

ORIGINAL RESEARCH

Antioxidative activity of statins and HDL-PON1 association in lacunar ischemic stroke with and without white matter hyperintensity

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Abstract

Purpose: Statins (HMG-coA reductase inhibitors) protect vessels from atherosclerosis through various mechanisms, but the clinical significance of statin-induced high-density lipoprotein cholesterol (HDL) changes has not been established. We evaluated the effects of statin treatment on the antioxidative activities of HDLs in ischemic stroke patients with and without white matter hyperintensity (WMH).

Methods: From January to December in 2013, eighty-two ischemic stroke patients (57 men, 25 women; mean age 67.0 ± 11.8 years) at the Wonkwang Medical Center were recruited retrospectively and antioxidant activity was assessed via paraoxonase 1 (PON1) activity. We studied changes in the patients' lipid profiles and assessed PON1 activity in patients with and without WMH, at baseline and 8 weeks after treatment with rosuvastatin 10 mg/d.

Results: All patients evaluated antioxidant activity using PON1 activity at admission. After 8 weeks of rosuvastatin treatment, the mean HDL concentration increased to 0.83 ± 10.1 mg/dL. The HDL levels increased in 54 patients (64.3%) and decreased in 30 patients (35.7%). PON1 activity increased to 15.0% in all patients, regardless of WMH after rosuvastatin treatment (+ 25.4% in subjects without WMH; $P < 0.001$). Baseline PON1 activity modestly correlated with HDL levels ($r = 0.365$, $P = 0.019$); however, PON1 activity after treatment did not correlate with HDL levels ($r = 0.149$, $P = 0.347$).

Conclusion: Our findings suggest that statins increase antioxidant activity, especially assessed via PON1 activity, in ischemic stroke patients who did not have WMH.

Keywords

Antioxidative effect; Ischemic stroke; Lipid profile; Paraoxonase 1; Statin; White matter hyperintensity

1. Introduction

Lowering cholesterol levels using statins has a protective effect on coronary and intracranial artery atherosclerosis [1–3]. Statins have an antioxidative effect by decreasing low-density lipoprotein (LDL) and increasing high-density lipoprotein (HDL) levels [3]. In general, statin treatment has been associated with a modest elevation of HDL levels [2]. The oxidation of LDLs leads to atherosclerotic lesions, and HDLs are known to have antioxidative properties that enable them to inhibit the oxidation of LDLs [3]. An enzyme in HDLs, HDL-associated enzyme paraoxonase 1 (PON1), plays an important role in these antioxidative processes [4]. PON1 is a calcium-dependent esterase that hydrolyses aromatic carboxylic acid esters, organophosphates, and carbamates, and it is associated with HDL [5]. PON1 plays an important role in the general prevention of peroxidative damage to cell membranes and the oxidation of biomolecules, such as LDL [6]. PON1

activity has been found to reduce the incidence of coronary artery disease by preventing the progression of atherosclerosis [7]. However, its association with cerebrovascular diseases remains unknown.

Although the pathogenesis of white matter hyperintensity (WMH) is not clearly understood, it is considered a sign of small vessel disease (SVD) associated with atherosclerosis [2]. In the case of SVD, oxidative stress damages the vasculature, causes changes in blood flow and the blood-brain barrier, and promotes neurodegenerative alterations in the brain tissue [8]. Oxidative stress is related to atherosclerosis, and atherosclerosis is a risk factor for stroke [8]. Therefore, oxidative stress may have an association with the risk of stroke [8]. And also, SVD is associated with oxidative stress. It is observed bilaterally and symmetrically on T2-weighted magnetic resonance imaging (MRI) [9]. In general, WMH is considered as a diffuse cerebral arteriopathy, and it is related to endothelial dysfunction [10]. However, how patients

with ischemic stroke are affected by the interactions between statin treatment-induced antioxidative activity and WMH is not clearly understood.

The antioxidative activities after statin therapy in patients with and without WMH were compared to define functional responses beyond HDL-C levels. Antioxidative activity in ischemic stroke patients was assessed by comparing lipid levels and PON1 activities at the beginning of and after 8 weeks of rosuvastatin treatment. We aimed to evaluate the antioxidative effects of statin treatment based on the presence of WMH. We tried to examine it using HDL-PON1, which is one of the antioxidative markers [8].

2. Methods

2.1 Patients

For this retrospective study, we evaluated 1,072 stroke patients (over 50 years old, 584 males and 488 females) who were hospitalized at the Wonkwang Medical Center (Iksan, South Korea) between January 2013 and December 2013. We excluded 332 patients who had hemorrhagic stroke and 592 patients who had other mechanisms of ischemic stroke. Total 558 patients with large-artery atherosclerosis (232 patients), cardioembolism (206 patients) and other mechanisms (120 patients), according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification [11], were excluded from the study. We also excluded 66 patients with a history of statin allergy, those receiving medication that could affect lipid levels (e.g., fish oil, niacin, ezetimibe, and probucol), and those (34 patients) with inflammatory, neoplastic, or infectious diseases. Only 82 patients with lacunar infarction, classified as small vessel occlusion according to the TOAST classification, were included (Fig. 1). All patients were treated in the same way according to the “Clinical Practice Guidelines for Stroke in Korea” [12]. All patients provided consent for the anonymization of the data in accordance with the protocol set forth by the review board of Wonkwang University Hospital (Iksan, South Korea, WKUHIRB-1460).

2.2 Serum paraoxonase and arylesterase activities of PON1 enzyme

Serum paraoxonase and arylesterase activities were determined using commercially available kits (Rel Assay Diagnostics, Mega Tip, Gaziantep, Turkey). Serum paraoxonase activity toward paraoxon was measured following the hydrolysis of paraoxon to p-nitrophenol and diethyl phosphate in the absence of NaCl (baseline activity). The molar extinction coefficient of p-nitrophenol was $17,000 \text{ M}^{-1} \text{ cm}^{-1}$ at a pH of 8; the results were expressed as U/L. Serum arylesterase activity was determined by the presence of phenol following the reaction of phenylacetate. The molar extinction coefficient of phenol was $4,000 \text{ M}^{-1} \text{ cm}^{-1}$; the results were expressed as kU/L. The total antioxidative status (TAS) assay was calibrated with a stable antioxidant standard solution, which is traditionally called the Trolox equivalent, a vitamin E analog. The results were expressed as mmol Trolox Equiv./L.

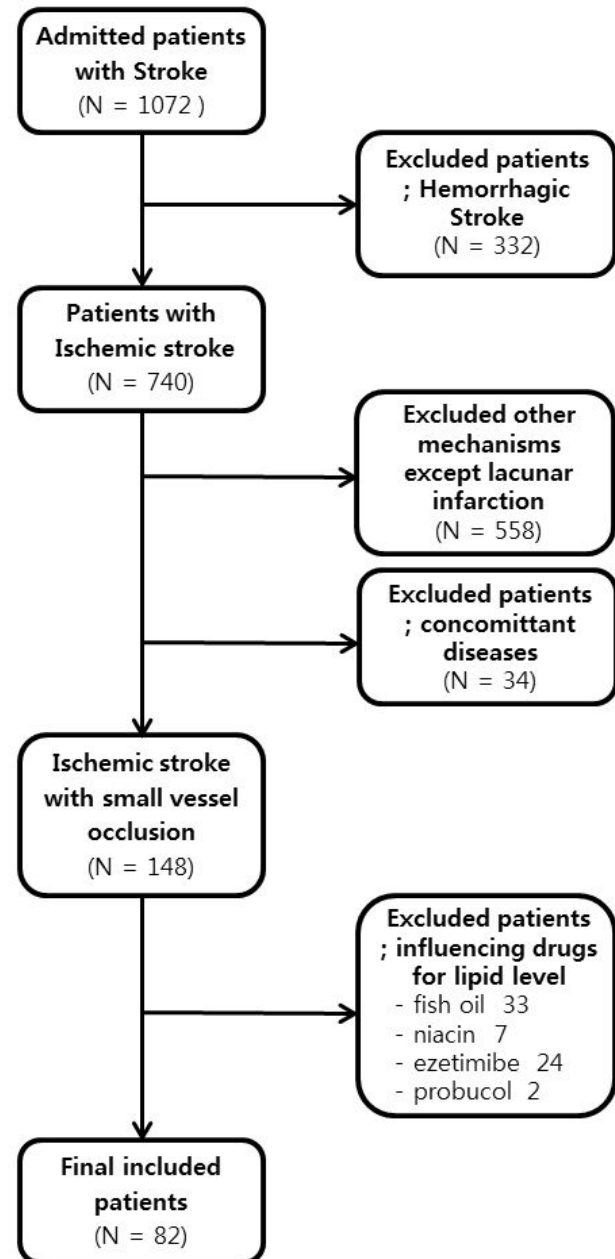


FIGURE 1. Selection of ischemic stroke with small vessel occlusion in the study cohort.

2.3 Data analysis

We investigated the demographic characteristics (age and sex) and the medical history of all the patients (hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, coronary heart disease, previous stroke history, current smoking, and heavy alcohol drinking). Moreover, laboratory tests including lipid analyses were conducted. Rosuvastatin 10 mg/d (Crestor, Cambridge, United Kingdom) was administered to all the patients after they had enrolled for statin treatment. No patient withdrew from the study due to the adverse effects of statins. The treating physician prescribed anti-hypertensive drugs, such as angiotensin-converting enzyme inhibitors, beta-blockers, and nitrates.

Two neurologists (H.G.K and J.S.C) independently evaluated all brain MRI images of the patients. To prevent bias, these physicians were neither informed of the clinical condi-

tions of the patients nor the laboratory assessments. Based on the Fazekas scale [13], WMH was assessed using white matter ratings. To evaluate and define the presence and absence of WMH, we classified Grade 0 on the scale as the absence of WMH and Grade 1 (or higher) as the presence of WMH.

Using an enzymatic colorimetric assay (U/L), total cholesterol (mg/dL), triglycerides (mg/dL), HDL-C (mg/dL), and LDL-C (mg/dL), in addition to lipid and lipoprotein (mg/dL) levels, were measured in patients who fasted overnight for 12 hours: first during the initial treatment phase (baseline) and after 8 weeks of treatment. The serum samples were analyzed using a fully automated paraoxonase activity measurement kit (Mega Tip, Gaziantep, Turkey) on the Hitachi 7600 automatic biochemical analyzer (Hitachi, Tokyo, Japan) to observe PON1 activity [14].

2.4 Statistical analysis

The demographic characteristics, medical history, and blood test results of the groups with and without WMH were compared. All the data were represented using either mean \pm standard deviation or percentage of patients (e.g., for categorical demographic characteristics). The categorical data were compared using the Chi-squared test, and Fisher's exact test was used when there were less than five variables. The continuous data were compared using independent two-sample *t*-tests. The Mann-Whitney U test was employed for non-parametric data. Pearson correlation coefficients were calculated to quantify the relationships between changes in lipid profiles and white matter and PON1 activities. All the analyses were conducted using SPSS 21.0 (IBM Corp., Armonk, NY, USA), and statistical significance was set at $P < 0.05$.

3. Results

A total of 1,072 stroke patients, 584 (54.7%) males and 488 (45.3%) females were hospitalized during the study period, and 740 (69.1%) of them were diagnosed with ischemic stroke. Eighty-two patients, also diagnosed with small vessel occlusion, were finally selected for the study after excluding patients who satisfied any of the exclusion criteria listed above (see Methods section) (Fig. 1). The mean age of all the patients in the study was 67.0 ± 11.8 years, and 25 of them (30.5%) were female. The patients were grouped into subjects with (36 patients; 43.9%) and without (46 patients; 56.1%) WMH based on the assessment of their MRI scans. The patients with WMH were significantly older than those without WMH, and the WMH group had a higher proportion of patients with diabetes than the non-WMH group (Table 1). In the group non-WMH group, no patient had previously suffered from cerebral infarction; twelve patients (26.1%) had a history of cerebral infarction in the WMH group. No other obvious differences were found between the demographical data and laboratory findings related to the presence or absence of WMH (Table 1).

The changes in laboratory findings were evaluated after an 8-week statin treatment (Rosuvastatin 10 mg, Crestor, Cambridge, United Kingdom). Regardless of the presence of WMH, total cholesterol (mg/dL), LDL (mg/dL), and Apolipoprotein A1/B1 (mg/dL) levels significantly decreased

after statin treatment in all patients (Table 2). However, for HDL (mg/dL) and PON1 (U/L) levels, we found different patterns. In the non-WMH group, both HDL (+ 8.7%, $P = 0.067$) and PON1 levels (+ 25.4%, $P < 0.001$) increased. The group that showed white matter changes did not show any significant relationship between HDL (-2.6%, $P = 0.635$) and PON1 (+ 6.5%, $P = 0.123$) levels over the course of the treatment (Table 2 & Fig. 2). Furthermore, the baseline PON1 activities correlated with HDL-C levels ($r = 0.365$, $P = 0.019$), unlike the PON1 activity after treatment, which did not correlate with HDL-C levels ($r = 0.149$, $P = 0.347$).

We also examined the TAS level before and after statin treatment. The pre-treatment TAS level in the non-WMH patients slightly increased after statin treatment (pre-treatment: 1.42 [1.39-1.56] mmol Trolox Equiv./l \rightarrow post-treatment: 1.43 [1.39-1.46] mmol Trolox Equiv./l), but the difference was not significant. The pretreatment TAS level in the WMH patients slightly decreased after statin treatment (pre-treatment: 1.55 [1.39-1.69] mmol Trolox Equiv./l \rightarrow post-treatment: 1.45 [1.42-1.55] mmol Trolox Equiv./l), but the difference was not significant.

4. Discussion

The objective of this study was to determine whether the antioxidative effects of statins were different in ischemic stroke patients with and without WMH. The main findings of this study are as follows. (1) Patients with WMH were significantly older, more often had diabetes, and were more likely to have a history of cerebral infarction than those without WMH. (2) Baseline laboratory findings showed that patients with WMH had significantly higher HDL and lower LDL and PON1 levels than patients without WMH. (3) After statin treatment, patients with WMH did not show any significant increase in HDL levels, but they showed a decrease in LDL levels. The PON1 antioxidative activity did not show any significant increase in patients with WMH. (4) In contrast, patients without WMH showed a significant decrease in LDL and increase in HDL levels and antioxidative activity after statin treatment.

Oxidative stress occurs when the physiological balance between oxidants and antioxidants is disrupted, causing damage to the organism [15]. Patients with early-stage ischemic stroke have low antioxidant levels [16]. Statins reduce cholesterol synthesis, and they affect oxidative stress through cholesterol-lowering independent effects (pleiotropic effects). And also, there are beneficial effect when first-ever ischemic stroke occurs in patient who are already pretreatment with statin [17]. Reduced oxidation due to statins plays an important role in reducing the number of dead neurons in ischemic lesions or penumbra [18]. Owing to this effect, statin treatment improves post-stroke outcomes [19], and statin pretreatment reduces infarct volume in ischemic strokes [20]. PON1, assumed to have antioxidative activity, is an enzyme in HDLs. PON1 activity is therefore an indicator of anti-inflammatory and antioxidant activities of HDL [21]. Studies related to PON1 have been reported in many diseases such as multiple sclerosis associated with brain antioxidative effects [22] or psoriasis associated with cardiovascular disease [23]. However, an association between the decrease in PON1 activity observed

TABLE 1. Demographic characteristics, medical history, and laboratory findings of ischemic stroke patients with and without white matter hyperintensity (WMH).

Variables	WMH (-) (n = 36)	WMH (+) (n = 46)	P-value
Demographics			
Age (years)	60.89 ± 11.91	71.54 ± 9.80	0.003
Female	10 (27.8)	15 (32.6)	0.742
Past History			
Hypertension	16 (44.4)	32 (69.5)	0.211
Diabetes mellitus	4 (11.1)	30 (65.2)	0.001
Dyslipidemia	6 (16.7)	4 (8.7)	0.636
Atrial fibrillation	0 (0.0)	4 (8.7)	0.498
Coronary heart disease	4 (11.1)	0 (0.0)	0.178
Previous stroke history	0 (0.0)	12 (26.1)	0.029
Current smoking	12 (33.3)	8 (17.4)	0.281
Heavy alcohol drinking	6 (16.7)	12 (26.1)	0.708
Baseline laboratory findings			
HbA1c (%)	6.08 ± 0.96	6.53 ± 1.24	0.213
hs-CRP (mg/dL)	1.24 ± 2.16	1.56 ± 2.62	0.676
D-dimer (ng/mL)	0.62 ± 0.96	0.54 ± 0.49	0.718
Fibrinogen (mg/dL)	249.58 ± 75.80	283.65 ± 79.88	0.170
Fasting glucose (mg/dL)	105.44 ± 24.99	125.71 ± 73.94	0.272
Total cholesterol (mg/dL)	199.50 ± 24.48	191.75 ± 16.09	0.223
Triglyceride (mg/dL)	143.22 ± 56.06	127.25 ± 64.26	0.405
HDL cholesterol (mg/dL)	39.39 ± 9.70	45.17 ± 9.59	0.062
LDL cholesterol (mg/dL)	118.67 ± 21.34	106.5 ± 18.28	0.054
Apoprotein A1/B1 (mg/dL)	1.25 ± 0.54	1.38 ± 0.38	0.178
Total Antioxidant status (mmol Trolox Equiv./l)	1.42 [1.39-1.56]	1.55 [1.39-1.69]	0.048
Paraoxonase 1 (U/L)	258.89 ± 105.43	249.42 ± 107.44	0.604

Values are presented as the percentage of patients (%) or mean ± SD unless otherwise indicated. Antioxidant status is indicated by the median value.

WMH = white matter hyperintensity; HbA1c = hemoglobin A1c; hs-CRP = high sensitive C-reactive protein; HDL cholesterol = high-density lipoprotein cholesterol; LDL cholesterol = low-density lipoprotein cholesterol.

in ischemic stroke and WMH is yet to be established.

In general, WMH is a sign of small vessel diseases [24]. However, it can also be a symptom of aging, and it is frequently observed in patients with diabetes. When WMH is severe, it can influence cognitive function and cause vascular dementia. In the current study, patients with WMH were older, and a higher proportion had diabetes, which was consistent with the findings of previous studies [9, 24]. And silent multiple lacunar infarction such as WMH is associated with mild neuropsychological abnormalities in patients with first-ever lacunar ischemic stroke [25]. The antioxidative effect of statins was not significant for patients with WMH; there was a significant increase in antioxidative activity for patients without WMH. Endothelium-related vasodilatation dysfunction is induced by the loss of nitric oxide activity in vessel walls, and it disrupts cerebral vascular homeostasis [26]. In consequence, it can cause chronic hypoperfusion of white

matter and trigger WMH. Reducing oxidative stress eventually improves endothelial function and decreases the risk of cardiovascular events [24]. In this study, statin treatment had a milder antioxidative effect, through PON1 activity, in patients with WMH than in those without WMH, suggesting that endothelial dysfunction influences the extent of the antioxidative effect.

5. Limitations of the study

This study has several limitations. First, to maintain the homogeneity of the sample, only a few patients were evaluated; they were patients with small vessel occlusion associated with WMH who visited a specific neurological center for ischemic stroke. Further analyses and large-scale studies are needed to confirm the results of this study. Second, this study was designed to evaluate the effects of rosuvastatin 10 mg, whereas other statins and their efficacies were not investigated. There-

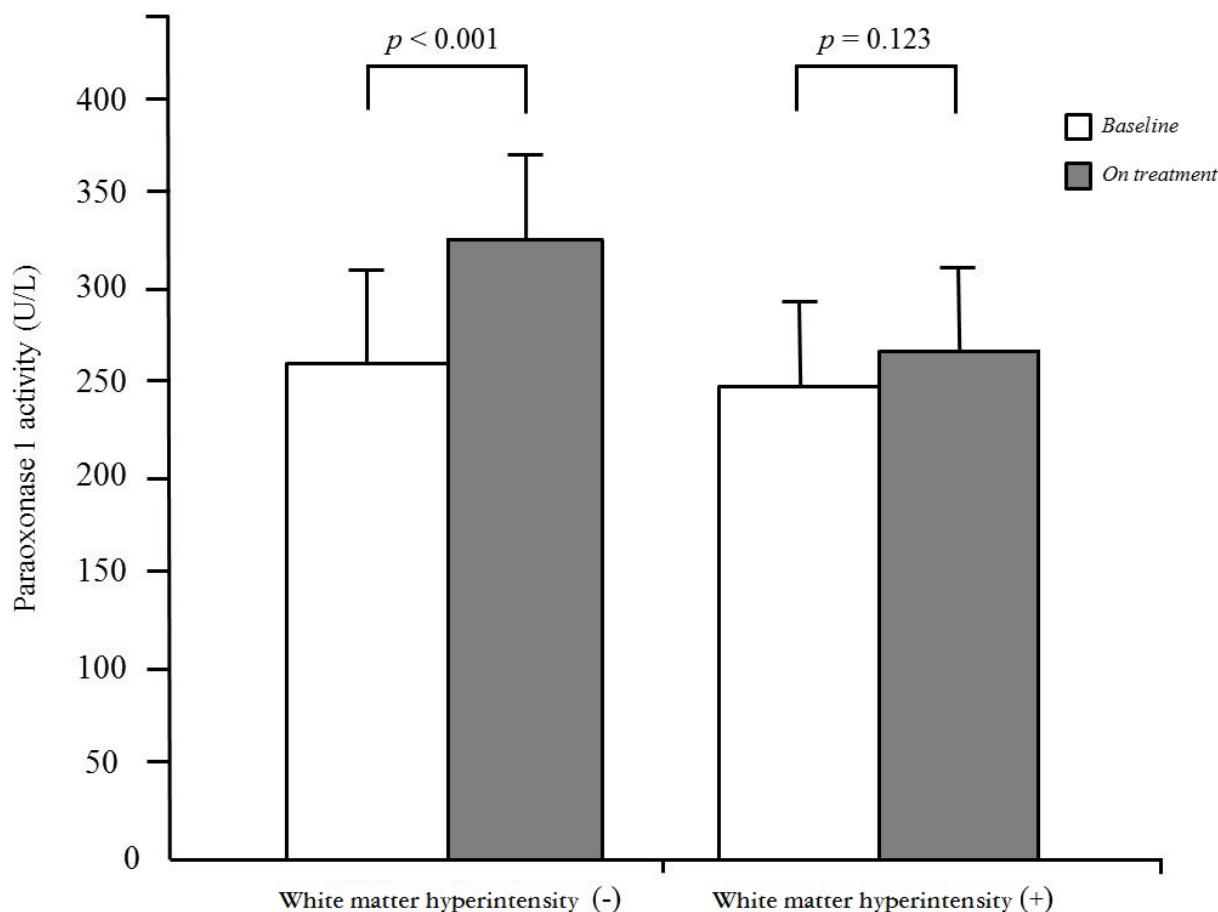


FIGURE 2. Changes in paraoxonase 1 activity after statin treatment stratified by white matter hyperintensity. To compare the change of paraoxonase 1 activity with or without white matter hyperintensity, we used paired *t* test.

TABLE 2. Comparison of laboratory findings before and after statin treatment.

Variable	Pre-treatment	Post-treatment	P-value	
WMH (-)	Total cholesterol (mg/dL)	199.50 ± 24.48	139.22 ± 17.62	< 0.001
	Triglyceride (mg/dL)	143.22 ± 56.06	133.56 ± 57.17	0.543
	HDL (mg/dL)	39.39 ± 9.70	42.83 ± 10.67	0.067
	LDL (mg/dL)	118.67 ± 21.34	70.06 ± 17.42	< 0.001
	Apolipoprotein A1/B1 (mg/dL)	1.12 ± 0.12	0.16 ± 1.05	< 0.001
WMH (+)	Paraoxonase 1 (U/L)	258.89 ± 105.43	324.72 ± 95.51	< 0.001
	Total cholesterol (mg/dL)	191.75 ± 16.09	126.96 ± 19.82	< 0.001
	Triglyceride (mg/dL)	127.25 ± 64.26	108.42 ± 29.43	0.088
	HDL (mg/dL)	45.17 ± 9.59	44.04 ± 10.51	0.635
	LDL (mg/dL)	106.50 ± 18.28	56.08 ± 16.42	< 0.001
Apolipoprotein A1/B1 (mg/dL)	1.31 ± 1.34	1.98 ± 0.95	0.034	
Paraoxonase 1 (U/L)	249.42 ± 107.44	265.79 ± 109.69	0.123	

Values indicate mean ± SD unless otherwise indicated.

WMH = white matter hyperintensity; HDL cholesterol = high-density lipoprotein cholesterol; LDL cholesterol = low-density lipoprotein cholesterol.

fore, a large-scale study that explored varying types and doses of statins will be required in the future. Third, although we measured TAS within 24 hours after the onset of ischemic stroke, there was a slight difference in the sampling time for each patient. The slight difference in sampling time may

have influenced TAS values, and the authors believe that it is a reason for the insignificance of the difference. However, unlike TAS, the PON values were significantly different. We speculated that TAS and PON responded differently to the slight sampling time difference. Therefore, we plan to con-

duct another study with more patients. Last, the relationship between the antioxidative effects and the severity of WMH was not analyzed in this study. Future studies should analyze the different antioxidative effects related to WMH severity in a larger group of patients.

6. Conclusions of the study

In conclusion, we confirmed that statin treatment improved the lipid profiles of patients with ischemic stroke. However, statin treatment had a significantly greater antioxidative effect in ischemic stroke patients without WMH than in those with WMH. The results of the current study imply that the antioxidative effect of statin treatment is less in ischemic stroke patients with WMH than without WMH. Therefore, moderate- to high-intensity statin treatments is thought to be helpful in secondary prevention of ischemic stroke in patients with WMH.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All patients provided consent for the anonymization of the data in accordance with the protocol set forth by the review board of Wonkwang University Hospital (WKUHIRB-1460).

AUTHOR CONTRIBUTIONS

Hyun Goo Kang and Hyun Young Park participated in the design of this research. Jin Sung Cheong, In Hwan Lim and Kyeong Ho Yun collected and analyzed the raw clinical data. Hyun Goo Kang, Kyeong Ho Yun and Hyun Young Park carried out computational studies and wrote the manuscript. All authors have read and approved the final manuscript.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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