Reduced Risk of Incident AD with Elective Statin Use in a Clinical Trial Cohort

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Abstract: Statins have been reported to reduce the risk and be of benefit in the treatment of Alzheimer's disease (AD). Individuals enrolling in the randomized controlled trial testing two anti-inflammatory agents for primary prevention of AD (Alzheimer's Disease Anti-inflammatory Prevention Trial; ADAPT) were allowed the elective use of statins. Our objective was to assess whether statin use is associated with reduced risk of incident AD among ADAPT participants. In primary ADAPT study , participants were assessed annually for cholesterol levels and cognitive status. If impairment in cognition was noted, a dementia evaluation was performed. Onset of mild cognitive impairment (MCI) or AD was taken as the date of this evaluation. Time-to-onset was analyzed in six-month intervals following enrollment. Without knowledge of primary treatment assignment in ADAPT, participants were grouped by their self-reported use of lipid-lowering agents (LLA). In the current ancillary ADAPT study we found that elective statin use was associated with significantly reduced risk of incident AD after adjustment for age, gender, education and Apolipoprotein E (ApoE) genotype. The findings were similar when comparing all LLA use (statin and non-statin LLA) to non-LLA use. Cholesterol levels were lower among statin users compared with non-LLA users, but the MMSE scores were equivalent. The data suggest that statin therapy may be of benefit in reducing the risk of AD.

INTRODUCTION

Some clinical data suggests that statin treatment may reduce the risk of AD later in life. Since the initial epidemiologic investigation assessing the effect of statin use on later risk of AD in the elderly, there have been 14 additional studies – all but two reporting benefit with cholesterol-lowering therapy. There have also been reports from three prospective studies assessing the effect of statins on cognitive function in younger individuals at risk of heart disease [1-3], and two randomized placebo controlled pilot studies testing a statin for benefit in the treatment of AD [4, 5]. In the study testing atorvastatin as a treatment for AD it was shown reduced cholesterol levels occurred in advance of clinical benefit [6], and that greater clinical benefit was identified among those patients harboring the ApoE-4 genotype [7], which is known to increase both the risk of AD and circulating cholesterol levels [8, 9].

Recently, Rockwood reported the results of an epidemiologic study assessing the effect of statin use and the risk of cognitive impairment without dementia (CIND) consistent with mild cognitive impairment (MCI) among the participants of the Canadian Study of Health and Aging (CSHA) [10]. Between 1991 and 1992 over 9000 cognitively normal individuals were recruited and their baseline MMSE and 3MS performance was established (CSHA-1) and re- evaluated 5 years later (CSHA-2) for conversion to AD. Secondary assessment of this population indicated that there was a significant reduction in the risk of CIND among statin users compared to individuals not using a lipid-lowering agent [10], similar to the reduction in the risk of AD [11]. The foregoing clearly supports further evaluating statin therapy for benefit among individuals at risk for cognitive impairment.

We report the observational results of elective statin use, in a clinical trial designed to test safety and efficacy of two anti-inflammatory medications for the primary prevention of AD and age-related cognitive decline (Alzheimer's Disease Anti-inflammatory Prevention Trial; ADAPT). A total of 2528 individuals were enrolled in the trial. We report on individuals returning for the six-month and subsequent visits during ADAPT and assess the association between self-reported use of lipid lowering statins or other lipid lowering agents (LLA's) and AD.

METHODS

ADAPT is a randomized, double-blind, placebo-controlled, multicenter, primary prevention trial testing whether NSAIDs prevent or delay incident AD in an at risk population of elderly individuals. Specifics regarding study design and eligibility criteria are available elsewhere [12]. Recruitment was accomplished primarily through mailings to Medicare beneficiaries targeted by age and by zip code to areas surrounding the trial's six field sites (Baltimore; Boston; Rochester, NY; Seattle; Sun City, AZ; and Tampa). Eligible participants were aged ≥70 years and had a history of at least one first-degree relative with Alzheimer-like dementia.

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Persons regularly using NSAIDs were excluded, but Lipid Lowering agent (LLA) use was permitted. All pertinent institutional review boards (IRBs) approved the study protocol. Consent for participation was obtained from each person and a collateral informant. Enrollment began in March of 2001, and treatment was discontinued December 17, 2004. Elective LLA use was assessed and recorded at each scheduled visit.

Eligible participants were randomly assigned to receive celecoxib (200 mg twice daily), naproxen sodium (220 mg twice daily), or matching placebos (assignment ratio of 1:1:1.5, respectively) without respect to LLA use. The association of statin and non-statin LLA with the risk of AD or MCI was analyzed without regard to or knowledge of the primary treatment assignment in the trial.

Procedures: The eligibility of prospective participants was established using specified health criteria and cut-off scores on an Eligibility Battery of cognitive tests, which included the Mini-Mental State Examination (MMSE) [13]. Eligible individuals returned for an enrollment visit at which time their baseline cognitive and functional abilities were assessed using a more elaborate Cognitive Assessment Battery (CAB) [12]. As part of the primary ADAPT study, blood samples were drawn for ApoE genotyping by a centralized commercial laboratory and genotype data was provided for this ancillary study adhering to HIPPA regulations.

Outcome assessment: Suspected cognitive syndromes were identified using a sensitive cut-off procedure on annual CAB assessments (including baseline measures) or, occasionally, upon referral from study clinicians. Participants with a suspected cognitive syndrome were invited to return for a dementia evaluation (DE). Expert physicians, trained study nurses, and psychometrists conducted the DEs following a protocol that included a detailed history from participants and informants, physical, neurologic, and mental status examinations, and a detailed psychometric assessment battery. Where appropriate, participants with a cognitive syndrome were referred for laboratory testing and neuroimaging for differential diagnosis. Participants with abnormal cognition received diagnoses of dementia using the DSM-IV criteria, or Alzheimer's dementia using the NINCDS/ADRDA criteria [14, 15]. Occurrence of mild cognitive impairment (MCI) and other syndromes identified as probable prodromal AD was established using published methods [16].

By convention, the date of onset of any cognitive syndrome was taken as the date of the relevant DE visit. In a number of instances CABs administered at enrollment triggered DEs, conducted at a later date, which resulted in a diagnosis of dementia. Because cognitive screening was performed only once a year, and treatment termination took place in the middle of an annual cycle of follow-up assessments, outcomes ascertained at DEs that were triggered by CABs conducted on or before 17 June 2005, 6 months after termination of treatments were analyzed. To contribute an "event," DEs must then have been completed within three months of this date and outcomes entered into the ADAPT database by 17 December 2005. Outcome analyses included only participants with at least one cognitive assessment after enrollment. Person-time was censored after participants' last completed cognitive assessment.

Each individual was coded for overall LLA use at each visit. We differentiated between statin and non-statin LLA use (predominantly ezetimibe), niacin, fenofibrate, cholestyramine or gemfibrozil. By convention, non-LLA using subjects did not report use of a statin or LLA at any visit or reported early and infrequent statin use (one of 5 visits if followed to month 36, 2 of 6 visits if followed to month 42). By contrast, statin users reported taking a statin at all visits or all visits after the 1-month visit. Non-statin LLA use was recorded at over half of a non-statin LLA user's visits. Those subjects considered mixed-statin users were on statin therapy for half of their visits and then off statin therapy or not on a statin and then on a statin medication. A few mixed-statin users were on then off, then on and then off again.

Statistical methods: For patient demographics means were compared between non-LLA and LLA groups by two-sample t-statistics and proportions were compared by chi-square statistics. The distribution of the time in six-month intervals until the occurrence of each event Alzheimer's disease was estimated for each group using Kaplan-Meier survival curves; these curves were then compared between groups using a log rank statistic. To estimate the hazard ratio for these events adjustments were made for gender, the presence of at least one apoliprotein 4 allele, age, and years of education using a Cox proportional hazards model.

RESULTS

A total of 2528 individuals were enrolled in ADAPT to test the efficacy of anti-inflammatory medications to alter the risk of AD. We report on cognitively normal individuals enrolling and returning for the six-month and subsequent visits during ADAPT to assess the effect of elective LLA use on the risk of AD blind to primary anti-inflammatory or placebo use.

After excluding individuals not returning for a 6-month visit including those 7 with AD at enrollment and those enrolling with or converting to other than AD, 2233 subjects were evaluated for change in risk of AD with statin use compared to non-LLA use during ADAPT. Based on this reclassification we considered four groups of ADAPT participants: 1309 non-LLA users, 759 statin LLA users, 75 non-statin LLA users and 90 mixed-statin use individuals.

A total of 25 participants converted to AD while assigned to treatment in ADAPT and were considered incident AD for analyses in this observational study. (As noted above 7 individuals with AD were allowed to enroll in ADAPT and were excluded from this assessment – 2 on statin and 5 non-LLA). One individual previously taking a statin was statin-free before converting to AD and considered a mixed-statin user. One individual converted to AD before starting on a statin therapy and was considered a non-LLA converter. According to this classification a total of 4 statin LLA users, 1 mixed-statin user and 20 subjects not using any LLA converted to AD.

Demographic data at enrollment for non-LLA and statin LLA individuals returning for their 6-month visit are presented in Table **1**. The non-LLA group has significantly more males than the statin LLA group (49.5% compared to 39.1%). This has little impact on other demographics except

Table 1. Baseline Demographic Data and Risk Factors (at Enrollment) for Subjects Returning for the One-Month Visit Grouped According to Overall Statin LLA or non-LLA use during the Trial (mean ± SD)

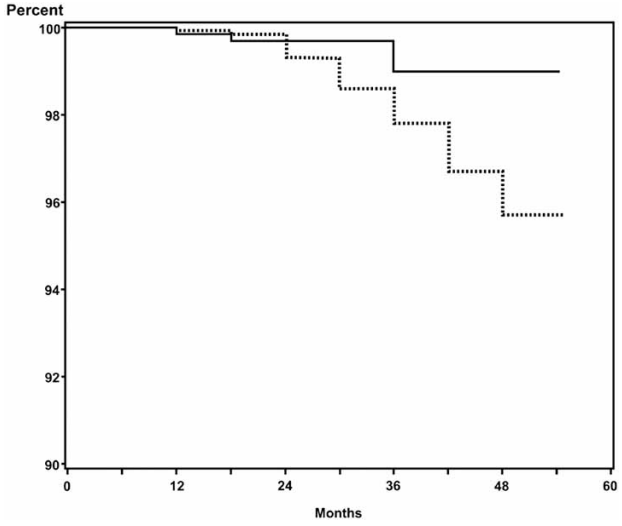
Demographic	Non-LLA	Statin LLA	P value
	n = 1,309	n = 759	-
Age	74.9 ± 3.9	74.5 ± 3.6	0.02
APOE*: At least one 4 allele	33.6 %	38.0 %	0.05
Male	49.5 %	39.1 %	< 0.001
Years education	15.0 ± 2.7	15.2 ± 2.7	0.08
Diastolic blood pressure	78.1 ± 8.7	77.4 ± 9.0	0.06
Systolic blood pressure	139.3 ±15.4	138.7± 14.8	0.49
Total cholesterol**	199.7 ± 34.7	174.8 ± 33.2	< 0.001
Weight	167.8± 33.8	175.1± 32.3	< 0.001

* n = 1,243 for non-LLA and 727 for statin LLA
** n = 1,208 for non-LLA and 748 for statin LLA

weight. A two-way analysis of variance shows that males have the same mean weight in each group while females are significantly heavier by twelve pounds on average in the statin LLA group (P < 0.001). Gender has no significant effect on the time until AD (P = 0.74). Although not medically meaningful, the half-year difference in mean age between the groups was statistically significant, while there were no significant differences in years of education, systolic blood pressure or diastolic blood pressure between the groups (Table **1**).

Time-to-event plots for AD (Fig. **1**) and proportional hazards ratios were determined employing only those individuals consistently on a statin during the preponderance of the trial period (Statin LLA) and those individuals not on a lipid-lowering agent (non-LLA) during the ADAPT treatment period. There was a 67% reduction in the risk of AD associated with ongoing statin use that was significant (95 % C.I. 2% to 89% reduction; Table **2**). When considering all individuals taking a LLA (statin-LLA, non-statin LLA and mixed statin use) a similar significant 67% reduction (p = 0.027) in the hazards risk of incident AD was observed (95% C.I. 11% to 88%). The 18% reduction in the risk of MCI associated with ongoing statin use was not significant (p = 0.51; adjusted HR = 0.82 (0.48 – 1.41)). When considering all individuals taking a LLA (statin-LLA, non-statin LLA and mixed statin use) compared to the non-LLA population, the reduced risk of incident MCI (adjusted HR = 0.69) remained non-significant (p = 0.17). There were an insufficient number of individuals to assess the effect of specific statins or after grouping by blood-brain barrier permeability, but atorvastatin (N = 345) and simvastatin (N = 221) comprised 75% of the statin using population. Two individuals on atorvastatin and two on simvastatin converted to AD (p = 0.65 by chi square).

Mean MMSE scores were not different between the statin using population of individuals compared to those not using a LLA at the 1, 12, and 24-month visits (Table **3**). In contrast there were significant reductions in total cholesterol, HDL-cholesterol and LDL-cholesterol levels (Table **3**).



Solid line = statin population
Dotted line = non lipid lowering agent population

Fig. (1). Kaplan-Meier plot of time until AD in each group (P = 0.044 by log rank test).
The data are presented as the percent of the statin using population and the non-lipid lowering agent population not converting to AD is plotted versus the time after enrollment in (6-month increments) incident AD occurred.

DISCUSSION

Although the present data are not results of a randomized experiment, this is the first prospective assessment of the influence of elective statin therapy on the risk of incident MCI and incident AD, during a randomized trial testing another class of medication. The data suggest that statins produce a significant reduction in the risk of AD.

Table 2. Proportional Hazard Ratios (HR), Confidence Intervals and Significance of Difference in the Risk of AD Among Individuals Electively Using a Statin Medication Compared to those not using a Lipid Lowering Agent

Event	Non-LLA No. Cases	Statin LLA No. Cases	Log rank Test	Adjusted hazard ratio* (95% C.I.)
AD	20 (1.5%)	4 (0.5%)	P = 0.044	0.33 (0.11 – 0.98)

*adjusted for gender, age, years of education, and presence of at least one APOE 4 allele. Total sample size reduced to 1,970 due to missing values on the APOE.

Table 3. Mean Total Cholesterol, HDL-Cholesterol, LDL-Cholesterol, and MMSE Scores {Mean ± (SD) SEM} for Statin Using Individuals (Statin) Compared to Subjects not Using a Lipid-Lowering Agent (non-LLA) at their 1, 12, and 24-Month ADAPT Visits

	visit	Non-LLA	Statin-LLA
Total cholesterol	f01	202.1 (33.2) 0.98	182.8 (35.1) 1.4*
	f12	204.3 (33.1) 0.98	178.9 (32.5) 1.2*
	f24	203.6 (32.5) 1.1	179.5 (31.8) 1.5*
HDL cholesterol	f01	56.8 (17.0) 0.50	51.4 (14.7) 0.57*
	f12	56.7 (16.4) 0.48	51.7 (14.7) 0.57*
	f24	55.8 (16.3) 0.56	50.8 (14.0) 0.64*
LDL cholesterol	f01	114.3 (29.9) 0.88	97.7 (29.7) 1.10*
	f12	116.6 (29.1) 0.85	93.8 (26.7) 1.0*
	f24	117.7 (28.0) 0.96	97.0 (27.6) 1.3*
MMSE	f01	28.8 (1.35) 0.04	28.8 (1.30) 0.05
	f12	28.7 (1.47) 0.04	28.7 (1.51) 0.06
	f24	28.5 (1.72) 0.06	28.6 (1.56) 0.07

* $p < 0.0001$

Our findings clearly support the majority of epidemiologic findings. Studies by Wolozin *et al.* showed benefit associated with the use of lovastatin and pravastatin, but not simvastatin or non-statin therapy [17], and Jick *et al.* showed benefit associated with cholesterol-lowering therapy, and not specifically with statin use [18]. Five further early epidemiologic studies suggested that prior statin use reduced the risk of dementia or AD in elderly [11, 19-22]. Green *et al.* [19], Rodriguez *et al.* [20], and Rockwood *et al.* [11] provided strong evidence of a possible association between statin use and reduced risk of AD. Yaffe *et al.* reported a modest reduction in the risk of AD associated with statin use in a study of women [21], and Hajjar *et al.* [22] reported a 60% reduction in the risk of AD among 655 predominantly female subjects. Similar to our prospective findings with atorvastatin treatment of AD patients [4], Hajjar *et al.* reported improvement or no change on the MMSE and the 'Clock draw' on follow-up evaluation among individuals taking statins [22]. Meta-analysis of the first 7 retrospective studies suggested a significant reduction in the risk of later cognitive impairment with statin use (0.43), but not with other lipid-lowering agents [23].

More recently, Zamrini *et al.* reported the results of a nested case-control study of newly diagnosed AD (N= 309) and non-AD controls (N=3088) assessing odds ratios between AD and statin use. They identified a 39% reduced risk of AD in statin users compared to non-statin users (OR 0.61, 95% 0.42-0.87) [24]. Authors of the French Three-city study of 9294 individuals identified a significant reduction in the risk of AD (OR 0.61) with statin use [25], and the three most recent epidemiologic studies suggest that statin therapy slows cognitive decline in AD [26-28].

In contrast, Li *et al.* [29] suggested that there was no association between statin use and a reduced incidence of probable AD using a time-dependent proportional hazards model, but if analyzed as a case-controlled study a significant protective effect was identified. These authors proposed that previous studies showing a positive effect of statins employed inappropriate statistical methods. We addressed this concern by performing proportional hazard ratios and found significantly reduced risk of incident AD with statin use.

Data published from the Cache County cohort indicated there was no significant reduction in the risk of AD with statin use, but allowed for the possibility that some benefit could be provided with longer-term statin therapy [30]. Our findings could support this contention in that our data spans a 4-year period of statin or non-LLA use. Conflicting results

were reported by Rea *et al*. [31]. On the one hand, they indicated that prior statin use did not decrease the risk of dementia. On the other hand, when they included individuals treated in the previous year there was a nearly significant reduction in the hazard ratio for all cause dementia and AD and when including individuals currently using a statin there was a significant reduction in the hazard ratio for risk of AD [31]. Most recently Wolozin *et al*. reported a significant 50% reduction in the risk of incident AD with the use of simvastatin in a Veterans Administration cohort [32]. Our study supports these observations in that the reduced risk of incident AD was identified among individuals who were consistently using statin medication throughout the study compared to individuals who were not using a lipid-lowering medication at any time during the trial.

Two very large prospective studies were published in 2002 suggesting statins produced no positive effect on cognition in younger individuals at risk for heart disease [1, 2]. Because of the sheer number of subjects involved many researchers place great weight on these two studies, but neither was designed to assess cognitive function. In contrast to our study where cognitive assessment was done *a priori*, the Prospective Study of Pravastatin in the Elderly (PROSPER) included evaluation of the MMSE at only the last clinical visit and found that the mean performance score was the same for the placebo and statin populations. Likewise the MRC Heart Protection study (using simvastatin) included a telephone interview of cognitive status (TICS) at the end of the investigation, and reported that there was no positive effect of statin use on cognitive performance in the absence of baseline data [2]. Without any evidence of baseline performance for the two groups the authors speculated statins produced no positive effect on cognitive performance [1, 2]. More recently a prospective study of atorvastatin versus placebo in younger subjects included baseline and follow-up assessment of cognitive function, and identified significantly superior performance on the MMSE, attention, psychomotor speed, mental flexibility, working memory and memory retrieval in the statin treated population compared to placebo [3]. It is of note that similar to the findings in the PROSPER study, there were no differences in the mean MMSE performance between statin users and non-LLA users (Table **3**), but there was a significant reduction in the risk of AD produced by elective statin use in ADAPT (Table **2**). It would seem that there is insufficient change in the MMSE produced by those few converting to AD to overwhelm the lack of change in the masses.

There are those who might argue that there could be selection bias introduced due to differential treatment with statins between the statin and non-LLA groups. Although there may be greater risk of AD with higher circulating cholesterol levels [8, 25, 33] and therefore greater conversion to MCI and AD in the untreated non-LLA subjects who might have been treated with a statin, we would suggest that the mean cholesterol levels in the non-LLA group are not alarmingly high (< 205 mg/dl; Table **3**), thus automatic statin therapy was not warranted.

Overall, the evidence, with limited exceptions, suggests that statin therapy provides some level of benefit in treating individuals with AD, and prior statin use may reduce the risk of AD later in life. It is clear that before expending the time and monies in testing statin medications as a preventative of AD, they should be tested for efficacy in the treatment of MCI. Positive results in a statin MCI treatment trial would support the rationale for a later AD statin prevention trial.

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