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Lack of Effect of Pravastatin on Cerebral Blood Flow or Parenchymal Volume Loss in Elderly at Risk for Vascular Disease

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Background and Purpose—Ageing is associated with a decline in cerebral blood flow. Animal studies have shown that cholesterol-lowering therapy with statins might preserve cerebral blood flow (CBF). We examined the effect of 40 mg pravastatin on the decline in CBF and brain volume in a subset of elderly subjects participating in the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) trial.

Methods—Randomization was not stratified according to whether or not subjects participated in the MRI substudy. In 391 men (n=226) and women (n=165) aged 70 to 82 years (mean±SD, 75±3.2), we measured total CBF (in mL/min) at baseline and after a mean±SD follow-up of 33±1.4 months with a gradient-echo phase-contrast MRI technique. Total CBF was defined as the summed flows in both internal carotid and vertebral arteries. Parenchymal volume (whole brain) was segmented with the use of in-house–developed semiautomatic software.

Results—Total CBF significantly declined in the placebo-allocated group, from 521±83 to 504±92 mL/min ($P=0.0036$) and in the pravastatin-allocated group from 520±94 to 506±92 mL/min ($P=0.018$). This decline was not significantly different between treatment groups ($P=0.56$). There was also a significant reduction in brain volume over time ($P<0.001$), which was not different between the treatment groups ($P=0.47$). When expressed per unit of parenchymal volume, the decline in CBF over time was no longer statistically significant.

Conclusions—Elderly people at risk for cerebral vascular disease had a significant decline in CBF with increasing age that was explained by a concomitant reduction in brain volume. Treatment with 40 mg pravastatin daily had no beneficial effect on total CBF. **(*Stroke*. 2005;36:1633-1636.)**

Key Words: cerebral blood flow ■ elderly ■ statins

Ageing is associated with a decline in cerebral blood flow (CBF).[1,2] From cross-sectional studies, the rate of this decline has been estimated at ≈4.8 mL/min per year.[1] Although the exact etiology of this age-dependent reduction in CBF is largely unknown, several causes have been proposed. Some studies have shown that total CBF is partly determined by brain volume.[3–5] Other studies have indicated that atherosclerotic disease, small-vessel disease, and a decline in metabolic need might also play a role in the decline in CBF with age.[2,6,7]

In animals, cholesterol-lowering therapy with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) has been shown to augment absolute CBF by enhancing endothelial nitric oxide synthase.[8] An improvement of 30% in CBF induced by statins has been reported in mice.[9] A study in humans with small-vessel disease showed that treatment with pravastatin improved cerebral vasomotor reactivity but not CBF.[10]

We investigated the effect of treatment with 40 mg pravastatin daily for 3 years compared with placebo on the decline in total CBF in elderly subjects at risk for vascular disease. Using MRI, we measured changes in CBF over time and analyzed all data of CBF as crude measurements and corrected for brain volume.

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Methods

Setting and Subjects

The PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) is a double-blind, randomized, placebo-controlled trial that examined the effect of cholesterol-lowering therapy with 40 mg pravastatin on vascular events in 5804 men and women, aged 70 to 82 years, with vascular disease or at risk for vascular disease.[11,12] A total of 554 Dutch participants in the PROSPER study had 2 successive MRI scans of the brain. The first MRI was during the placebo lead-in period and the second MRI after a mean±SD follow-up of 33±1.4 months. In 391 participants, total CBF was measured on these 2 occasions. The Leiden University Medical Center institutional ethics review board approved the protocol for the MRI study, and all participants gave written, informed consent.

CBF and Parenchymal Volume

We performed MRI of the brain on a system operating at 1.5 T field strength (Philips Medical Systems). CBF was measured in both internal carotid arteries and both vertebral arteries by using a gradient-echo, phase-contrast MRI. We used a triggered gradient-echo, phase-contrast technique with 1 signal average and retrospective gating with a peripheral pulse unit. Repetition time (TR)/echo time (TE) was 14.7/9;1 ms; flip angle, 7.5°; slice thickness, 5 mm, scan matrix, 256×256; and field of view (FOV), 250×250 mm. The scans were performed in a plane perpendicular to the carotid and vertebral arteries.[13] All subjects refrained from smoking at least 90 minutes before CBF was measured. For the parenchyma measurements, we obtained proton density-T2/dual fast-spin-echo images of all subjects at baseline and follow-up (TE, 27/120 ms; TR, 3000 ms; echo train length factor, 10; 48 contiguous 3-mm slices; matrix 256×256; FOV, 220).

Postprocessing Techniques

The images were analyzed with use of the FLOW software package (Division of Image Processing, Department of Radiology, Leiden University Medical Center).[14] An automatic method was added to the package to manually indicate the vessel, after which delineation of the vessel was drawn automatically.[15] With this method, partial-volume effects were excluded. Volume of flow was calculated by integrating the flow velocity within this contour multiplied by the area. Phase differences were calculated according to standard methodology.[16] Total CBF was calculated by adding the flow from the left and right internal carotid arteries to the flow in both vertebral arteries.[13] Parenchyma (whole-brain) volume was segmented with use of in-house–developed semiautomated software (Division of Image Processing, Department of Radiology, Leiden University Medical Center).[17] The volume of parenchyma was expressed in cubic centimeters.

Statistics

Using an α of 5%, we calculated that our study had 80% power to detect a 20 mL/min (SD, 70 mL/min) difference between the pravastatin and placebo groups.[13] Baseline characteristics for placebo- and pravastatin-allocated participants are reported as mean and SD for continuous variates and number (%) for categorical variates. Baseline CBF depending on various clinical characteristics was assessed with Student's *t* test. The decline in CBF and brain parenchyma in the placebo- and pravastatin-treated groups was analyzed with paired *t* tests. Moreover, a linear mixed model was performed to study the effect of pravastatin on the progression of total ischemic lesion load. In some models, CBF was analyzed as a crude value and later corrected for parenchymal volume.

Results

Baseline characteristics for the 391 participants are shown in Table 1. No significant differences were found, except for smoking: 32 subjects (17%) in the pravastatin group were smokers versus 57 subjects (29%) in the placebo group (P=0.004). Table 2 shows baseline CBF in relation to various clinical characteristics. Women had significant lower CBF (mean±SD, 507±89 mL/min) than men (mean±SD, 530±87 mL/min; P=0.01). There was no significant difference in CBF for any of the other characteristics, including a history of vascular disease, stroke, or transient ischemic attack.

TABLE 1. Baseline Characteristics

Characteristic	Placebo (n=198)	Pravastatin (n=193)	*P*
Age, y	75.1 (3.3)	75.0 (3.1)	0.91
Men	120 (60.6)	106 (54.9)	0.26
Systolic blood pressure, mm Hg	156.5 (20.4)	157.8 (22.2)	0.55
Diastolic blood pressure, mm Hg	86.6 (10.8)	85.0 (11.2)	0.17
Total cholesterol, mmol/L	5.7 (0.9)	5.7 (0.8)	0.73
LDL cholesterol, mmol/L	3.9 (0.8)	3.9 (0.8)	0.43
HDL cholesterol, mmol/L	1.3 (0.3)	1.2 (0.3)	0.40
Current smoker	57 (28.8)	32 (16.6)	0.004
History of diabetes	36 (18.2)	28 (14.5)	0.33
History of hypertension	116 (58.6)	128 (66.3)	0.11
History of myocardial infarction	26 (13.1)	22 (11.4)	0.60
History of stroke or transient ischemic attack	40 (20.2)	26 (13.5)	0.08
History of any vascular disease	89 (45.0)	83 (43.0)	0.70

Continuous variates are mean and (SD); categorical variates as n and (%).

To assess the effect of pravastatin on cholesterol reduction, we calculated the 3-months reductions in total cholesterol, LDL cholesterol, and HDL cholesterol in our study groups. After 3 months of follow-up, mean total cholesterol in the 193 subjects allocated to pravastatin was significantly reduced, from 5.7±0.8 to 4.3±0.7 mmol/L. Total cholesterol remained unaltered at 5.7±0.9 mmol/L in the 198 placebo-treated subjects. In the pravastatin-treated subjects, LDL cholesterol was reduced, from 3.9±0.8 to 2.5±0.6 mmol/L, and HDL cholesterol increased from 1.2±0.3 to 1.3±0.4 mmol/L. LDL and HDL cholesterol remained unaltered in the placebo-treated subjects. The total cholesterol, LDL, and HDL changes in the 193 pravastatin-treated patients were similar to the changes reported in the total group of subjects in the PROSPER study.[12]

The decline in CBF during the study period was 14.0 mL/min (95% confidence interval, 2.4 to 25.5, P=0.018) in the pravastatin group and 17.7 mL/min (95% confidence interval, 5.8 to 29.5, P=0.0036) in the placebo group (Table 3). This translates to a decline of 5.1 mL/min per year in the pravastatin group and a decline of 6.4 mL/min per year in the placebo group. The reduction in CBF was not significantly different between the 2 treatment groups (P=0.56). In both treatment groups, a similar significant reduction in brain volume over time was also observed (P<0.001 within both treatment groups, P=0.47 between groups; Table 3). When CBF was expressed per unit parenchymal volume, the decline in CBF over time was no longer significant (Table 3). Results from the linear mixed models also indicated no significant differences between treatment groups, P=0.66 for crude CBF and P=0.56 for CBF corrected for parenchymal volume.

TABLE 2. Baseline CBF Dependent on Various Clinical Characteristics

	No.	Mean (SD)	Mean Difference (95% CI)	*P*
Age, y				
≤74.6	195	527.8 (94.6)	14.3 (−3.2, 31.8)	0.11
>74.6	196	513.6 (81.0)		
Sex				
Men	226	530.4 (86.7)	23.1 (5.5, 40.7)	0.01
Women	165	507.3 (88.7)		
Systolic blood pressure, mm Hg				
≤158	203	522.9 (92.7)	4.6 (−13.0, 22.2)	0.61
>158	188	518.3 (83.3)		
Diastolic blood pressure, mm Hg				
≤85	200	524.4 (91.0)	7.6 (−10.0, 25.1)	0.40
>85	191	516.8 (85.3)		
Total cholesterol, mmol/L				
≤5.7	195	519.9 (88.2)	−1.5 (−19.1, 16.0)	0.87
>5.7	196	521.4 (88.4)		
LDL cholesterol, mmol/L				
≤3.8	198	518.6 (89.9)	−4.2 (−21.8, 13.3)	0.64
>3.8	193	522.8 (86.6)		
HDL cholesterol, mmol/L				
≤1.2	197	516.2 (83.4)	−9.1 (−26.7, 8.4)	0.31
>1.2	194	525.3 (92.8)		
Current smoker				
Yes	89	533.3 (91.4)	16.3 (−4.5, 37.2)	0.12
No	302	517.0 (87.0)		
History of diabetes				
Yes	64	517.9 (89.0)	−3.4 (−27.1, 20.4)	0.78
No	327	521.2 (88.2)		
History of hypertension				
Yes	244	519.1 (86.0)	−4.2 (−22.3, 14.0)	0.65
No	147	523.3 (92.0)		
History of myocardial infarction				
Yes	48	506.5 (89.6)	−16.2 (−42.9, 10.5)	0.23
No	343	522.7 (87.9)		
History of stroke or transient ischemic attack				
Yes	66	518.3 (72.8)	−2.9 (−26.3, 20.5)	0.81
No	325	521.2 (91.1)		
History of any vascular disease				
Yes	172	517.2 (84.2)	−6.3 (24.0–11.4)	0.49
No	219	523.4 (91.3)		

CI indicates confidence interval.
Continuous variates were dichotomized at the median.

Discussion

In this elderly population at risk for vascular disease, we found a significant decline in total CBF over an average period of 33 months. This reduction was not influenced by 40 mg pravastatin daily and disappeared when we corrected for the concomitant decrease in brain parenchymal volume.

A previous cross-sectional study estimated the age-dependent decline in CBF in a small group of 88-year-old subjects at 4.8 mL/min per year.[1] In this age group of 70 to 82 years, we found a decline of 5.8 mL/min per year. However, when total CBF was expressed per unit brain parenchymal volume, CBF did not decline with increasing age. This indicates that in the elderly, perfusion of brain tissue is kept constant, most likely by the same vascular autoregulatory mechanisms operative at younger ages.[18,19] Although the causal relation between brain tissue and total CBF in the elderly is yet unclear, the present finding indicates that the reduction in total CBF with increasing age may be caused by a reduction in brain volume and not primarily by a reduction in brain perfusion.

In contrast to animal studies, in our study we found no effect of pravastatin on total CBF. We have shown previously that our method is sensitive to detect CBF changes, based on widespread small-vessel disease.[20] Therefore, we also expected to demonstrate total CBF changes due to atherosclerosis of the large vessels. However, our results provide evidence that statins do not preserve brain perfusion and are consistent with earlier reports of PROSPER that treatment with 40 mg pravastatin daily does not reduce the risk of cerebral vascular disease in an elderly population.[12]

We found a significant difference in CBF between men and women. We think that this difference does not affect the interpretation of our results because (1) the decline in CBF over time was analyzed with paired *t* tests, which takes into account intraindividual differences, and (2) the distribution of men and women was similar

TABLE 3. Mean Total CBF (SD), Parenchymal Volume (SD), and CBF per cm³ of Parenchymal Volume (SD) at Baseline and After an Average Follow-Up of 33 Months

	Placebo (n=198)			Pravastatin (n=193)		
	Baseline	Follow-Up	Mean Difference (95% CI)	Baseline	Follow-Up	Mean Difference (95% CI)
Total CBF, mL/min	521 (83)	504 (92)	−17.7 (−29.5, −5.8)*	520 (94)	506 (92)	−14.0 (−25.5, −2.4)†
Parenchymal volume, cm³	1045 (101)	1021 (98)	−24.1 (−28.3, −19.9)‡	1025 (102)	1004 (100)	−21.9 (−26.1, −17.7)‡
Total CBF by parenchymal volume, mL/min per cm³	0.501 (0.080)	0.494 (0.085)	−0.006 (−0.018, 0.006)§	0.508 (0.091)	0.506 (0.088)	−0.001 (−0.013, 0.010)¶

*P=0.0036, †P=0.018, ‡P<0.001, §P=0.32, ¶P=0.86.

in the placebo and pravastatin groups. Moreover, current smoking was more prevalent in the placebo group. This could have caused a greater decline in CBF over time compared with the group treated with pravastatin. This means that any possible benefit of pravastatin on CBF would have been more pronounced. Therefore, we think that the unequal distribution of smoking between the 2 treatment groups did not influence our results.

In conclusion, in this study we found a significant decline in CBF with increasing age that was explained by a concomitant reduction in brain volume. Both the uncorrected change of CBF over time and the change in CBF corrected for parenchymal volume were not influenced by 40 mg pravastatin daily.

Appendix

PROSPER Study Group

Executive Committee:

(Glasgow) J. Shepherd (chairman and principal investigator), S.M. Cobbe, I. Ford, A. Gaw, P.W. Macfarlane, C.J. Packard, D.J. Stott; (Leiden) G.J. Blauw (principal investigator), E.L.E.M. Bollen, A.M. Kamper, R.G.J. Westendorp; (Cork) M.B. Murphy (principal investigator), B.M. Buckely, M. Hyland, I.J. Perry.

Endpoint Committee:

S.M. Cobbe (chairman), W.J. Jukema, P.W. Macfarlane, A.E. Meinders, D.J. Stott, B.J. Sweeny, C. Twomey.

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