves on a scientific advisory board for Medivation, Inc.; serves as a consultant for Bayer Schering Pharma, Bristol-Meyers Squibb, Elan Corporation, Genentech, Inc., Medivation, Inc., Medpace Inc., Pfizer Inc, Janssen, Takeda Pharmaceutical Company Limited, and United Biosource Corporation; and receives research support from the NIH (NIA/NCRR). Dr. Bell serves on speakers' bureaus for and has received speaker honoraria from Eisai Inc. and Forest Laboratories, Inc.; and receives research support from Baxter International Inc., Wyeth, Pfizer Inc, Janssen Alzheimer Immunotherapy Research & Development, LLC, and the NIH/NIA. Dr. Galasko serves on a scientific advisory board for Janssen/Elan Corporation; serves as Co-Editor for *Alzheimer's Research and Therapy*; serves as a consultant for United BioSource Corporation; and receives research support from Eli Lilly and Company, Avid Radiopharmaceuticals, Inc., and the NIH/NIA. Dr. Galvin serves on a scientific advisory board for the American Federation for Aging Research and on the Board of Directors and the Scientific Advisory Council for the Lewy Body Dementia Association; serves on the editorial boards of *Alzheimer's Disease and Associated Disorders* and *Acta Neuropathologica*; serves on speakers' bureaus for Pfizer Inc, Eisai Inc., Novartis, and Forest Laboratories, Inc.; has served as a consultant for Novartis, Forest Laboratories, Inc., Pfizer Inc, Eisai Inc., Janssen, and Medivation, Inc.; has received license fee payments for AD8 dementia screening test (copyrighted): license agreements between Washington University and Pfizer Inc, Eisai Inc., and Novartis; and receives research support from Novartis, Eli Lilly and Company, Elan Corporation, Wyeth, Bristol-Myers Squibb, the NIH/NIA, and the Alzheimer Association. Dr. Thomas has served on a scientific advisory board for Myriad Genetics, Inc.; has served as a consultant for Medivation, Inc., Myriad Genetics, Inc., Bristol-Meyers Squibb, and Neurochem Inc.; and receives research support from the US Department of Defense and the NIH/NIA. Dr. van Dyck has served on scientific advisory boards for Elan Corporation, Pfizer Inc, GlaxoSmithKline, Bristol-Myers Squibb, and Forest Laboratories, Inc.; has received funding for travel and speaker honoraria from Forest Laboratories, Inc.; his spouse owns or has applied for patents re: Use of guanfacine in the treatment of behavioral disorders, Use of lofexidine in the treatment of behavioral disorders, Chelerythrine, analogs thereof and their use in the treatment of bipolar disorder and other cognitive disorders (formerly licensed to Marinus Pharmaceuticals, Inc.); his spouse receives publishing royalties for *The Neuropharmacology of Stimulant Drugs: Implications for AD/HD* (Oxford University Press, 2000); serves as a consultant for Elan Corporation, Pfizer Inc, GlaxoSmithKline, Bristol-Myers Squibb, Forest Laboratories, Inc., and Merck Serono, and his spouse serves as a consultant for Shire plc; served on the speakers' bureau for Forest Laboratories, Inc.; receives/has received research support from Wyeth, Eli Lilly and Company, Pfizer Inc, Bristol-Myers Squibb, Medivation, Inc., Bayer Schering Pharma, Abbott, Elan Corporation, GlaxoSmithKline, Myriad Genetics, Inc., Neurochem Inc, Sanofi-Synthelabo Research, Janssen, Eisai Inc., Merck Serono, Mitsubishi Tanabe Pharma Corporation, the NIH (NIA, NIMH), Alzheimer's Association, American Health Assistance Foundation, and the National Alliance for Research on Schizophrenia and Affective Disorders (NARSAD); his spouse receives research support from Shire plc, the NIH (NIA, NINDS), the Kavli Neuroscience Institute at Yale, and NARSAD; and his spouse has received license fee payments and receives royalties from Shire plc for a patent re: Use of guanfacine in the treatment of behavioral disorders. Dr. Aisen serves on a scientific advisory board for NeuroPhage and Novartis; serves on the editorial boards of *BMC Medicine* and *Alzheimer's Research & Therapy*; is listed as inventor on a patent re: DHA therapy for apolipoprotein E4 negative Alzheimer's disease (potential royalties assigned in full to UCSD); serves as a consultant to Elan Corporation, Wyeth, Eisai Inc., Schering-Plough Corp., Bristol-Myers Squibb, Eli Lilly and Company, NeuroPhage, Merck & Co., Roche, Amgen, Genentech, Inc., Abbott, Pfizer Inc, Novartis, Bayer Schering Pharma, Astellas Pharma Inc., Dainippon Sumitomo Pharma, BioMarin Pharmaceutical Inc., Solvay Pharmaceuticals, Inc., Otsuka Pharmaceutical Co., Ltd., Daiichi Sankyo, AstraZeneca, Janssen, and Medivation, Inc.; receives research support from Pfizer Inc, Bayer Schering Pharma, Baxter International Inc., and the NIH/NIA; and has received stock options from Medivation, Inc. and NeuroPhage.

Received November 9, 2010. Accepted in final form April 5, 2011.

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