

# Lipid lowering agents are associated with a slower cognitive decline in Alzheimer's disease

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**Background:** Data from epidemiological studies and animal models imply that disturbances in cholesterol metabolism are linked to Alzheimer's disease susceptibility. Lipid lowering agents (LLAs) may have implications for the prevention of Alzheimer's disease.

**Objective:** To investigate whether LLAs are associated with a slower cognitive decline in Alzheimer's disease.

**Methods:** An observational study in 342 Alzheimer patients followed in a memory clinic for 34.8 months (mean age 73.5 years, mini-mental state examination score (MMSE) 21.3 at entry); 129 were dyslipaemic treated with LLAs (47% with statins), 105 were untreated dyslipaemic, and 108 were normolipaemic. The rate of cognitive decline was calculated as the difference between the first and last MMSE score, divided by the time between the measurements, expressed by year. Patients were divided into slow and fast decliners according to their annual rate of decline (lower or higher than the median annual rate of decline in the total population).

**Results:** Patients treated with LLAs had a slower decline on the MMSE (1.5 point/year,  $p=0.0102$ ) than patients with untreated dyslipaemia (2.4 points/year), or normolipaemic patients (2.6 points/year). Patients with a slower decline were more likely to be treated with LLAs. Logistic regression analysis, with low annual cognitive decline as the dependent variable, showed that the independent variable LLA (treated with or not) was positively associated with the probability of lower cognitive decline (odds ratio = 0.45,  $p=0.002$ ).

**Conclusions:** LLAs may slow cognitive decline in Alzheimer's disease and have a neuroprotective effect. This should be confirmed by placebo controlled randomised trials in patients with Alzheimer's disease and no dyslipaemia.

Raised plasma concentrations of cholesterol have been implicated as a risk factor for Alzheimer's disease,<sup>1–5</sup> and low serum concentrations of high density lipoprotein cholesterol are associated with cognitive impairment and dementia.<sup>6</sup> In vitro studies suggest that cholesterol favours the formation of  $\beta$ -amyloid (A $\beta$ ) in the brain,<sup>7–8</sup> a hallmark of Alzheimer's disease. In transgenic animal models of Alzheimer's disease, hypercholesterolaemia accelerates the development of Alzheimer amyloid pathology.<sup>9–10</sup> Cholesterol-fed rabbits develop extracellular deposits of  $\beta$ -amyloid, and when they are placed subsequently on a control diet, a significant reduction in identifiable  $\beta$ -amyloid immunoreactivity is observed.<sup>11</sup> A strong association of late life high density lipoprotein (HDL) cholesterol levels with the number of neuritic plaques and neurofibrillary tangles in a population based necropsy series also support the view that cholesterol plays a role in the formation of Alzheimer's disease pathology.<sup>12</sup> A recent study showed that disease progression in the no-APOE epsilon4 allele/high cholesterol subgroup was greater than in the normal cholesterol subgroups with or without epsilon4.<sup>13</sup> In addition, hypercholesterolaemia is associated with increased microglial activation and leucocyte infiltration.<sup>14</sup> Activated microglial cells are concentrated in amyloid plaques. Such accumulation of activated microglia may contribute to neurodegeneration through the production of cytokines and free radicals.

Relations between cholesterol and Alzheimer's disease raised the hope that cholesterol lowering strategy might influence the progression of Alzheimer's disease.<sup>15–16</sup> Vascular risk factors are known to be risk factors for Alzheimer's disease,<sup>17</sup> including stroke.<sup>18–19</sup> Statins ( $\beta$ -hydroxy- $\beta$ -methylglutaryl-CoA reductase inhibitors), which can reduce intracellular cholesterol levels and prevent coronary heart disease,

have an inhibiting effect on  $\beta$ -amyloid production in cultured cells.<sup>20–21</sup> Besides having a preventive effect against the occurrence of dementia, lipid lowering agents (LLAs) may also have an effect on Alzheimer's disease progression, because of additional properties: the so called pleiotropic effects.<sup>22</sup> These include endothelial protection through actions on the nitric oxide synthase system, as well as antioxidant, anti-inflammatory, and antiplatelet effects. Statins in therapeutically relevant doses interfere with CNS cholesterol metabolism, but do not seem to be associated with significantly altered CSF alteration of A $\beta$  in non-demented elderly subjects.<sup>23</sup> Some epidemiological studies have provided evidence of a lower prevalence of diagnosed Alzheimer's disease and vascular dementia in patients with hypercholesterolaemia treated with statins<sup>24–26</sup> or other LLAs,<sup>26</sup> although this was not confirmed in a recent study.<sup>27</sup> A randomised trial with pravastatin in non-demented patients (mean (SD) MMSE = 28.0 (1.6)) did not show significant effect on cognitive function or disability.<sup>28</sup>

Our aim in the present study was to investigate whether LLAs are associated with a slower cognitive decline in patients with Alzheimer's disease in an observational study.

## METHODS

An observational study was carried out from the computerised database of the University outpatients memory clinic of Lille, France. This multidisciplinary memory clinic was

**Abbreviations:** AChEI, acetylcholinesterase inhibitor; DRS, dementia rating scale; HDL, high density lipoprotein; LLA, lipid lowering agent; MMSE, mini-mental state examination score; NSAID, non-steroidal anti-inflammatory drug; PROSPER, prospective study of pravastatin in elderly at risk; SSRI, selective serotonin reuptake inhibitor

**Table 1** Characteristics of patients according to treatment with lipid lowering agents and lipaemic status

	Total population (n=342)	Patients with dyslipaemia treated with LLAs (n=129)	Patients with untreated dyslipaemia (n=105)	Normolipaemic patients (n=108)	p Value
Men	110 (32.2)	46 (35.7)	25 (23.8)	39 (36.1)	0.088
Age (years) at the end of the study	76.5 (7.5)	75.3 (7.1)	76.9 (7.3)	77.5 (8.0)	0.065
Arterial hypertension	197 (57.6)	72 (55.8)	59 (56.2)	66 (61.1)	0.783
Diabetes mellitus	56 (16.4)	25 (19.4)	12 (11.4)	19 (17.6)	0.241
Dyslipaemia	234 (68.4)	129 (100)	105 (100)	0	<0.0001
Hypercholesterolaemia	213 (62.3)	124 (96.1)	89 (84.8)	0	<0.0001
Hypertriglyceridaemia	76 (22.2)	32 (24.8)	44 (41.9)	0	<0.0001
Small vascular lesions on imaging	85 (24.9)	27 (24.8)	22 (21)	36 (33.3)	0.048
Duration of disease at entry	35.8 (89.8)	32.9 (24)	47.4 (111.2)	27.9 (113.1)	0.258
MMSE score at entry	21.3 (5.1)	22.2 (5.1)	21 (5.1)	20.5 (5.1)	0.034
DRS score at entry	112 (19.2), NA=37	116.4 (16.2), NA=11	109.7 (21.8), NA=9	108.6 (19.1), NA=17	0.006
AChEI at entry:	279 (81.6)	104 (80.6)	87 (82.9)	88 (81.5%)	0.908
Treatment with AChEI (end of follow up)	229 (67.0), NA=23	90 (69.8), NA=7	63 (60.0), NA=15	78 (72.2), NA=1	0.012
Total duration of AChEIs (months)	21.8 (16), NA=10	23.3 (16.8) NA=4	22.5 (16.7), NA=3	19.4 (14), NA=3	0.237
Antidepressant (SSRI)	158 (46.2)	57 (44.2)	57 (54.3)	44 (40.7)	0.118
Follow up duration (months)	34.8 (18.9)	37.1 (21.5)	35.5 (18)	31.3 (16)	0.053
Delay between first and last MMSE scores (months)	30.9 (17.7)	33.6 (20)	31.6 (16.2)	27.1 (15.3)	0.017
Annual decline on MMSE score	2.1 (2.8)	1.5 (2.5)	2.4 (2.6)	2.6 (3.3)	0.010
Follow up duration (months)	34.8 (18.9)	37.1 (21.5)	35.5 (18)	31.3 (16)	0.053
Death	35 (10.2)	13 (10.1)	11 (10.5)	11 (10.2)	0.995

Values are n (%).

AChEI, acetyl choline esterase inhibitor; DRS, dementia rating scale<sup>26</sup>; LLA, lipid lowering agent; MMSE, mini-mental state examination; NA, not available; SSRI, selective serotonin reuptake inhibitor.

opened in 1992. From the start, all patients are assessed with a comprehensive standardised clinical examination conducted by a senior staff neurologist, a psychiatrist, a neuropsychologist, a speech therapist, and a nurse. They have cerebral imaging and laboratory investigation including fasting plasma total cholesterol and triglycerides. A standardised file is completed, which includes demographic data, comprehensive personal and family history, especially vascular risk factors, mini-mental state examination (MMSE),<sup>29</sup> and previous and current treatments. During confrontation meetings with all the staff, a consensual diagnosis is given for each patient according to the current diagnostic criteria.<sup>30–33</sup> Most patients are followed up on a regular basis (every six to 12 months) if cognitive decline is confirmed.<sup>34</sup>

The inclusion criteria were as follows:

- all patients had to have a clinical diagnosis of probable Alzheimer's disease<sup>30</sup> or Alzheimer's disease associated with cerebrovascular lesions, but not fulfilling criteria for probable vascular dementia<sup>32</sup> (so called "mixed dementia");
- the first examination took place between July 1993 and July 2000 inclusive;
- at least two MMSE scores had to be available, at six months intervals or greater;
- lipid status had to be available in all cases.

The final cut off date for data collection was February 2002. Patients with clinical features compatible with other diagnosis of dementia, especially degenerative dementia such as frontotemporal dementia<sup>31</sup> or dementia with Lewy bodies,<sup>33</sup> and patients without dyslipaemia and treated with vitamin E ( $\alpha$ -tocopherol) were excluded.

Data were collected from the standardised files and from all the available sources (general practitioners, dispensing chemists, patients, and families). Hyperlipidaemia was defined as fasting serum level of triglycerides  $\geq 1.7$  mmol/l or fasting cholesterol level  $\geq 6.5$  mmol/l, threshold for people older than 60 years without additional risk factor, or current treatment with LLAs. Arterial hypertension was defined as systolic blood pressure  $\geq 140$  mm Hg or diastolic blood pressure  $\geq 90$  mm Hg or current treatment with antihypertensive

drugs. Diabetes mellitus was defined as fasting serum glucose level  $\geq 6.0$  mmol/l or current use of antidiabetic drugs. Drug prescriptions were collected according to the following classification: non-steroidal anti-inflammatory drugs (NSAIDs), antidepressants, fibrates, statins, and acetylcholinesterase inhibitors (AChEI). For AChEIs and LLAs, the compound, dosage, and duration of treatment were noted. When patients took consecutively LLAs of two different pharmacological classes, both treatments were taken into account. Homogeneity of corticoid and postmenopausal hormone therapy prescriptions was controlled between groups, because these might be confounding factors. All available MMSE scores, and dementia rating scale (DRS)<sup>35</sup> scores at the first visit were also collected.

The rate of cognitive decline was calculated as the difference between the first and the last MMSE score, divided by the time between the two measurements and expressed by year.

### Statistical analysis

The first step of the analysis consisted of a comparison of, first, patients with dyslipidaemia who received either statin, fibrate, or other LLAs; second, patients with untreated hyperlipaemia; and third, patients with normal lipid status. Analyses of variance (ANOVA) with Fisher's PLSD tests were used to compare quantitative variables between groups. We used  $\chi^2$  tests with Yates correction or Fisher's exact test as appropriate to compare qualitative factors between groups. The second step comprised a bivariate analysis comparing variables between patients with a slow cognitive decline and those with a fast decline. We defined a threshold of progression of cognitive decline by the median of all the calculated annual rates of MMSE decline. A measure lower than the median value reflected a slower progression of dementia, while a measure higher than or equal to the median value reflected a faster rate of cognitive decline. We used  $\chi^2$  tests with Yates correction or Fisher's exact test as appropriate to compare qualitative factors between groups, and the odds ratio (OR) with 95% confidence interval (CI) to compare qualitative factors between groups. The unpaired *t* test was used to compare quantitative variables. The third step consisted in a forward stepwise logistic regression

**Table 2** Characteristics of patients according to the rate of cognitive decline on the mini-mental state examination and effect of lipid lowering agents on the progression of cognitive decline

Variable	Frequency (%)		Odds ratio	95% CI	p Value
	Slow cognitive progression (<1.8 point/year) (n = 172)	Fast cognitive progression (>1.8 point/year) (n = 170)			
<b>Qualitative</b>					
Men	51 (29.7)	59 (34.7)	1.26	0.80 to 1.99	0.317
Arterial hypertension	97 (56.4)	100 (58.8)	1.10	0.72 to 1.70	0.650
Diabetes mellitus	34 (19.8)	22 (12.9)	0.60	0.34 to 1.08	0.088
Antidepressant (SSRI)	73 (42.4)	85 (50)	1.36	0.88 to 2.08	0.161
AChEI at entry	138 (80.2)	141 (82.9)	1.20	0.69 to 2.08	0.518
Treatment with AChEI at the end of follow up	120 (69.8), NA=12	111 (65.3) NA=11	0.77	0.47 to 1.26	0.094
NSAIDs	81 (47.1)	80 (47.1)	1.00	0.65 to 1.53	0.995
Vascular lesion on imaging	45 (26.2)	40 (23.5)	0.87	0.53 to 1.42	0.573
Education <8 years	139 (80.8)	129 (76.3) NA=1	0.77	0.45 to 1.29	0.488
Education 8–12 years	19 (11)	26 (15.4) NA=1	1.46	0.77 to 2.77	
Education >12 years	14 (8.1)	14 (8.3) NA=1	1.02	0.47 to 2.21	
Lipid lowering agents	79 (45.9)	50 (29.4)	0.49	0.31 to 0.77	<b>0.002</b>
Fibrates	39 (22.7)	24 (14.1)	0.56	0.32 to 0.98	<b>0.041</b>
Statins	37 (21.5)	24 (14.1)	0.60	0.34 to 1.06	0.074
Others hypolipaeamic agents	18 (10.5)	14 (8.2)	0.77	0.37 to 1.60	0.479
Hypercholesterolaemia	114 (66.3)	99 (58.2)	1.41	0.91 to 2.19	0.125
<b>Quantitative (mean (SD))</b>					
Total duration of LLAs (months)	49.9 (50), NA=6	32.3 (29.2), NA=4			<b>0.033</b>

AChEI, acetyl choline esterase inhibitor; DRS, dementia rating scale<sup>26</sup>; LLA, lipid lowering agent; NA, not available; NSAID, non-steroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitor.

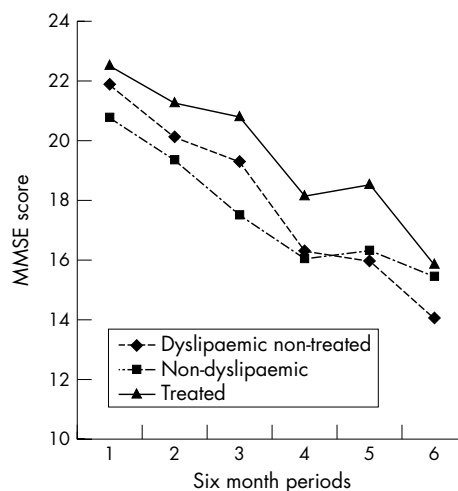
analysis assuming the rate of cognitive decline as dependent variable. The independent variables included in the analysis were selected from the bivariate analyses, with a 0.25 level as screening criterion.<sup>36</sup> Colinearity between variables (defined as  $r > 0.6$ ) was excluded. Analyses were done using the SPSS 11.0/Windows package.

In addition, prospective change in the MMSE score was analysed using a mixed random effect model (SAS 8.02, PROC MIXED). The regression model allowing adjustment provides estimates of the association between MMSE scores and LLA treatment/lipaemic status, time, and the interaction of LLA treatment/lipaemic status and time. A significant time effect indicates a change in MMSE scores over time. A significant interaction effect of LLA treatment/lipaemic status and time indicates a differential change in the MMSE scores as a function of LLA/lipaemic status groups. Covariables included in the model were sex, age, education, diabetes, baseline MMSE scores, continuous treatment with AChEIs, or antidepressant treatment. This analysis was done for a total period of 2.5 years. These analyses were done using SAS 8.02 (Carey, North Carolina, USA).

## RESULTS

Between July 1993 and July 2000, 1371 patients examined in the memory clinic were diagnosed as having possible or probable Alzheimer's disease. Among this population, 342 consecutive patients fulfilling our inclusion criteria were recruited to the study. The others 1029 patients were excluded from this analysis because they had an insufficient follow up (less than six months), or only one MMSE, or the diagnosis changed to mixed dementia, or the lipid status was not available. However, the 342 patients of the study population were representative of the whole database population of Alzheimer's disease for demographic data, age at onset, and MMSE score at first visit.

The study population consisted in 232 women and 110 men, with a mean (SD) age of 70 (7.4) years at onset, 73.5 (7.3) years at first visit, and 76.5 (7.5) years at the end of the follow up (range 42 to 99). Table 1 shows the baseline characteristics of the patients according to dyslipaemia and



**Figure 1** Adjusted analysis of decline in mini-mental state examination (MMSE) score over time, according to LLA/lipaemic status group.

lipid lowering treatment. Among the study population, 68.4% were dyslipaemic (54.9% in the total database Alzheimer population); 57.6% (197 of 342) suffered from hypertension (41% in the total database Alzheimer population), 81.6% (279 of 342) received AChEIs (64.5% in the total database Alzheimer population), and the mean duration of this treatment was 21.8 (16) months. As the study period includes the era in which the first AChEI then the second generation of AChEIs were available, we checked for the repartition of inclusion years between groups and did not find any significant difference. Corticosteroid or postmenopausal hormone treatment involved only a few patients (12 of 342) and there was no significant difference in the distribution of these treatments between the groups. The average first MMSE score was 21.3 (5.1) points. The patients had an average annual decline of 2.1 (2.8) points.

Of these 342 patients, 234 were dyslipaemic, of whom 129 were treated with LLAs, while 108 were normolipaemic without LLAs (table 2). Among the 129 treated patients, 63 were treated with fibrates (60 with fibrates only and three were treated with statins before fibrates), 61 with statins, (55 with statins only, and six with fibrates before statins), and 32 with other LLAs (14 with other LLAs only, and 18 associated with fibrates or statins). We kept in the analysis patients who were treated with only one therapeutic class (60+55+14 = 129). The mean duration of lipid lowering treatments was 43.1 (43.7) months; 76% of the patients who were treated with LLAs received this treatment before Alzheimer's disease diagnosis, and 95.3% were prescribed LLAs during the follow up. The mean follow up of patients was 34.8 (18.9) months. Comparison between the three groups according to lipid lowering drugs and dyslipidaemia showed a significantly slower decline in patients with dyslipidaemia treated with LLAs (1.5 (2.5) points/year,  $p = 0.0102$ ) than in patients with untreated dyslipidaemia (2.4 (2.6) points/year), or in normolipaemic patients without LLAs (2.6 (3.3) points/year) (comparison with patients with untreated dyslipidaemia, NS (table 1)). The three groups did not differ significantly, especially with regard to level of education, arterial hypertension, and diabetes mellitus. However, cerebrovascular lesions were surprisingly more common in normolipaemic patients than in the other groups ( $p = 0.05$ ). With respect to current treatments with AChEIs, patients with untreated dyslipidaemia were less often treated with AChEIs until the end of follow up than the others ( $p = 0.01$ ). Nevertheless, the groups did not differ for treatment with AChEIs at entry ( $p = 0.91$ ), or for the duration of treatment with AChEIs ( $p = 0.24$ ). Cognitive scores were also higher at entry in dyslipaemic patients treated with LLAs (MMSE  $p = 0.034$ ; DRS  $p = 0.0056$ ), and the delay between first and last MMSE scores was longer ( $p = 0.0169$ ).

The median value of annual decline was 1.8 points. Two groups of patients were then determined according to their rate of cognitive decline: slow decliners had an annual loss <1.8 points, and rapid decliners had an annual loss >1.8 points on the MMS. Comparison between patients with slow and rapid annual decline on the MMS score showed that patients with a slower decline were more likely to have hypertriglyceridaemia (1.4 (1) v 1.1 (0.5) mmol/l,  $p = 0.0049$ ), high scores on the DRS scores at entry (116.6 (17.7) v 107.3 (19.6),  $p < 0.0001$ ; scores not available in 37 patients), and to be treated with LLAs and fibrates (table 2). MMSE at entry was not significantly different between the two groups ( $p = 0.7544$ ). Most vascular risk factors did not differ between the two groups according to the progression of decline, especially with regard to hypercholesterolaemia, arterial hypertension, and diabetes mellitus. Variables that may influence the progression of Alzheimer's disease (age ( $p = 0.6433$ ), sex, MMSE score at entry ( $p = 0.7544$ ), and level of education) were added in the model despite a  $p$  value greater than 0.25. We excluded co-linear variables such as triglycerides (we chose cholesterol), fibrates (we chose LLAs), and DRS score (we chose MMSE score at the first visit). Finally, we added variables with a  $p$  value of less than 0.25: diabetes mellitus, treatment with AChEIs at the end of the study, and antidepressants (table 3). Under these conditions, logistic regression analysis with annual cognitive decline as the dependent variable showed that LLA intake was independently ( $p = 0.001$ ) associated with a slower rate of cognitive decline (adjusted OR = 0.45 (95% CI, 0.27 to 0.74),  $p = 0.002$ ).

The adjusted analysis of the MMSE decline over time according to the LLA/lipaemic status group is shown in fig 1. As it would be expected, there was a significant time effect,

indicating that the MMSE score declined over time in all three groups ( $p < 0.001$ ). In addition, the decline in MMSE over time was statistically different between the three groups; as in the univariate analysis, the decline was significantly less important for patients with dyslipidaemia treated with LLAs than for the other two groups ( $p = 0.04$ ).

## DISCUSSION

This observational study conducted in a memory centre in 342 patients followed up over an average of 34.8 months suggests that LLAs may decrease the rate of progression of cognitive decline in Alzheimer's disease. This conclusion was reached through two different types of analysis. First, a comparison of the rate of cognitive decline between patients with dyslipaemia who received LLAs, patients with untreated dyslipaemia, and normolipaemic patients not exposed to LLAs showed a significantly lower rate of decline in the group treated with LLAs. Patients treated with LLAs had a higher MMSE score at entry than non-treated patients, and more often continued on treatment with AChEIs at the end of the follow up than untreated dyslipaemic patients, which may have contributed to our finding. However, the effect was still significant in the adjusted analysis, and patients with a low annual decline on the MMSE score were more likely to be treated with LLAs. Second, the logistic regression analysis showed that exposure to LLAs was independently associated with a lower annual rate of decline independently, in particular, of plasma cholesterol concentrations. However, the efficacy of LLAs on the level of cholesterol and triglycerides could not be assessed in this study. The lack of statistical power did not allow us to make a comparison between statins and fibrates.

Our study limits "indication bias"<sup>37</sup>—an argument against the findings of Wolozin *et al*<sup>25</sup> and Jick *et al*<sup>24</sup> that a patient with dementia may be less likely than one without dementia to be prescribed statins<sup>38</sup>—as in the present study all patients has already been diagnosed with Alzheimer's disease and 76% of LLAs had been prescribed before the diagnosis was made. Selection bias favouring good health outcomes,<sup>39</sup> education level,<sup>40 41</sup> co-prescription of anti-inflammatory drugs or aspirin,<sup>40</sup> and cholesterol levels<sup>42</sup> was controlled for. Alzheimer's disease was diagnosed in a memory centre by trained neurologists, psychiatrists, and geriatricians according to a multidisciplinary approach, and the diagnoses are reliable: among the first 38 clinically diagnosed cases of Alzheimer's disease that came to necropsy, 36 were histologically confirmed. These specialist/memory centre based diagnoses answer the criticism made by Birkenhager *et al*,<sup>39</sup> based on the findings of Jick's study.<sup>24</sup> However, in this observational study, confusion between the efficacy of the drugs and the indications for which they are prescribed cannot be ruled out,<sup>37</sup> and a causal nature of the association is not proven.

Some other potential confounding factors can be identified, although these were not significant in the multivariate analysis. Small cerebrovascular lesions on cerebral imaging were more common in patients with normolipaemia. Cerebrovascular lesions may aggravate the effects of Alzheimer pathology and hasten cognitive decline,<sup>43 44</sup> although the co-occurrence of cerebrovascular lesions in patients with Alzheimer's disease has not been found to influence cognitive performance or disease course.<sup>45 46</sup> Mungas *et al* found that Alzheimer's disease progressed more rapidly in patients older than 80 years if there was cerebrovascular disease than if there was no associated cerebrovascular pathology, but progression was slower in patients younger than 80 years.<sup>47</sup> The mean age of our study population was 78.6 (7.2) years at the time of the study and 71.0 (7.4) years at onset, and it was not significantly different

between the groups. Treatment with AChEIs throughout the period of follow up was less frequent in patients with untreated dyslipaemia, in concordance with management being more difficult in some patients than others. In addition, cognitive scores at entry were higher in patients treated with LLAs. Subjects with higher initial MMSE scores tend to decline less than patients with lower initial MMSE scores.<sup>48–49</sup> MMSE may have limited value in measuring the progression of Alzheimer's disease in individual patients for periods of less than three years because of a large measurement error and substantial variation in change in annual score,<sup>48</sup> and may be less reliable than the DRS.<sup>49</sup> DRS scores were not used as a measure of cognitive decline in this observational study, as not all the patients had this test on a regular basis. The average annual decline was 2.1 (2.8) points (median 1.8) on the MMSE score, which is lower than in other observational studies.<sup>49–51</sup> In our study, 81.6% of patients were treated with AChEIs, while the number of patients treated with these agent in previous studies is unknown (but probably low). Patients treated with AChEIs have a more stable cognitive state in the first years of treatment than those who are not given AChEIs.<sup>52–53</sup> Nonetheless, these potential limitations are partly overcome by the logistic regression analysis, which showed that LLAs were an independent variable associated with a slower annual rate of cognitive decline.

A slower rate of cognitive decline in Alzheimer patients treated with LLAs is consistent with the findings of other studies. Statin users were found to have higher mean modified MMSE scores than non-users at the end of a four year follow up of 1037 postmenopausal women with coronary heart disease (92.7 (7.1) v 93.7 (6.1);  $p = 0.02$ ), and a trend for a lower likelihood of cognitive impairment, independent of lipid levels (OR = 0.67 (95% CI, 0.42 to 1.05)).<sup>54</sup> The PROSPER study—a randomised controlled study in more than 5000 elderly people (mean MMSE = 28) with a history of, or risk factor for, vascular disease and followed up for three years—did not show significant effect of pravastatin compared to placebo on cognitive functions as measured by the MMSE over time.<sup>28</sup> The MRC/BHF Heart Protection Study—an even larger randomised controlled study in more than 20 500 adults with coronary disease, other occlusive arterial disease, or diabetes, and followed up for five years—also did not show any significant effect of simvastatin on cognitive function compared with placebo, but cognition was not a specific outcome.<sup>55</sup> However, in a 26 week randomised, placebo controlled, double blind trial, a smaller decrease in MMSE score was observed in 20 Alzheimer patients treated with 80 mg per day of simvastatin (17.8 (5.0) to 17.2 (4.8)) than in 17 control Alzheimer patients who received placebo (17.1 (4.9) to 14.4 (5.6),  $p < 0.02$ ).<sup>56</sup> The number of patients treated with AChEI was not specified. Our study involved many more patients, and at a milder stage, than in the study by Simons *et al.*,<sup>56</sup> in which the changes in the concentration of A $\beta$ 40 in the CSF (consistent with a possible mechanism of action of simvastatin) were only observed in the less severely affected patients.<sup>56</sup>

Contrary to the findings of Jick *et al.*,<sup>24</sup> but in agreement with the Canadian Study of Health and Aging,<sup>26</sup> we did not find any significant difference between statins and other LLAs. However, we lacked statistical power, and both treatments have properties that could account for such a beneficial effect.

Antidepressants used in the study population were mainly selective serotonin reuptake inhibitors (SSRIs) prescribed for the treatment of non-cognitive symptoms such as depressive symptoms, anxiety, irritability, and aggression.<sup>57</sup> Absence of the need for such treatments was correlated with a lower annual rate of cognitive decline. This could be a reflection of

psychosis as predictor of cognitive decline,<sup>58</sup> or any concomitant disease likely to interfere with cognition and behaviour that would have needed SSRIs.

Borroni *et al* recently showed that high cholesterol levels correlated with faster decline at a one year follow up in Alzheimer patients on AChEIs.<sup>59</sup> They suggested that if serum cholesterol level is a modulating factor for treatment response, then additional therapy aimed at reducing treatable high cholesterol levels may improve AChEI efficacy and slow the rate of disease progression. This may not explain our results, as cholesterol levels were lower in normolipaemic patients than in treated dyslipaemic patients. Thus our findings support a neuroprotective effect of LLAs and suggest that these agents may have therapeutic benefit in Alzheimer's disease through a mechanism independent of their cholesterol lowering action<sup>22</sup>; dyslipaemia (hypercholesterolaemia or hypertriglyceridaemia, or both) was not associated with the annual rate of MMSE change, whereas LLAs were associated with a lower rate of cognitive decline. In addition to their beneficial effects on cholesterol levels, LLAs have other pharmacological effects that may play a role in Alzheimer's disease pathogenesis. These additional effects related to inflammation could decrease Alzheimer's disease progression by prophylactic neuroprotection. Statins, which are compounds that inhibit HMG-CoA reductase, a key enzyme in the synthesis of cholesterol, have effects linked to a range of functions—blockade of macrophages and platelet activation, improvement in endothelial cell vasomotor function, enhancement of endothelial fibrinolytic function, and anti-inflammatory actions through inhibition of induction of NO synthase II or the cytokines tumour necrosis factor and interleukin 1 in rat macrophages, microglia, and astrocytes.<sup>60</sup> In addition, statins have antioxidative properties.<sup>61</sup> Fibrate also has anti-inflammatory effects, through activation of the nuclear factor peroxisome proliferator activated receptor  $\alpha$  (PPAR $\alpha$ ) which influences lipid metabolism and decreases the activity of NF $\kappa$ B, which inhibits NO synthase type II and the cyclooxygenase II. These proteins are responsible for enhancing excitotoxicity, DNA lesions, apoptosis, inflammatory actions, and interference with energy metabolism. PPAR $\alpha$  also activates antioxidant enzymes.<sup>22–62–63</sup> NSAIDs used over a long period could protect against Alzheimer's disease,<sup>64</sup> which is consistent with a beneficial effect of LLAs through their anti-inflammatory properties.

This study contributes to the increasing evidence that LLAs may decrease the rate of progression of Alzheimer's disease, and this is supported by biological arguments, though we cannot prove the causal nature of the association between LLAs and slower cognitive decline. However, in an observational study, the correctness of such assumptions is impossible to test thoroughly. Placebo controlled randomised trials in patients with Alzheimer's disease without dyslipaemia will provide a definitive answer. LLAs should now be taken into account in pharmaceutical trials assessing the progression of Alzheimer's disease.

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