Prestroke Statins, Progression of White Matter Hyperintensities, and Cognitive Decline in Stroke Patients with Confluent White Matter Hyperintensities

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Abstract Cerebral white matter hyperintensities (WMH) are a consequence of cerebral small vessel disease. Statins have been shown to reduce recurrent stroke among patients with various stroke subtypes, including lacunar stroke, which also arises from small vessel disease. In this study, we investigated the hypothesis that prestroke statin use would reduce the progression of WMH and/or cognitive decline among stroke patients with confluent WMH. Patients (n=100) were participants of the VITamins To Prevent Stroke magnetic resonance imaging substudy. All patients had confluent WMH on magnetic resonance imaging at baseline. Eighty-one patients completed the 2-year follow-up. We assessed general cognition and executive function using the mini-mental state examination and Mattis dementia rating scale–initiation/perseveration subscale, respectively. We compared the change in volume of WMH and cognition between prestroke statin use and

prestroke nonstatin use groups. We also evaluated the effects of prestroke statin use on incident lacunes and microbleeds. The prestroke statin use group (n=51) had less WMH volume progression ($1.54 \pm 4.52 \text{ cm}^3$ vs $5.01 \pm 6.00 \text{ cm}^3$, $p=0.02$) compared with the prestroke nonstatin use group (n=30). Multivariate linear regression modeling identified prestroke statin use as an independent predictor of WMH progression ($\beta=-0.31$, $p=0.008$). Prestroke statin use was also associated with less decline (Mattis dementia rating scale–initiation/perseveration subscale; $\beta=0.47$, $p=0.001$). No association was observed with changes in mini-mental state examination scores. There were no between group differences on incident lacunes or incident microbleeds. Prestroke statin use may reduce WMH progression and decline in executive function in stroke patients with confluent WMH.

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Introduction

Confluent white matter hyperintensities (WMH) on magnetic resonance imaging (MRI) are common among elderly patients, and are closely associated with cognitive impairment and dementia [1, 2]. Confluent WMH tend to progress rapidly, and WMH progression parallels cognitive decline [3]. Given the clinical consequences of confluent WMH and its progression, authorities have proposed that studies and clinical trials in vascular cognitive impairment should target confluent WMH, and use the progression of WMH as a surrogate marker [1, 4].

Confluent WMH are currently considered to result from cerebral small vessel disease. Vascular risk factors, particularly hypertension, are strongly associated with the presence and

progression of WMH [5]. Control of hypertension has been shown to delay WMH progression in stroke patients, especially among those with severe WMH at baseline [6].

Thus far, only a few studies have assessed the effect of statins in slowing the progression of small vessel disease-related brain changes. The Cardiovascular Health Study, an observational population-based study, examined the association of statin use with changes in white matter measures on serial MRI scans over a 5-year period. The authors described no differences in evolution of white matter measures between treated and nontreated groups. Data from treatment trials on statin effects on small vessel disease-related brain lesions arise from *post hoc* analyses [7]. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study showed that statins reduced incident strokes across various stroke subtypes, including lacunar stroke. Data on the effects of statins on WMH are controversial [8]. While the Regression of Cerebral Artery Stenosis (ROCAS) study reported less WMH progression among a small subset of stroke-free patients who had WMH at baseline compared with placebo, no such effect was found in the MRI substudy of the Prospective Study of Pravastatin in Elderly at Risk (PROSPER) [9].

In this study, we aimed to investigate the effects of prestroke statins and possible interactive effects between prestroke statins and vitamin B (Vit B) supplementation, and between prestroke statins and antihypertensive drugs upon WMH progression and cognitive decline in stroke patients with confluent WMH at baseline. We also explored the association between prestroke statin use with incident lacunes and microbleeds, which are also consequences of cerebral small vessel disease. We hypothesized that prestroke statin use might reduce the progression of WMH and/or cognitive decline.

Methods

Subjects

Subjects were participants of the VITamins TO Prevent Stroke (VITATOPS) study, which is a multicenter, randomized, double-blind, placebo-controlled trial evaluating the effects of homocysteine-lowering treatment using B vitamins (2 mg folic acid, 25 mg vitamin B6, and 0.5 mg vitamin B12) on secondary stroke prevention (clinical trial: NCT00097669) [10]. In our center, we recruited ischemic stroke patients with confluent WMH on MRI. We defined confluent WMH as a score of ≥ 2 based on the Age-related White Matter Changes scale [11] in at least 1 brain region. The details of the MRI substudy in our center have previously been published [12]. Briefly, all patients were recruited from the acute stroke unit of the Prince of Wales Hospital in Hong Kong. Brain MRI examinations were performed within 1 week of

hospitalization. We classified stroke subtypes into large-artery disease, cardioembolism, small vessel disease, and undetermined cause. Recruitment began in October 2004 and was completed in November 2006. Medical history (hypertension, hyperlipidemia, diabetes mellitus, ischemic heart disease, smoker, drinker, and medications) and laboratory tests [fasting lipids profile: low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein-cholesterol, total cholesterol (TC), and total triglyceride, vitamin B12 levels, folate, and homocysteine] were obtained for all available patients at admission and at 2-year follow-up. Strategies for secondary stroke prevention and management of vascular risk factors, including statin use, followed international guidelines [13]. All patients provided written informed consent, and the study was approved by the joint Chinese University of Hong Kong and New Territories East Cluster clinical research ethics committee. A total of 100 patients were recruited; 16 were discontinued from the study because of reaching study endpoints of death ($n=5$) or incident nonfatal stroke ($n=11$). Among the five deaths, one was due to fatal stroke. No patients were lost to follow-up. Thus, 84 patients had repeated MRI data. However, interpretation of MRI images in 3 patients was not possible because of poor resolution or movement artifact. Thus, 81 patients were included in this study. There were no significant differences in age, education, vascular risk factors profile, and imaging features (baseline WMH volume, number of infarcts, and presence of microbleeds) between patients included and not included in the study [12].

MRI Imaging Variables

All MRI examinations were performed using a 1.5-Tesla scanner (Sonata; Siemens Medical System, Erlangen, Germany) with a standard protocol, including T1-weighted imaging (Repetition time/Echo time (TR/TE) = 425/14 ms), T2-weighted imaging (TR/TE=2500/120 ms), fluid attenuated inversion recovery (FLAIR; TR/TE=8000/100 ms), and gradient recall echo T2*-weighted MRI (TR/TE=350/30 ms), all with 5-mm slice thickness, 0.5-mm slice gap, a field of view of 230 mm, a matrix size of 256 $\times$ 256, and time-of-flight magnetic resonance angiography.

Neuroimaging measurements were conducted by an expert rater at another center (Austria), who was blinded to the patients' clinical data. WMH volume was quantified using a semiautomated local thresholding technique on the FLAIR sequence, as previously described [14, 15]. Briefly, lesion load measurements were done on FLAIR images on a LINUX workstation by a trained operator using DISPIImage [16]. All lesions were outlined on the computer image, and the lesion areas were then provided by the DISPIImage program. The total lesion volume (cm³) was calculated by multiplying the total lesion area by slice thickness. Details on the

methodology and the reproducibility of the volumetric assessments of WMH have been described previously [15]. In case of errors in the automatic lesion definition because of structures with similar signal intensity, the lesions were traced manually by the operator.

Lacunes were defined as focal lesions of cerebrospinal fluid signal intensity that involved the basal ganglia, internal capsule, thalamus, white matter, or brain stems, not exceeding a diameter of 15 mm. We recorded incident lacunes, which were consistent lesions not present on the baseline scan. Microbleeds were defined as rounded areas of signal loss, 2–10 mm in diameter on gradient-echo T2*-weighted MRI [17]. We recorded incident microbleeds and the number of new microbleeds.

Cognitive Assessment

We assessed changes in global cognition and executive function using the Chinese mini-mental state examination (MMSE) [18] and the Mattis dementia rating scale–initiation/perseveration subscale (MDRS I/P) [19], respectively, at baseline, and at 12, 18, and 24 months. We calculated changes in MMSE and MDRS I/P using the last follow-up cognitive score minus the baseline cognitive score.

Statistical Analyses

Independent sample *t* tests, Mann–Whitney *U* tests, and χ^2 tests according to data type were used to compare prestroke statin use and prestroke nonstatin use groups on demographic data, medical history, WMH progression, incident infarcts, incident microbleeds, MMSE change, and MDRS I/P change. To determine whether prestroke statin use was associated with WMH progression, we used Pearson or Spearman rank correlation to explore the association between WMH volume progression and potential predictors (demographic data, medical history, laboratory tests, and baseline WMH volume). Next, multivariate linear regression using significant factors from univariate analysis ($p < 0.05$) was performed to identify independent predictors for WMH progression. The collinearity between variables and interaction terms of “prestroke statin use $\times$ Vit B supplementation” and “prestroke statin use $\times$ antihypertensive drugs” was also tested in the regression model. To explore the association between prestroke statin use and cognitive progression, multivariate regression with age, education years, WMH progression, and baseline cognitive scores as covariates was performed.

Results

Table 1 summarizes the comparisons between prestroke statin use and prestroke nonstatin use groups. Compared with the

prestroke nonstatin use group, the prestroke statin use group had more smokers, higher baseline TC and LDL-C, and a greater reduction in TC and LDL-C at 2-year follow-up, and tended to be younger with a higher proportion of patients taking antiplatelet drugs. Table 2 shows baseline and follow-up MRI results in the comparative subsets. At baseline, no differences in WMH volume, number of infarcts, and number of microbleeds were observed. At 2-year follow-up, the increase in WMH volume was lower in patients treated with prestroke statins (1.54 cm^3 vs 5.01 cm^3 , $p = 0.02$). No differences were observed between prestroke statin use and prestroke nonstatin use groups in incident lacunes and incident microbleeds.

The interaction term “prestroke statin $\times$ Vit B supplementation” was associated with WMH progression in the univariate correlation test ($r = -0.265$, $p = 0.022$), but “prestroke statin $\times$ antihypertensive drugs” was not correlated with WMH progression ($r = -0.212$, $p = 0.067$). Other significant variables in the univariate correlation tests for WMH progression were prestroke statin use ($r = -0.244$, $p = 0.035$), baseline TC ($r = -0.244$, $p = 0.035$), baseline LDL-C ($r = -0.303$, $p = 0.009$), and baseline WMH volume. Given the collinearity between baseline LDL-C and change in LDL-C ($r = -0.89$, $p < 0.001$), we put baseline LDL-C into a multivariate linear regression model. As can be seen in Table 3, prestroke statin use ($\beta = -0.31$, $p = 0.008$) was independently associated with WMH progression, with age, baseline TC, baseline LDL-C, “prestroke statin use Vit B supplementation”, and baseline WMH volume as covariates. Considering the unbalanced factors between prestroke statin use and prestroke nonstatin use, we performed a further linear regression with age, antiplatelet drugs, and smoking as covariates, which showed that prestroke statin use was a robust predictor ($\beta = -0.32$, $p = 0.010$) of WMH progression.

Table 4 shows the association between prestroke statin use and cognitive measures. There were no differences between the prestroke statin use groups in baseline MMSE and MDRS I/P scores. The treated group had significantly less decline in the MDRS I/P, but no significant difference was observed for changes in the MMSE (Table 4). WMH progression was associated with MDRS I/P change ($r = -0.25$, $p = 0.04$), but not with MMSE change ($r = -0.12$, $p = 0.32$). Multivariate linear regression with age, education years, baseline MDRS I/P score, and WMH progression as covariates revealed that prestroke statin use predicted a better outcome on the MDRS I/P ($\beta = 0.47$, $P = 0.001$), while WMH progression was not significant in the regression model. A further mediation analysis for prestroke statin use, WMH progression, and cognitive impairment was performed. Prestroke statin use correlated with MDRS I/P change ($r = 0.50$, $p < 0.001$) and WMH progression ($r = -0.24$, $p = 0.035$). When putting both prestroke statin use and WMH progression into the regression model with MDRS I/P change as the dependent variable, prestroke

Table 1 Patient characteristics

Variables	Prestroke nonstatin use (n=30)	Prestroke statin use (n=51)	<i>p</i>
Age (years)	76.87±7.87	73.59±7.82	0.07
Male	12 (40.0 %)	28 (54.9 %)	0.19
VITATOPS active group	16 (53.3 %)	25 (49.0 %)	0.71
Stroke mechanism			0.33
Large artery disease	9 (30.0 %)	20 (39.2 %)	
Small vessel disease	19 (63.3 %)	27 (52.9 %)	
Cardioembolism	1 (3.3 %)	0 (0 %)	
Undetermined	1 (3.3 %)	4 (7.8 %)	
Antiplatelet drugs	26 (86.7 %)	50 (98.0 %)	0.06
Hypertension	27 (90.0 %)	44 (86.3 %)	0.70
Antihypertension drugs	21 (84.0 %)	38 (74.5 %)	0.40
Hyperlipidemia	2 (6.7 %)	51 (100 %)	< 0.001
Diabetes mellitus	13 (43.3 %)	17 (33.3 %)	0.37
Ischemic heart disease	4 (13.3 %)	8 (15.7 %)	1.00
Smoker	10 (33.3 %)	29 (56.9 %)	0.04
Drinker	3 (10.0 %)	7 (13.7 %)	0.74
Baseline SBP, mmHg	154.59±16.08	152.8±21.54	0.70
Baseline DBP, mmHg	83.69±11.13	85.1±11.58	0.60
Change in SBP, mmHg	−15.04±22.52	−15.40±22.95	0.95
Change in DBP, mmHg	−6.21±15.76	−10.98±12.73	0.17
Baseline TC, mmol/L	4.67±0.65	5.19±1.02	0.01
Change in TC, mmol/L	−0.6±0.98	−1.2±1.13	0.05
Baseline LDL-C, mmol/L	2.46±0.68	3.26±0.91	< 0.001
Change in LDL-C, mmol/L	−0.22±0.86	−1.17±1.09	0.002
Baseline HDL-C, mmol/L	1.47±0.45	1.41±0.42	0.58
Change in HDL-C, mmol/L	0.1±0.31	−0.08±0.36	0.08
Baseline TG, mmol/L	1.57±0.87	1.51±0.83	0.77
Change in TG, mmol/L	−0.31±1.09	−0.05±0.79	0.28
Baseline homocysteine, μ mol/L	16.45±6.23	17.31±5.75	0.54
Change in homocysteine, μ mol/L	−2.35±5.71	−3.00±5.82	0.67
Baseline vitamin B12, pmol/L	326.9±139.41	375.96±153.54	0.16
Change in vitamin B12, pmol/L (range)	152.0 (44.5–793.8)	303.0 (12.3–647.8)	0.70
Baseline folate, nmol/L	22.94±8.62	22.62±8.27	0.87
Change in folate, nmol/L	11.31±15.15	11.58±13.43	0.94

Values given as mean±SD, unless otherwise indicated

VITATOPS = Vitamins TO Prevent Stroke; SBP = systolic blood pressure; DBP = diastolic blood pressure; TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; HDL = high-density lipoprotein-cholesterol; TG = total glyceride

statin use was significantly associated with MDRS I/P change ($\beta=0.43$, $p<0.001$), whereas WMH progression ($\beta=-0.08$, $p=0.486$) was not significant in the model.

Discussion

This observational study showed that prestroke statin use was associated with less WMH progression and less decline in executive function over a 2-year period in stroke patients with confluent WMH. There was no association between prestroke statin use and incident lacunes, or between prestroke statin use and incident microbleeds. No interaction was found between

prestroke statins and Vit B supplementation on WMH progression.

The findings of this study are consistent with those of the ROCAS study, which found that among a small subset of stroke-free patients with confluent WMH at baseline, active treatment with statin was associated with less WMH progression relative to placebo. However, our findings must be interpreted in light of the PROSPER study, which failed to find a beneficial effect of statin in retarding WMH progression compared with placebo over a mean follow-up of 33 months [9]. Note that the median WMH volume in the PROSPER study (1.8 cm³ in the placebo group and 1.6 cm³ in the active group) was 15 times smaller than in our study (~26 cm³), and

Table 2 Progression of small vessel disease between groups

MRI variables	Prestroke nonstatin use		Prestroke statin use		<i>p</i>
	(n=30)		(n=51)		
	Total	Value	Total	Value	
First MRI					
Baseline WMH volume, cm ³	28	25.6±11.1	47	26.7±19.2	0.76
Baseline number of lacunes (range)	30	3.0 (2.0–6.3)	51	3.0 (1.0–5.0)	0.25
Baseline number of microbleeds (range)	30	4.5 (0–19.0)	50	2.5 (1.0–11.7)	0.84
Second MRI					
WMH volume progression, cm ³	28	5.01±6.00	47	1.54±4.52	0.02
Incident lacunes (%)	30	3.0 (10.0)	51	4.0 (7.8)	0.71
Number of new microbleeds (range)	29	1 (0–1)	50	0 (0–1)	0.42
Incident microbleeds (%)	29	17.0 (58.6)	50	23.0 (46)	0.28

Values given as mean±SD, unless otherwise indicated

MRI = magnetic resonance imaging; WMH: white matter hyperintensities

the progression rate seen in the control group was minimal. Hence, the potential treatment effect of statin would not be easily detected in the PROSPER study [9].

We found that prestroke statin use was associated with less WMH progression irrespective of the unbalanced age, smoking, and use of antiplatelet drugs between the groups. Furthermore, the association was independent of its lipid-lowering effect, which is, again, similar to findings of the ROCAS study. Although it is tempting to postulate that the observed effects were secondary to the pleiotropic effects of statins on endothelial function [20], our study was unable to investigate the effect of statins on endothelial function. Recent evidence suggests that endothelial dysfunction of cerebral small vessels, with subsequent breakdown of the blood–brain barrier and leakage of toxic blood substances, might be a contributing factor in the pathogenesis of WMH [21]. For future trials, inclusion of endothelial markers (e.g., intracellular adhesion molecule) will help to investigate the association between prestroke statin use, endothelial function, and WMH progression.

Table 3 Predictors for white matter hyperintensity (WMH) progression

Variables	Model	
	β	<i>p</i>
Age	−0.02	0.843
Prestroke statin use	−0.31	0.008
Prestroke statin use × Vit B supplementation	−0.15	0.261
Baseline TC	−0.17	0.145
Baseline LDL-C*	−0.21	0.088
Baseline WMH volume	0.03	0.779

*Baseline LDL-C and change in LDL-C had collinearity

Vit B = vitamin B; TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol

The finding that prestroke statin use was associated with less decline in executive function compared with prestroke nonstatin use is of clinical importance. Studies among patients with small vessel disease have shown that executive function is closely associated with the performance of activities of daily living [22]. Interestingly, although WMH progression was associated with executive dysfunction in the univariate analysis, it was not significant in the multivariate analysis. This finding might possibly be explained by the small sample size of our study. A *post hoc* power calculation was performed using PASS 11.0 (NCSS, Kaysville, UT, USA); the detected power for the association between WMH progression and MDRS I/P change was 0.56, with a significance level of 0.05, which is insufficient to detect a significant association. Another explanation is that the effect of statins on cognition might be mediated by brain atrophy. Earlier analysis of the same group of patients with confluent WMH showed that executive dysfunction was mediated mainly by frontal cortical atrophy [23]. Thus, statins may retard WMH progression, leading to less brain atrophy, and finally resulting in less cognitive decline. Further study is needed to explore the relationship between prestroke statin use, WMH progression, brain atrophy, and cognitive decline.

Table 4 Cognitive progression between prestroke statin groups

Variables	Non-prestroke statin use (n=30)	Prestroke statin use (n=51)	<i>p</i>
Baseline MMSE	20.40±5.46	22.29±4.98	0.11
MMSE change	−1 (−4 to 2)	0 (−3 to 2)	0.31
Baseline MDRS I/P	24.61±6.20	26.15±5.68	0.27
MDRS I/P change	−5.21±4.68	0.63±5.63	< 0.001

Values given as mean±SD, unless otherwise indicated

MMSE = mini-mental state examination; MDRS I/P = Mattis dementia rating scale initiation/preservation subset

We did not find any difference between prestroke statin groups on incident lacunes or incident microbleeds. These data contradict the view that statin use is associated with an increased risk of intracerebral hemorrhage [8]. However, whether more aggressive statin treatment may increase the risk of incident microbleeds in stroke patients with confluent WMH requires further investigation.

The strengths of our study include the prospective design and the collection of a broad range of serial clinical, cognitive, laboratory, and imaging data. We used a validated method to quantify the volume of WMH, and all imaging measures were performed by a different center experienced in recording MRI measurements and blinded to the clinical data. However, certain limitations need to be addressed. First, this was not a randomized controlled study, and certain confounders might not have been controlled for. Second, the sample size was relatively small. Third, had no data on statin dosage, so we could not determine the dose effect on WMH progression and cognitive decline. Finally, all patients were enrolled in a clinical trial, and our results might not be generalizable to stroke patients with confluent WMH in general.

In conclusion, this study suggests that prestroke statin use may reduce WMH progression and cognitive decline among stroke patients with confluent WMH. Further clinical trials are warranted to evaluate the effects of prestroke statins upon WMH progression and cognitive decline in this group of patients. Inclusion of other surrogate markers, such as markers for endothelial activation and brain volumes, will help to better determine the mechanisms of statins' beneficial effect on cerebral small vessel disease.

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Conflict of Interests None.

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