

## Pravastatin and cognitive function in the elderly. Results of the PROSPER study

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**Abstract** Observational studies have given conflicting results about the effect of statins in preventing dementia and cognitive decline. Moreover, observational studies are subject to prescription bias, making it hard to draw definite conclusions from them. Randomized controlled trials are therefore the preferred study design to investigate the association between statins and cognition. Here we present detailed cognitive outcomes from the randomized placebo-controlled PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). Cognitive function was assessed repeatedly in all 5,804 PROSPER participants at six

different time points during the study using four neuropsychological performance tests. After a mean follow-up period of 42 months, no difference in cognitive decline at any of the cognitive domains was found in subjects treated with pravastatin compared to placebo (all  $p > 0.05$ ). Pravastatin treatment in old age did not affect cognitive decline during a 3 year follow-up period. Employing statin therapy in the elderly in an attempt to prevent cognitive decline therefore seems to be futile.

**Keywords** Statins · Clinical trial · Cognition · Elderly

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## Introduction

Lowering cholesterol levels to preserve cognitive function has received much attention with the increasing emphasis on vascular disease as a risk factor of dementia and cognitive impairment [1, 16]. Observational studies have shown that high cholesterol levels in middle age are a risk factor for cognitive impairment later in life [17]. Besides increasing the risk of cardiovascular disease with subsequent increased risks of cognitive decline, high cholesterol levels might also directly influence the risk of cognitive decline. High total serum cholesterol levels have been shown to associate with lower cerebral spinal fluid levels of  $\beta$ -amyloid and larger amounts of  $\beta$ -amyloid deposition in brain autopsy studies [9, 10].

Numerous observational studies have investigated the possible beneficial effect of statins in preventing dementia and cognitive decline. Cross-sectional and case-control studies have generally indicated a beneficial effect of statins on cognitive outcomes [5, 12, 18], while observational studies with long follow-up periods have failed to confirm these results [17, 19]. This discrepancy might be explained by prescription bias, in that subjects who are cognitively impaired are less likely to have been prescribed a statin. Therefore, randomized controlled trials are the necessary instrument to investigate the effect of statins on cognitive function.

Until now only two large scale randomized controlled trials have examined the influence of statins on cognitive function. The Heart Protection Study showed that use of simvastatin did not decrease the risk of developing dementia [2]. However, cognitive function was not an initially specified endpoint and was only assessed once at the end of the study by a telephone questionnaire. In contrast, the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) [14] is as yet the only randomized controlled trial that has been set up to test whether use of pravastatin preserved cognitive function, and therefore involved repeated assessment of various cognitive domains both at baseline and during follow-up as one of the major prespecified outcomes. In order to help clarify the ongoing debate on the effects of statins on cognition, we present here these observations in full detail, which strongly extends our earlier preliminary conclusions presented in the main PROSPER manuscript [14].

## Methods

A detailed description of the study has been published elsewhere [14, 15]. A short summary is provided here.

## Participants

PROSPER was a prospective multicentre randomized placebo-controlled trial to assess whether treatment with pravastatin diminishes the risk of major vascular events in elderly people. Between December 1997 and May 1999, we screened and enrolled subjects in Scotland (Glasgow), Ireland (Cork), and the Netherlands (Leiden). Men and women aged 70–82 years were recruited if they had pre-existing vascular disease or increased risk of such disease because of smoking, hypertension, or diabetes. A total number of 5,804 subjects were randomly assigned to pravastatin or placebo.

## Cognitive function assessment

The Mini-Mental State Examination (MMSE) was used to measure global cognitive function. Participants with poor cognitive function (MMSE <24) were not eligible to participate. Four neuropsychological performance tests were used to measure various cognitive domains. Executive functioning was assessed with the Stroop-Colour-Word-test for attention and the Letter-Digit Coding Test (LDT) for processing speed. The outcome parameter for the Stroop test was the total number of seconds required to complete the third Stroop card containing 40 items. The outcome variable for the LDT was the total number of correct entries completed in 60 s. Memory was assessed with the 15-Picture Learning test (PLT) which measures immediate and delayed recall. The main outcome variable for immediate recall was the accumulated number of pictures recalled over the three learning trials and for delayed recall the number of pictures recalled after 20 min. The reliability and sensitivity of these tests in an elderly population have been assessed and presented elsewhere [7]. Cognitive function was tested before randomisation, at baseline, after 9, 18, and 30 months, and at the end of the study. The time point of this last measurement was different for the participants (at 36–48 months) therefore we performed the analyses with their individually varying time-point but report the results for the mean of these time points (at 42 months). The pre-randomized measurement was discarded in all analyses to preclude possible learning effects. Since the MMSE is not suitable for longitudinal research in this age group because of learning and ceiling effects, sequential MMSE scores are not reported here.

## Statistical analyses

The effect of statin use on cognitive function during follow-up was assessed using linear mixed models for repeated measurements which included interim measures taken

between the baseline and the final assessment [6]. The model incorporated time, statin treatment, and the interaction term of time with statin treatment. The main variable of interest in the model was the estimate for the interaction between time and statin treatment. A significant difference in this term would indicate that cognitive decline over 42 months differed between the statin and placebo treated groups. All analyses were adjusted for sex, age, educational status, country, and version of test where appropriate. Subjects were defined as the random factor; all other variables were fixed within the model. Furthermore we analysed the association between pravastatin treatment and cognitive function in males or females, in subjects with or without a history of vascular disease or diabetes, with or without *APOE*  $\epsilon 4$  carriership, and with low or high HDL or total cholesterol levels at baseline. SPSS software (version 14.0, SPSS Inc, Chicago, Ill) was used for all statistical analyses. *p* values lower than 0.05 were considered statistically significant.

## Results

Table 1 shows the baseline characteristics of the 5,804 participants in PROSPER. A total of 2,913 subjects were randomized to placebo and 2,891 to pravastatin treatment. The mean age of all subjects at study entry was 75.3 years and approximately 50% of the participants were female. The mean follow-up period of this trial was 42 months (range 36–48 months). The two treatment groups were well balanced with respect to all relevant baseline characteristics except for the Stroop-Colour-Word test which, at baseline, was significantly different between the groups (Table 1). This we presume was due to the play of chance.

Figure 1 represents graphically the effect of pravastatin on various domains of cognitive function over time. The mean cognition scores at baseline, different from those given in Table 1, are adjusted for sex, age, educational status, country and version of test where appropriate. All cognitive tests showed a significant decline over time, confirming their adequate sensitivity to pick up deterioration of cognitive function in old age. Users of pravastatin did not show any difference in the change in any of the cognitive tests compared to placebo users during follow-up (all *p* > 0.3).

Table 2 shows the association between pravastatin treatment and cognitive decline in pre-specified subgroups. There was no pravastatin versus placebo difference in cognitive decline in males or females, subjects with or without a history of vascular disease or history of diabetes, with or without *APOE*  $\epsilon 4$  carriership, with low or high HDL and total cholesterol levels (all *p* > 0.05). Although the effect of pravastatin on processing speed within the

**Table 1** Baseline characteristics of the participants in the PROSPER study

	Placebo ( <i>n</i> = 2,913)	Pravastatin ( <i>n</i> = 2,891)
Continuous variables (mean, SD)		
Age (years)	75.3 (3.4)	75.4 (3.3)
Education (years)	15.1 (2.0)	15.2 (2.1)
Systolic blood pressure (mmHg)	154.6 (21.8)	154.7 (21.9)
Diastolic blood pressure (mmHg)	83.9 (11.7)	83.6 (11.2)
Height (m)	1.7 (0.1)	1.7 (0.1)
Weight (kg)	73.4 (13.5)	73.4 (13.3)
Body mass index (kg/m <sup>2</sup> )	26.8 (4.3)	26.8 (4.1)
Alcohol (units per week)	5.1 (8.9)	5.3 (9.7)
Total cholesterol (mmol/L)	5.7 (0.9)	5.7 (0.9)
LDL cholesterol (mmol/L)	3.8 (0.8)	3.8 (0.8)
HDL cholesterol (mmol/L)	1.3 (0.3)	1.3 (0.4)
Triglycerides (mmol/L)	1.5 (0.7)	1.5 (0.7)
Mini mental state examination score	28.0 (1.6)	28.0 (1.5)
Stroop-Colour-Word test	67.5 (28.3)	65.5 (25.5)
Letter-Digit Coding Test	22.9 (7.8)	23.2 (7.9)
Picture Learning test immediate	9.3 (1.8)	9.3 (1.9)
Picture Learning test delayed	10.2 (2.6)	10.1 (2.6)
Categorical variates ( <i>n</i> , %)		
Males	1,408 (48.3)	1,396 (48.3)
Current smoker	805 (27.6)	753 (26.0)
History of diabetes	320 (11.0)	303 (10.5)
History of hypertension	1,793 (61.6)	1,799 (62.2)
History of angina	753 (25.8)	806 (27.9)
History of claudication	192 (6.6)	198 (6.8)
History of myocardial infarction	399 (13.7)	377 (13.0)
History of stroke or TIA	321 (11.0)	328 (11.3)
History of vascular disease <sup>a</sup>	1,259 (43.2)	1,306 (45.2)

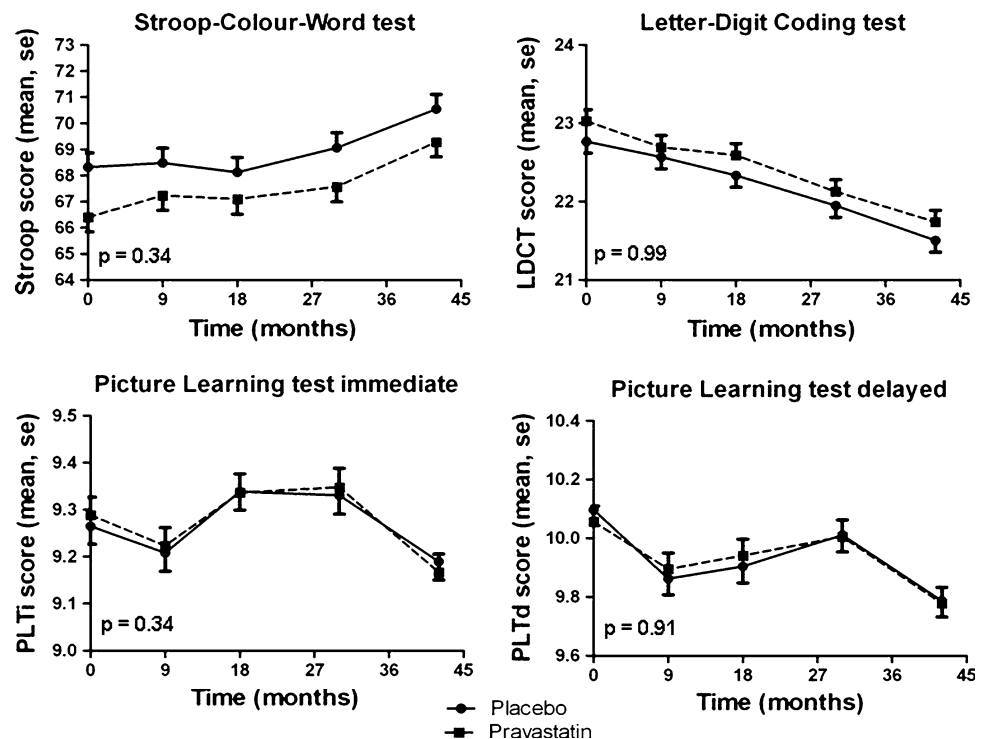
<sup>a</sup> Any of stable angina, intermittent claudication, stroke, transient ischemic attack, myocardial infarction, peripheral artery disease surgery, or amputation for vascular disease more than 6 months before study entry

*APOE*  $\epsilon 2$  carriers and within the low cholesterol group was significant (*p* = 0.01), this finding lost statistical significance after correction for multiple testing, and there was no consistent parallel change in the other cognitive performance tests.

## Discussion

In this large scale randomized controlled trial in an elderly population at risk of cognitive decline we found no effect (beneficial or detrimental) of pravastatin on cognitive function. This association was assessed with a sensitive, well-validated cognitive test battery, using repeated measurements in a large homogenous group of elderly people.

**Fig. 1** Effect of pravastatin on cognitive function over time. *p* values represent the statistical significance of the difference in test score changes over time between statin users and non-users. Means were assessed using linear mixed models adjusted for sex, age, educational status, country, and version of test where appropriate



**Table 2** Difference in cognitive decline between subjects treated with pravastatin and placebo in various subgroups

	Stroop-Colour-Word test		Letter-Digit Coding test		Picture Learning test immediate		Picture Learning test delayed	
	Est	95% CI	Est	95% CI	Est	95% CI	Est	95% CI
<b>Sex</b>								
Females	0.25	-0.10; 0.61	-0.01	-0.09; 0.07	-0.01	-0.04; 0.02	-0.02	-0.07; 0.03
Males	0.004	-0.39; 0.40	0.01	-0.07; 0.09	-0.01	-0.04; 0.02	0.02	-0.02; 0.07
<b>History of vascular disease</b>								
No	-0.05	-0.41; 0.32	0.002	-0.08; 0.08	-0.02	-0.05; 0.01	-0.03	-0.07; 0.02
Yes	0.36	-0.02; 0.74	-0.02	-0.08; 0.09	0.002	-0.03; 0.04	0.04	-0.01; 0.09
<b>History of diabetes</b>								
No	0.22	-0.06; 0.49	0.01	-0.05; 0.07	-0.01	-0.03; 0.01	0.01	-0.03; 0.04
Yes	-0.56	-1.52; 0.40	-0.11	-0.29; 0.07	-0.02	-0.09; 0.05	-0.04	-0.14; 0.06
<b>APOE genotype</b>								
$\epsilon 2$ Carriers	-0.27	-1.09; 0.56	0.15	-0.02; 0.32	-0.09	-0.17; -0.04**	-0.01	-0.11; 0.08
$\epsilon 3/\epsilon 3$	0.30	-0.03; 0.63	-0.03	-0.10; 0.04	-0.01	-0.03; 0.02	0.00	-0.04; 0.05
$\epsilon 4$ Carriers*	-0.16	-0.70; 0.37	-0.003	-0.11; 0.12	0.02	-0.03; 0.07	0.02	-0.06; 0.09
<b>Plasma total cholesterol</b>								
Low	0.21	-0.17; 0.59	0.02	-0.06; 0.10	-0.04	-0.08; -0.01**	-0.03	-0.08; 0.02
High	0.05	-0.32; 0.41	-0.02	-0.10; 0.06	0.02	-0.01; 0.06	0.03	-0.02; 0.08
<b>Plasma HDL cholesterol</b>								
Low	0.25	-0.13 (0.62)	-0.002	-0.08; 0.08	-0.01	-0.04; 0.02	0.01	-0.04; 0.05
High	-0.01	-0.36; 0.38	0.003	-0.08; 0.08	-0.01	-0.04; 0.02	-0.004	-0.05; 0.04

Estimates (Est) and 95% confidence intervals (95% CI) were assessed with linear mixed models adjusted for age, educational status, country and, where appropriate, for sex and version of test. Estimates represent the additional annual change of the pravastatin treatment group compared to placebo treatment. \*  $\epsilon 2/\epsilon 4$  carriers ( $n = 119$ ) were included in the  $\epsilon 4$  carriers subgroup. \*\*  $p$  value = 0.01

Our results are in line with the end of study survey in the Heart Protection Study, the only other large-scale randomized clinical trial that has investigated this association, which showed that treatment with simvastatin did not affect cognition [2]. Taken together, outcomes from randomized clinical trials do not confirm the findings from observational studies that statins might reduce the risk of dementia or decelerate cognitive decline [18].

Strong evidence indicates that cardiovascular disease and some of its risk factors are important determinants for the development of dementia. Within PROSPER we have previously shown that statin treatment successfully reduces the risk of cardiovascular disease [14]. Therefore, it is surprising that this beneficial effect on cardiovascular events is not reflected in a decreased cognitive decline. Treatment with antihypertensives in the HYVET-COG study also showed that pharmacological intervention reduced cardiovascular disease risk of older people, including strokes, but did not reduce not the risk of dementia [11].

The relation between cholesterol and risk of cardiovascular disease is complicated in the sense that observational studies have shown that, unlike in middle age, high total serum cholesterol levels are no longer associated with cardiovascular disease and cognitive impairment in old age [8, 17]. Moreover, it might be that the association between cardiovascular disease and cognitive decline is primarily driven by clinical strokes, and statin treatment in PROSPER did not decrease the risk of stroke. Therefore, the lack of cognitive benefit in old age does not preclude that use of statins in middle age, lowering cardiovascular risk, could be beneficial for cognitive function later in life. The data from the randomized controlled trials in old age merely show that starting statin therapy in old age in an attempt to prevent cognitive decline does not seem worthwhile, and a similar message may hold when treating hypertension.

Because of its study design with prespecified repeated cognitive measures over time, our study signifies the absence of effect of statin treatment on cognitive function in an unparalleled manner. The random allocation of treatment prevented prescription bias, which is frequently present in observational research of intended effects. Prescription bias might explain why cross-sectional studies and short follow-up studies found positive associations between statin use and cognitive function. We had cognitive follow-up data of over 5,000 subjects over 42 months with little loss to follow-up. Linear mixed models for statistical analyses were used because this method handles repeated measurements within subjects accurately. These results are in agreement and supplement strongly the previously reported results of the difference in last on-treatment measurement and the baseline measurements using linear regression [14]. Moreover, our population was very

suitable for assessing the effects of statins on cognitive function because only subjects with a MMSE above 24 points could participate, which makes it a homogenous and relevant study group.

A possible limitation of PROSPER is extrapolation to the general population. All subjects had either a history of vascular disease or were at an increased risk for such disease. Moreover, another possible limitation is that, in PROSPER, hydrophilic pravastatin was used and not one of the lipophilic statins. Pravastatin does not reach the cerebral spinal fluid, whereas lovastatin and simvastatin do penetrate the blood–brain barrier. It is unlikely that this explains the absence of a beneficial effect of pravastatin on cognitive decline, since our results are in line with the Heart Protection Study, which did not find a difference in cognitive function in simvastatin users compared to placebo users.

Two major statin trials are currently under way to assess the effects of statins in delaying the progression of AD in patients with serum cholesterol levels that do not require therapeutic intervention [13]. The Cholesterol Lowering Agent to Slow Progression of Alzheimer's Disease (CLASP) study is a double-blind trial that randomized approximately 400 patients with Alzheimer's disease to either simvastatin 20 mg/day or placebo for 6 weeks [4]. The Lipitor's Effect in Alzheimer's Dementia (LEADe) study is a double-blind trial that randomized approximately 600 patients with Alzheimer's disease to either atorvastatin 80 mg/day or placebo for a period of 72 weeks. Preliminary results showed no difference in disease progression between the statin treated subjects compared to placebo users [3].

In conclusion, pravastatin treatment in old age did not affect cognitive decline during a 3 year follow-up period. Since high cholesterol levels in midlife are associated with accelerated cognitive decline in late-life, additional studies are necessary to study a possible beneficial effect of statin treatment in midlife on cognitive decline in late-life. But starting statin therapy in the elderly simply to decelerate cognitive decline seems to be a futile exercise.

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