A MRI study into the effect of pravastatin on cerebrovascular pathologies

Dam, V.H. ten

4. Impact of cardiovascular risk factors on the progression of periventricular and deep white matter hyperintensities

DMJ van den Heuvel, VH ten Dam, AJM de Craen, F Admiraal-Behloul, ELEM Bollen, HM Murray, GJ Blauw, RGJ Westendorp, MA van Buchem

Abstract

We longitudinally investigated the association between various cardiovascular risk factors and the presence and progression of deep and periventricular white matter hyperintensities (WMH) in a sample of 554 non-demented subjects at risk for vascular disease. All data come from the nested MRI substudy of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). Dual Echo MR images at baseline and after a mean follow-up of 33 (SD 1.4) months were obtained from all subjects. Volumes of deep and periventricular WMHs were assessed semi-automatically. All subjects had various measurements of cardiovascular risk factors taken at baseline. Linear mixed models were used to assess the association between cardiovascular risk factors and baseline WMH volumes as well as between these risk factors and change in WMH volumes over time.

In the cross-sectional analysis, history of hypertension was significantly associated with volume of total ($p=0.029$) and deep WMH ($p=0.025$). In the longitudinal analysis, smoking at baseline was significantly associated with the 3-year progression of total ($p=0.034$) and periventricular WMH ($p=0.017$). After adjustment for prevalent and incident cerebral infarcts, the association between history of hypertension and baseline total WMH volume weakened ($p = 0.053$), while the association with baseline deep WMH remained ($p = 0.046$). Moreover, the longitudinal association between smoking and progression of total and periventricular WMH persisted ($p = 0.037$ and $p = 0.018$, respectively). We found history of hypertension to be related to presence of deep WMHs and smoking to be associated with periventricular WMHs. This indicates that different pathological processes probably underlie the development of deep and periventricular WMHs.

Introduction

Cerebral white matter hyperintensities (WMHs) are frequently observed on magnetic resonance images (MRI) of elderly individuals [1-4]. Although WMHs have been related to cognitive disability and depressive symptoms [3, 5, 6], their clinical relevance in the elderly is not yet fully understood.

WMHs are thought to be a consequence of arteriosclerosis, cerebral hypoperfusion, and ischemia [4, 7, 8]. Cross-sectional MRI studies have revealed a number of risk factors for WMHs including age [1, 9, 10], hypertension [1, 11-13], high and low blood pressure levels [11,14], smoking [13], and a history of vascular and cerebrovascular disease [1,15]. In longitudinal studies with serial MRI, blood pressure [16-18] and hypertension [16, 19] have been found independent predictors of progression of WMHs in elderly individuals. These observations provide support for a causal relationship between vascular disease and the development of WMHs [16-21].

Pathological studies have suggested that the etiology of WMHs in the periventricular area is different from the etiology in the subcortical or deep white matter [22-24]. Therefore, risk factors for the development of periventricular WMHs might be different from risk factors for deep WMHs [2-, 25, 26]. In the present study we investigated the association between various cardiovascular risk factors and the presence and progression of periventricular and deep WMHs in a non-demented elderly population.

Methods

Setting All data in this study are from the MRI substudy of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). The PROSPER study was a randomised, double blind, placebo-controlled trial testing the hypothesis that treatment with pravastatin 40 mg/day would reduce the risk of vascular disease in elderly men and women with pre-existing vascular disease or with a significant risk of developing this condition [27,28].

Subjects Inclusion and exclusion criteria of the PROSPER study have been described in detail elsewhere [27,28]. Of the 1100 Dutch PROSPER participants, all aged 70-82 years at baseline, 646 consented for participation in the MRI substudy. From these original 646 subjects, 92 dropped out of the study. Seven participants were claustrophobic during the first MRI and two had no MRI due to technical problems. By the time of follow-up 40 subjects had died, 3 subjects had developed a contraindication for MRI, 6 had withdrawn informed consent, and 34 subjects refused a second MRI because of claustrophobia or illness. Hence, a total number of 554 subjects had a MRI measurement at baseline and at end of follow-up. Loss of participants to follow-up was studied. Compared with the follow-up participants the dropouts had higher total baseline WMH volume and more often had a history of myocardial infarction.

Image acquisition MRI was performed on a clinical MR-system operating at 1.5 Tesla field strength (Philips Medical Systems, Best, the Netherlands). Dual fast spin echo images (echo time (TE) 27/120 ms, repetition time (TR) 3000ms, echo train length factor 10, 48 continuous 3 mm slices, matrix 256x256, field of view (FOV) 220). Fluid Attenuated Inversion Recovery (FLAIR) (TE 100 ms, TR 8000 ms, 48 continuous 3 mm slices, matrix 256x256, FOV 220) and Susceptibility-weighted (TE 48 ms, TR 2593 ms, 22 slices, matrix 256x256, FOV 220) images were obtained from all 554 subjects at baseline and after a mean follow-up of 33 (SD 1.4) months.

WMH measurements For post processing, the dual fast spin echo images were transferred to an offline workstation. Quantification of volume of WMHs was performed using in-house developed semi-automated software [29]. By combining fuzzy clustering, connectivity rules and mathematical morphology, WMH segmentations were automatically generated. WMHs were defined as hyperintense lesions on both proton density and T2-weighted images. WMHs connected to the lateral ventricles were categorised as periventricular. WMHs not connected to the lateral ventricles were categorised as deep. To correct for misclassification of cerebrospinal fluid (CSF) and grey matter as WMH, the automatically generated WMH segmentations were manually edited by two trained raters (DMJvdH and

VHtD). FLAIR hardcopies were used as a reference to rule out other pathologies and the entanglement of WMH with Virchow-Robin spaces. Infratentorial lesions (brain stem and cerebellum) were excluded. To prevent the possibility of over-reading WMH progression in a direct scan comparison setting, we analysed baseline and follow-up MR scans in random order. Fifteen MR scans were segmented twice to assess the intra- and interrater reliability of the volumetric WMH measurements. Intraclass correlation coefficients for both periventricular and deep WMH volumes were all above 0.99.

Cerebral infarcts Cerebral infarcts were identified on hard copies by three experienced neuroradiologists. A cerebral infarct was defined as a parenchymal defect i) having the same signal intensity as CSF on all pulse sequences, ii) surrounded by a rim of tissue with increased signal intensity on T2, PD and FLAIR, iii) with a vascular distribution, and iv) without mass effect. Haemorrhagic infarcts and parenchymal haemorrhages were detected by the presence of hemosiderin on susceptibility-weighted scan and excluded. We were able to distinguish parenchymal defects of 1 mm or larger because of continuous 3 mm slices. Their location and lack of surrounding rim of high signal intensity on FLAIR images helped differentiating Virchow-Robin spaces from lacunar infarcts [30].

Risk factors Risk factors were divided into factors from subjects' medical history and factors actually measured at baseline. Past risk factors were history of diabetes, history of hypertension, history of myocardial infarction, and history of any vascular disease and were obtained by interview and by checking the medical history. Current risk factors were pulse pressure, total cholesterol and lipoprotein fractions, and smoking status. Pulse pressure was used as measure of generalized atherosclerosis and was calculated as the difference between systolic and diastolic blood pressure, which was measured on an automatic sphygmomanometer (OMRON 705 CP) with subjects in sitting position. Plasma total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglyceride concentrations were assessed by the Lipid Research Clinics Manual of Laboratory Operations [31]. Cholesterol and lipoprotein fractions were measured using

Boehringer Mannhein enzymatic reagents. Triglyceride was assessed with the fully enzymatic kit. Smoking status was obtained by interview.

Statistical analysis Statistical analyses were performed using SAS (SAS Institute, Cary, N.C., USA). Linear mixed models were used to assess the associations between the risk factors and baseline WMH volumes as well as between these risk factors and change in WMH volumes over time. In all analyses total, deep, or periventricular WMH volume were the dependent variables. The independent variables were the risk factor, visit (baseline or follow up) and the interaction between the risk factors and visit. All models were adjusted for age, gender, and treatment (placebo/pravastatin). After these analyses, all associations were also simultaneously adjusted for all other risk factors and for the presence of cerebral infarcts. The level of significance was set at $p<0.05$.

Results

Mean age of the 554 participants of our study was 75 years (SD 3.2) and 44% was female. The cardiovascular risk factors are shown in table 1. Of all subjects, 63% had a history of hypertension, while 12% had a history of myocardial infarction. At baseline, mean deep WMH volume was 1.1 mL (SD 1.6) and mean periventricular WMH volume was 4.1 mL (SD 8.5). At the end of follow up mean volume of deep WMH was 1.5 mL (SD 2.2) and volume of periventricular WMH was 5.7 mL (SD 10.0). The increase in both deep and periventricular WMH volume had increased significantly over time (both $p<0.001$).

We used linear mixed models to examine the influence of various cardiovascular risk factors on WMH volume at baseline (i.e., the cross-sectional analysis) and the rate of change in WMH volume after 33 months follow up (i.e. the longitudinal analysis). In the cross-sectional analysis, history of hypertension was significantly associated with volume of total ($p=0.029$) and deep WMH ($p=0.025$) (table 2). The association of history of hypertension with periventricular WMH volumes was borderline significant ($p=0.051$). All other vascular risk factors had no influence on either type of WMH volume at baseline (table 2). Smoking at study entry was significantly associated with the 3-year progression of total ($p=0.034$) and

periventricular WMH (p=0.017) (table 3). The other risk factors had no influence on the progression of total, deep, or periventricular WMHs.

To estimate the independent effect of each risk factor on the presence and progression of WMH we simultaneously entered all risk factors in a single full model. The significance of all results remained unaltered. Moreover, after adjusting for prevalent and incident cerebral infarcts, the association between history of hypertension and baseline total WMH volume weakened (p = 0.053), while the association with baseline deep WMH remained (p = 0.046) (data not shown). Moreover, the longitudinal association between smoking and progression of total and periventricular WMH also persisted (p = 0.037 and p = 0.018, respectively) (data not shown).

Discussion

In the present study we assessed the association between various cardiovascular risk factors and the presence and progression of periventricular and deep WMHs. Cross-sectional, we observed that a history of hypertension was related to the volume of total and deep WMHs at baseline. After adjustment for other cardiovascular risk factors and cerebral infarcts, the association between history of hypertension and deep WMH remained. In the longitudinal analyses we found current smoking status to be associated with the progression of total and periventricular WMHs. These associations remained when we adjusted for other cardiovascular risk factors and subjects with cerebral infarcts.

Cardiovascular risk factors for WMHs have been investigated in many cross-sectional studies[32]. From these studies, hypertension has been shown to be one of the main risk factors for prevalent WMHs. For example, the Cardiovascular Health Study found that history of hypertension at baseline was independently associated with severity of WMHs [1]. Moreover, the Atherosclerosis Risk in Communities Studies also found that subjects with hypertension were at increased odds of having WMHs [13]. Our cross-sectional findings are in line with these previous observations. It may take many years before hypertension causes structural changes of the cerebral small vessels, which is reflected in structural changes of

the white matter [12, 14]. Therefore, the observed association between history of hypertension and prevalence of WMHs most likely reflects such accumulated structural changes due to longstanding hypertension. The relatively short follow-up period in our study for change in WMHs might not have been sufficient to reflect this longstanding process.

The temporal relation between cardiovascular risk factors and WMHs can only be assessed by a longitudinal design. The majority of published studies had a longitudinal design, with repeated measurements of the cardiovascular risk factors (determinant) but with single measurements of the WMHs (outcome). Longitudinal studies with serial measurements of WMHs, enabling association of cardiovascular risk factors in relation to progression of WMHs, have been scarce [16-20, 33]. In the Austrian Stroke Prevention Study hypertension and diastolic blood pressure were significantly related to progression of WMHs [17, 19]. Veldink et al [18] also found that increased diastolic blood pressure was related to the progression of WMHs, whereas Martin et al [16] found systolic blood pressure to be associated. In the study of Taylor et al [33] diabetes was the most important contributor to progression of WMHs. Recently, the large population-based study reported by Longstreth et al [20] found complex relations of WMH progression with cardiovascular risk factors. In that study, smoking was the only cardiovascular risk factor to be consistently associated with progression of WMH. Our results are in line with this finding. In particular, smoking status was associated with progression of periventricular WMH.

We found deep WMHs but not periventricular WMHs to be independently associated with hypertension. In the elderly, WMHs are considered to be primarily of ischemic origin [34]. Hypertension can induce changes in the wall of cerebral blood vessels, which can eventually compromise cerebral perfusion and consequentially damage white matter. Several pathological studies have suggested that mainly deep WMHs are ischemic in origin whereas periventricular WMHs can have both an ischemic and a non-ischemic origin [22-24]. For example, besides hypoperfusion decreased interstitial fluid drainage or leakage of cerebrospinal fluid into the adjacent parenchyma could be the cause of the development of periventricular WMHs [22]. The contribution of different etiologies in the development of

periventricular WMHs might have concealed the independent contribution of ischemic risk factors, like hypertension, in the development of periventricular WMHs. We think our finding might reflect the different ischemic and non-ischemic etiologies of the WMHs.

Our study benefits from the large series of baseline and follow-up scans that were analyzed in order to measure change in WMH over time. Furthermore, in contrast with other serial MR studies on cardiovascular risk factors [16-20, 33], we used a volumetric method of quantifying both deep and periventricular WMH. A possible limitation of our study is the relatively short follow up period. With short follow up periods the progression of WMHs is likely to be small. Moreover, we were not able to further explore the observed relation between a history of hypertension and presence and progression of WMHs because the available information on the history of hypertension was limited.

In summary, we found history of hypertension to be related to volume of total and deep WMHs and current smoking status to be associated with the progression of total and periventricular WMHs. Our data indicate that the development and progression of WMHs may take many years and that different pathological processes probably underlie the development of deep and periventricular WMHs. In view of preventive and therapeutic intervention it is essential to further identify these pathological processes, and the risk factors contributing to it, in large-scale long-term prospective follow-up studies.

References

1. Longstreth WT jr, Manolio TA, Arnold A, Burke GL, Bryan N, Jungreis CA, Enright PL, O'Leary D, Fried L: Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people The Cardiovascular Health Study. *Stroke* 1996;27:1274-1282.
2. Ylikoski A, Erkinjuntti T, Raininko R, Sarna S, Sulkava R, Tilvis R: White matter hyperintensities on MRI in the neurologically nondiseased elderly Analysis of cohorts of consecutive subjects aged 55 to 85 years living at home. *Stroke* 1995;26:1171-1177.
3. De Groot JC, De Leeuw FE, Oudkerk M, Van Gijn J, Hofman A, Jolles J, Breteler MM: Cerebral white matter lesions and cognitive function: the Rotterdam Scan Study. *Ann Neurol* 2000;47:145-151.
4. Awad IA, Spetzler RF, Hodak JA, Awad CA, Carey R: Incidental subcortical lesions identified on magnetic resonance imaging in the elderly I. Correlation with age and cerebrovascular risk factors. *Stroke* 1986;17:1084-1089.
5. Barber R, Scheltens P, Gholkar A, Ballard C, McKeith I, Ince P, Perry R, O'Brien J: White matter lesions on magnetic resonance imaging in dementia with Lewy bodies Alzheimer's disease vascular dementia and normal aging. *J Neurol Neurosurg Psychiatry* 1999;67:66-72 .
6. O'Brien J, Desmond P, Ames D, Schweitzer I, Harrigan S, Tress B: A magnetic resonance imaging study of white matter lesions in depression and Alzheimer's disease. *Br J Psychiatry* 1996;168:477-485.
7. Van Swieten JC, van den Hout JH, van Ketel BA, Hijdra A, Wokke JH, Van Gijn J: Periventricular lesions in the white matter on magnetic resonance imaging in the elderly A morphometric correlation with arteriolosclerosis and dilated perivascular spaces *Brain* 1991;114(Pt 2):761-774.
8. Meyer JS, Kawamura J, Terayama Y: White matter lesions in the elderly. *J Neurol Sci* 1992;110:1-7.
9. Lindgren A, Roijer A, Rudling O, Norrving B, Larsson EM, Eskilsson J, Wallin L, Olsson B, Johansson BB: Cerebral lesions on magnetic resonance imaging heart disease and vascular risk factors in subjects without stroke. A population-based study. *Stroke* 1994;25:929-934.
10. Longstreth WT Jr, Dulberg C, Manolio TA, Lewis MR, Beauchamp NJ, Jr O'Leary D, Carr J, Furberg CD: Incidence manifestations and predictors of brain infarcts defined by serial cranial magnetic resonance imaging in the elderly: the Cardiovascular Health Study. *Stroke* 2002;33:2376-2382.

11. Dufouil C, Kersaint-Gilly A, Besancon V, Levy C, Auffray E, Brunnereau L, Alperovitch A, Tzourio C: Longitudinal study of blood pressure and white matter hyperintensities: the EVA MRI Cohort. *Neurology* 2001;56:921-926.
12. De Leeuw FE, De Groot JC, Oudkerk M, Witteman JC, Hofman A, Van Gijn J, Breteler MM: Hypertension and cerebral white matter lesions in a prospective cohort study. *Brain* 2002;125:765-772.
13. Liao D, Cooper L, Cai J, Toole JF, Bryan NR, Hutchinson RG, Tyroler HA: Presence and severity of cerebral white matter lesions and hypertension its treatment and its control: The ARIC Study Atherosclerosis Risk in Communities Study. *Stroke* 1996;27:2262-2270.
14. van Dijk EJ, Breteler MM, Schmidt R, Berger K, Nilsson LG, Oudkerk M, Pajak A, Sans S, De Ridder M, Dufouil C, Fuhrer R, Giampaoli S, Launer LJ, Hofman A: The association between blood pressure hypertension and cerebral white matter lesions: cardiovascular determinants of dementia study. *Hypertension* 2004;44:625-630 .
15. Breteler MM, Van Swieten JC, Bots ML, Grobbee DE, Claus JJ, van den Hout JH, van Harskamp F, Tanghe HL, de Jong PT, Van Gijn J: Cerebral white matter lesions vascular risk factors and cognitive function in a population-based study: the Rotterdam Study. *Neurology* 1994;44:1246-1252 .
16. Martin CGM, Van Swieten JC, Scheltens P, Pieterman H, Breteler MM: Change in white matter lesions in 60 healthy elderly over a 5 years period. *J Neurol* 1997;244: suppl 3 (S23).
17. Schmidt R, Fazekas F, Kapeller P, Schmidt H, Hartung HP: MRI white matter hyperintensities: three-year follow-up of the Austrian Stroke Prevention Study. *Neurology* 1999;53:132-139.
18. Veldink JH, Scheltens P, Jonker C, Launer LJ: Progression of cerebral white matter hyperintensities on MRI is related to diastolic blood pressure. *Neurology* 1998;51:319-320.
19. Schmidt R, Enzinger C, Ropele S, Schmidt H, Fazekas F: Progression of cerebral white matter lesions: 6-year results of the Austrian Stroke Prevention Study. *Lancet* 2003;361:2046-2048.
20. Longstreth WT Jr, Arnold AM, Beauchamp NJ Jr, Manolio TA, Lefkowitz D, Jungreis C, Hirsch CH, O'Leary DH, Furberg CD: Incidence manifestations and predictors of worsening white matter on serial cranial magnetic resonance imaging in the elderly: the Cardiovascular Health Study. *Stroke* 2005;36:56-61.

21. Charil A, Zijdenbos AP, Taylor J, Boelman C, Worsley KJ, Evans AC, Dagher A: Statistical mapping analysis of lesion location and neurological disability in multiple sclerosis: application to 452 patient data sets. *Neuroimage* 2003;19:532-544.
22. Fazekas F, Kleinert R, Offenbacher H, Schmidt R, Kleinert G, Payer F, Radner H, Lechner H: Pathologic correlates of incidental MRI white matter signal hyperintensities. *Neurology* 1993;43:1683-1689.
23. Leifer D, Buonanno FS, Richardson EP Jr: Clinicopathologic correlations of cranial magnetic resonance imaging of periventricular white matter. *Neurology* 1990;40:911-918.
24. Braffman BH, Zimmerman RA, Trojanowski JQ, Gonatas NK, Hickey WF, Schlaepfer WW (1988) Brain MR: pathologic correlation with gross and histopathology 2 Hyperintense white-matter foci in the elderly. *AJR Am J Roentgenol* 1988;151:559-566.
25. De Leeuw FE, De Groot JC, Bots ML, Witteman JC, Oudkerk M, Hofman A, Van Gijn J, Breteler MM: Carotid atherosclerosis and cerebral white matter lesions in a population based magnetic resonance imaging study. *J Neurol* 2000;247z;291-296.
26. De Leeuw FE, De Groot JC, Oudkerk M, Kors JA, Hofman A, Van Gijn J, Breteler MM: Atrial fibrillation and the risk of cerebral white matter lesions. *Neurology* 2000; 54:1795-1801.
27. Shepherd J, Blauw GJ, Murphy MB, Cobbe SM, Bollen EL, Buckley BM, Ford I, Jukema JW, Hyland M, Gaw A, Lagaay AM, Perry IJ, Macfarlane PW, Meinders AE, Sweeney BJ, Packard CJ, Westendorp RG, Twomey C, Stott DJ. The design of a prospective study of Pravastatin in the Elderly at Risk (PROSPER). PROSPER Study Group PROspective Study of Pravastatin in the Elderly at Risk. *Am J Cardiol* 1999;84:1192-1197.
28. Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, Ford I, Gaw A, Hyland M, Jukema JW, Kamper AM, Macfarlane PW, Meinders AE, Norrie J, Packard CJ, Perry IJ, Stott DJ, Sweeney BJ, Twomey C, Westendorp RG: Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002;360:1623-1630.
29. van der Flier WM, Middelkoop HA, Weverling-Rijnsburger AW, Admiraal-Behloul F, Spilt A, Bollen EL, Westendorp RG, van Buchem MA: Interaction of medial temporal lobe atrophy and white matter hyperintensities in AD. *Neurology* 2004;62: 1862-1864.
30. Bokura H, Kobayashi S, Yamaguchi S. Distinguishing silent lacunar infarction from enlarged Virchow-Robin spaces: a magnetic resonance imaging and pathological study. *J Neurol* 1998;245:116-122.

31. Lipid Research Clinics Program. Lipid and Lipoprotein Analysis Manual of Laboratory Operations. 1974 Vol 1 Department of Health Education and welfare Publication No 75-628 National Institutes of Health Bethesda MD.
32. Kuo HK, Lipsitz LA: Cerebral white matter changes and geriatric syndromes: is there a link? *J Gerontol A Biol Sci Med Sci* 2004;59:818-826.
33. Taylor WD, MacFall JR, Provenzale JM, Payne ME, McQuoid DR, Steffens DC, Krishnan KR: Serial MR Imaging of Volumes of Hyperintense White Matter Lesions in Elderly Patients: Correlation with Vascular Risk Factors. *AJR Am J Roentgenol* 2003;181:571-576

Table 1:. Clinical characteristics study sample (N = 554) at baseline.

Risk factors	
History	
diabetes (yes/no)	91 (16.4)
hypertension (yes/no)	350 (63.2)
myocardial infarction (yes/no)	67 (12.1)
any vascular disease (yes/no)	241 (43.5)
Measured at baseline	
Pulse pressure (mmHg)	71.7 (17.4)
Total cholesterol (mmol/L)	5.8 (0.8)
LDL cholesterol (mmol/L)	3.9 (0.7)
HDL cholesterol (mmol/L)	1.2 (0.3)
Triglyceride (mmol)	1.5 (0.7)
Smoking (yes/no)	115 (20.8)

Data shown are mean (SD) for continuous variables and n (%) for categorical variables.
LDL; low-density lipoprotein. HDL; high-density lipoprotein.

Table 2: Cross-sectional associations of cardiovascular risk factors with volume of total, deep, and periventricular WMHs.

Risk factor	total WMH			deep WMH			periventricular WMH		
	β	SE	p	β	SE	p	β	SE	p
History									
Diabetes (yes/no)	-0.69	1.08	0.46	-0.19	0.18	0.32	-0.48	0.96	0.53
Hypertension (yes/no)	1.98	0.85	0.029*	0.27	0.15	0.025*	1.62	0.76	0.051
Myocard infarction (yes/no)	0.32	1.24	0.95	0.03	0.21	0.83	0.34	1.10	0.98
Any vascular disease (yes/no)	-0.35	0.82	0.90	0.06	0.14	0.57	-0.40	0.73	0.80
Measured at baseline									
Pulse pressure (mm Hg)	0.01	0.02	0.84	-0.00	0.00	0.81	0.01	0.02	0.86
Total cholesterol (mmol/L)	0.11	0.49	0.98	-0.05	0.08	0.91	0.10	0.44	0.92
LDL cholesterol (mmol/L)	0.11	0.55	0.98	-0.05	0.09	0.92	0.11	0.49	0.92
HDL cholesterol (mmol/L)	0.57	1.31	0.57	0.06	0.22	0.45	0.36	1.16	0.71
Triglyceride (mmol)	0.07	0.60	0.94	-0.00	0.10	0.98	0.06	0.53	0.91
Smoking (yes/no)	-0.30	1.01	0.94	0.25	0.17	0.22	-0.42	0.90	0.98

Associations were assessed by linear mixed models, adjusted for age, sex and treatment (placebo/pravastatin). Each estimate presents the baseline association of cerebrovascular risk factors with WMH volumes. *p<0.05. WMH; White matter hyperintensities. LDL; low-density lipoprotein. HDL; high-density lipoprotein. WMH volumes are absolute measurements (mL)

Table 3: Longitudinal associations of baseline risk factors with change in volume of total, deep, and periventricular WMH after three years of follow up.

Risk factor	total WMH			deep WMH			periventricular WMH		
	β	SE	p	β	SE	p	β	SE	p
History									
Diabetes (yes/no)	-0.38	0.39	0.33	-0.03	0.12	0.81	-0.35	0.36	0.33
Hypertension (yes/no)	0.12	0.30	0.71	0.18	0.09	0.052	-0.06	0.28	0.82
Myocard infarction (yes/no)	-0.80	0.45	0.074	-0.16	0.14	0.25	-0.64	0.41	0.12
Any vascular disease (yes/no)	0.47	0.30	0.11	0.05	0.09	0.56	0.41	0.27	0.13
Measured at baseline									
Pulse pressure (mm Hg)	-0.00	0.01	0.74	0.00	0.00	0.077	-0.01	0.01	0.34
Total cholesterol (mmol/L)	-0.19	0.17	0.26	0.09	0.05	0.094	-0.28	0.16	0.075
LDL cholesterol (mmol/L)	-0.25	0.20	0.20	0.09	0.06	0.16	-0.33	0.18	0.063
HDL cholesterol (mmol/L)	0.47	0.46	0.31	0.25	0.14	0.080	0.22	0.42	0.60
Triglyceride (mmol)	-0.23	0.22	0.28	0.00	0.07	0.99	-0.24	0.20	0.24
Smoking (yes/no)	0.77	0.36	0.034*	-0.03	0.11	0.80	0.79	0.33	0.017*

Associations were assessed by linear mixed models, adjusted for age, sex and treatment. Each estimate presents the longitudinal effect of baseline cerebrovascular risk factors on decline in WMH volumes after three years of follow up. *$p<0.05$. WMH; White matter hyperintensities. LDL; low-density lipoprotein. HDL; high-density lipoprotein. WMH volumes are absolute measurements (mL)