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Effects of azilsartan administration on the progression of cerebral small vessel disease

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Abstract

Abnormal circadian rhythm of blood pressure (BP) is known as a risk factor of cerebral small vessel disease (cSVD), such as white matter hyperintensiy (WMH). Azilsartan has been reported to normalize the BP circadian rhythm. Thus, we investigated whether azilsartan was effective for suppressing cSVD progression.

We prospectively enrolled patients with hypertension treated by angiotensin II receptor blockers (ARBs) other than azilsartan. At the baseline, patients underwent magnetic resonance imaging (MRI) and ambulatory BP monitoring (ABPM). Six months later, patients were randomized into the group administered with azilsartan and the control group administered with other ARBs. Eighteen months later, the patients underwent MRI and ABPM. Longitudinal changes in cSVD were compared between the groups.

Seventy-one of 101 patients were eligible for further analyses. The mean systolic/diastolic BPs were significantly decreased, and the BP circadian rhythm was significantly normalized in the azilsartan group ($p = 0.04/0.03$ and 0.007, respectively). However, there were no significant differences in cSVD progression between the groups, although the increase in WMH volume was significantly suppressed in patients with normal BP circadian rhythm at 18 months ($p = 0.04$). In conclusion, we found no substantial effects of azilsartan on suppression of cSVD progression.

Key words: azilsartan, angiotensin II receptor blocker, cerebral small vessel disease, magnetic resonance imaging, ambulatory blood pressure monitoring

I. Introduction

Hypertension is one of the cardinal risks for stroke and its recurrence and is closely related to cerebral small vessel disease (cSVD), which is a pathological process that affects the small arteries, arterioles, capillaries, and venules. Magnetic resonance imaging (MRI) can detect various asymptomatic abnormalities due to cSVD, such as lacunes, cerebral microbleeds (CMBs), and white matter hyperintensities (WMHs), which are well-known risk factors

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for stroke events [1-8]. Hence, antihypertensive therapies involving calcium channel blockers, diuretic agents, angiotensin-converting-enzyme (ACE) inhibitors and/or angiotensin II receptor blockers (ARBs) are commonly employed for primary and secondary prevention of stroke events. In particular, ARBs have been reported to prevent recurrence and aggravation of strokes [9, 10].

Recently, ambulatory blood pressure monitoring (ABPM) has been shown to provide detailed information of circadian rhythm of blood pressure (BP). The BP circadian rhythm normally demonstrates the dipper type, in which nighttime systolic BP drops 10-20% and rises from early morning. In contrast, abnormal BP circadian rhythms demonstrate the non-dipper type in which nighttime systolic BP drops less than 10%, the riser type in which nighttime systolic BP rises , and the extreme-dipper type in which nighttime systolic BP drops more than 20%. These abnormalities in the BP circadian rhythm as well as mean BP have been reported as independent risk factors for stroke events [11, 12] and cSVD [13, 14].

Among various antihypertensive agents, azilsartan, a new ARB, has been reported to exhibit characteristic effects on normalizing the BP circadian rhythm [15, 16]. However, it remains unclear whether azilsartan administration can suppress the progression of cSVD, including lacunes, CMBs, and WMHs by correcting the BP circadian rhythm. Hence, we prospectively evaluated the effects of azilsartan on cSVD progression.

II. Materials and Methods

1. Patients

From March 2013 to January 2015, we prospectively enrolled patients with hypertension treated by administration ARBs other than azilsartan. These clinical profiles of the patients were checked for hypertension, diabetes mellitus, dyslipidemia, as well as histories of stroke, heart disease, and peripheral artery disease. The institutional ethics committee approved the study protocol (H24-155), and written informed consent was obtained from all patients.

2. Randomization protocol

The patients underwent MRI and ABPM to generate baseline data, and continued administration of the ARBs. Six months after the baseline, the patients were randomized into the azilsartan group and the control group, using a prospective randomized open blinded-endpoint (PROBE) method. In the azilsartan group, the patients were switched from conventional ARBs to azilsartan. The administration of azilsartan was set to a daily dose of 20 mg, which was allowed to increase to 40 mg or decrease to 10 mg when necessary, based on the guidelines for the management of hypertension 2009 and 2014 [17, 18]. In the control group, the patients continued with conventional ARBs. Eighteen months after the baseline, the patients underwent follow-up MRI and ABPM.

3. ABPM and MRI protocols

We used an ABPM device (FM-800, Fukuda Denshi Corporation, Tokyo, Japan) to examine the circadian rhythm of BP as well as mean BP levels. The ABPM device was attached to the patients and was removed after 24 h at our outpatient clinic. The BP was automatically

measured at 30-min intervals between 7 a.m. and 9 p.m., and at 60-min intervals between 9 p.m. and 7 a.m. By analyzing the obtained data, the mean, daytime, and nighttime BPs were calculated. In addition, the types of BP circadian rhythm were divided into the normal dipper type and other pathological types, such as the non-dipper, riser, and extreme-dipper types. The conversion from the pathological types to the dipper types at 18 months after the baseline was defined as the normalization of BP circadian rhythm.

During MRI examinations, T1-weighted (T1W), T2-weighted (T2W), fluid-attenuated inversion recovery (FLAIR), and T2*-weighted (T2*W) images of the brain were obtained by using a 3T MRI scanner (Discovery MR750, GE Healthcare, Milwaukee, WI, USA). The pulse sequence parameters of the T1W images were as follows: sagittal 3-dimensional (3D) spoiled gradient echo; repetition time (TR)/echo time (TE), 5.9 ms/1.9 ms; flip angle, 15° ; matrix size, 256 × 256; slice thickness, 1.5 mm; partitions, 120; and acquisition time, 2 min 6 s. Those of the T2W images were: sagittal 3D fast spin-echo (FSE); TR/TE, 3000/76 ms; matrix size, 288 × 256; slice thickness, 1.0 mm; partitions, 190; and acquisition time, 4 min 28 s. Those of the FLAIR images were: sagittal 3D-FSE; TR/TE, 6400/127 ms; inversion time, 236 ms; matrix size, 256 × 224; slice thickness, 1.4 mm; partitions, 130; and acquisition time, 3 min 56 s. Those of the T2*W images were: axial gradient echo; TR/TE, 800/20 ms; matrix size, 512 × 192; slice thickness, 3.0 mm; number of sections, 46; and acquisition time, 2 min 36 s. The other parameters used in every sequence were as follows: field of view, 24 × 24 cm^2; number of excitations, 1. Reformatted axial T1W, T2W, and FLAIR images with slice thickness of 3.0 mm were then generated from the 3D source data.

4. Data processing and statistical analyses

The images were examined for cSVD lesions, such as lacunes, CMBs, and WMHs including periventricular hyperintensity (PVH) and deep white matter hyperintensity (DWMH) at the baseline and after 18 months by two board-certified neurologists (S.N. and T.N.) who were unaware of patient information. The numbers of lacunes and CMBs were evaluated according to the imaging criteria proposed by Wardlaw, et al [19]. The extent of WMHs, including PVH and DWMH, was evaluated using Fazekas score [20]. The assessments with randomized orders were performed two times with a 2-week interval. Differences between the interpretations were resolved by consensus. In addition, volume of WMHs on FLAIR images was calculated by one of the authors (K.I.), who was blind to patient information, using a software package (3D Slicer 4.8, http://www.slicer.org). A circular region of interest (ROI) of 2.5 mm in radius was manually set on the corpus callosum, and the areas showing hyperintensity more than +5 standard deviation of the ROI were defined as WMHs (Fig. 1). The WMH volume was then calculated automatically. The measurements were performed two times and the values were then averaged.

Differences in the patient characteristics between the azilsartan group and the control group were examined using the Mann–Whitney U test or Fisher's exact test. Differences in the BPs, WMH volume, and BP circadian rhythm between the baseline and after 18 months were

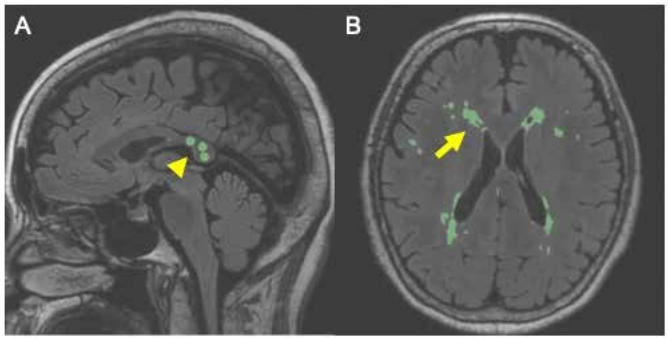

Fig. 1. Semi-automated measurement of cerebral white matter hyperintensity volume
A circular region of interest (ROI) of 2.5 mm in radius was set on the corpus callosum on sagittal FLAIR image (A, arrowhead), and the areas showing hyperintensity more than 5 standard deviation of the ROI were automatically calculated as the white matter hyperintensity volume (B, arrow).

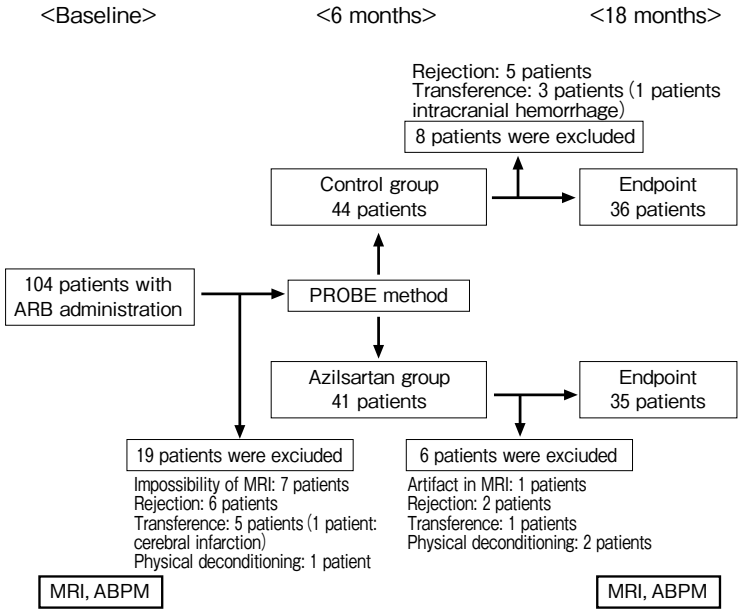

Fig. 2. Flowchart of participants in the present study

examined using the Wilcoxon sighed-rank test or McNemar's test; whereas differences in the BP circadian rhythm between the azilsartan group and the control group were examined by Fisher's exact test. Furthermore, differences in the number of patients showing temporal progression of the lacunes, CMBs, Fazekas scores, and WMH volume between the two groups and between the patients with the dipper and other types at 18 months were examined by Fisher's exact test or the Mann-Whitney U test. Intra-/inter-rater agreements were examined using the kappa coefficient or intraclass correlation coefficient (ICC). In addition, multivariable logistic regression analysis with a stepwise method was used to identify the factors that were independently related to the progression of cSVD lesions. The alpha level used was 0.05.

Table 1. Clinical characteristics and imaging findings of the patients receiving angiotensin II receptor blockers.

	All patients (n = 71)	Azilsartan group (n=35)	Control group (n=36)	p-value
Age (years)	68 (51–83)	66 (51–82)	70 (55–83)	0.38*
Men	46 (64.8)	22 (62.9)	24 (66.7)	0.81 †
Hypertension	71 (100)	35 (100)	36 (100)	—
Diabetes mellitus	23 (32.4)	11 (31.4)	12 (33.3)	1.00 †
Dyslipidemia	33 (46.5)	13 (37.1)	20 (55.6)	0.16 †
CVD	65 (91.5)	30 (85.7)	35 (97.2)	0.11 †
Heart disease	17 (23.9)	8 (22.9)	9 (25.0)	1.00 †
PAD	21 (29.6)	7 (20.0)	14 (38.9)	0.12 †
ARBs Valsartan	35 (49.3)	18 (51.4)	17 (47.2)	0.81 †
Telmisartan	10 (14.1)	7 (20)	3 (8.3)	0.19 †
Losartan	4 (5.6)	2 (5.7)	2 (5.6)	1.00 †
Olmesartan	4 (5.6)	2 (5.7)	2 (5.6)	1.00 †
Candesartan	18 (25.4)	6 (17.1)	12 (33.3)	0.17 †
Antiplatelet drugs	56 (78.9)	27 (77.1)	29 (80.6)	0.78 †
Anticoagulants	7 (9.9)	4 (11.4)	3 (8.3)	0.71 †
Mean SBP (mmHg)	121 (93–150)	122 (101–145)	117 (93–150)	0.47*
Mean DBP (mmHg)	78 (57–100)	78 (66–98)	78 (57–100)	0.52*
Dipper-type circadian rhythm	39 (54.9)	18 (51.4)	21 (58.3)	0.64 †
Lacunes	1 (0–7)	1 (0–7)	1 (0–5)	0.61*
Cerebral microbleeds	0 (0–15)	0 (0–15)	0 (0–6)	0.46*
Fazekas score (PVH)	1 (0–3)	1 (0–3)	1 (0–3)	0.75*
Fazekas score (DWMH)	2 (0–3)	2 (1–3)	2 (0–3)	0.53*
WMH volume (cm^3)	7.5 (0.9–31.9)	7.3 (0.9–31.9)	7.9 (0.9–27.2)	0.51*

Values are expressed as median (range) or number (percentage); ARBs, angiotensin II receptor blockers; CVD, cerebrovascular disease; DBP, diastolic blood pressure; DWMH, deep white matter hyperintensity; PAD, peripheral artery disease; PVH, periventricular hyperintensity; SBP, systolic blood pressure; WMH, white matter hyperintensity; *Mann-Whitney U test; † Fisher's exact test.

III. Results

We enrolled 104 patients (age range: 42–86 years [median: 72 years]; 66 men and 38 women) in this study. The clinical profiles of these patients were hypertension (n = 104), diabetes mellitus (36), dyslipidemia (47), and history of stroke (95), heart disease (22), and peripheral artery disease (22). Among these, 33 patients were excluded before or after the randomization because of contraindication for MRI due to metallic implants (n = 7), refusal of examinations (13), transference to other hospitals or departments (9) [including patients with acute ischemic stroke (1) and intracerebral hemorrhage (1)], profound motion artifacts on the baseline MR images (3), or physical deconditioning by antihypertensive agents (3). Therefore, 71 patients (age range: 51–83 [median: 68.0 years]; 46 men and 25 women) were eligible for further analysis. Among these, 35 and 36 patients were randomized into the azilsartan group and the control group, respectively (Fig. 2). There were no significant differences in the backgrounds of the patients between the groups (Table 1). In the azilsartan group, the dosage of azilsartan at 18 months was 10 mg (n = 1), 20 mg (19), or 40 mg (15).

Table 2. Temporal changes in blood pressure and its circadian rhythm of the patients receiving azilsartan or other ARBs

Blood pressure	Group	Baseline	18 months	p-value
Mean SBP(mmHg)	Azilsartan Control	122 (101–145) 117 (93–150)	116 (94–144) 122 (98–147)	0.04* 0.08*
Mean DBP(mmHg)	Azilsartan Control	78 (66–98) 78 (57–100)	75 (58–91) 81 (52–91)	0.03* 0.18*
Daytime SBP(mmHg)	Azilsartan Control	126 (105–149) 122 (97–152)	123 (96–149) 125 (100–151)	0.06* 0.16*
Daytime DBP(mmHg)	Azilsartan Control	80 (68–107) 80 (62–103)	79 (61–94) 82 (64–95)	0.05* 0.11*
Nighttime SBP(mmHg)	Azilsartan Control	107 (91–139) 107 (84–147)	106 (85–138) 112 (83–142)	0.10* 0.06*
Nighttime DBP(mmHg)	Azilsartan Control	72 (58–86) 72 (49–94)	68 (50–83) 75 (50–87)	0.02* 0.16*
Dipper-type circadian rhythm	Azilsartan Control	18/35 (51.4) 21/36 (58.3)	24/35 (68.6) 16/36 (44.4)	0.15** 0.13**
Normalized circadian rhythm	Azilsartan Control		9/17 (52.9) 1/15 (6.7)	0.007 †

Values are expressed as median (range) or number (percentage); DBP, diastolic blood pressure; SBP, systolic blood pressure; *Wilcoxon signed-rank test, **McNemar's test, † Fisher's exact test.

Table 3. Progression of cerebral small vessel disease in the patients receiving azilsartan or other ARBs.

cSVD	Group	Baseline	18 months	p-value	Progression	p-value
Lacunes	Azilsartan Control	1 (0–7) 1 (0–5)	1 (0–7) 1 (0–5)	– –	0/35 (0) 0/36 (0)	–
Cerebral microbleeds	Azilsartan Control	0 (0–15) 0 (0–6)	1 (0–15) 1 (0–7)	0.038* 0.102*	5/35 (14.3) 3/36 (8.3)	0.48 †
Fazekas score (PVH)	Azilsartan Control	1 (0–3) 1 (0–3)	1 (0–3) 1 (0–3)	– –	0/35 (0) 0/36 (0)	–
Fazekas score (DWMH)	Azilsartan Control	2 (1–3) 2 (0–3)	2 (1–3) 2 (0–3)	– –	0/35 (0) 0/36 (0)	–
WMH volume (cm^3)	Azilsartan Control	7.3 (0.9–31.9) 7.9 (0.9–27.2)	6.9 (1.1–33.3) 9.5 (1.3–34.4)	0.049* 0.003*	0.3 (-4.6–11.1) 0.9 (-4.8–9.6)	0.23 ‡

Values are expressed as median (range) or number (percentage); cSVD, cerebral small vessel disease; DWMH, deep white matter hyperintensity; PVH, periventricular hyperintensity; WMH, white matter hyperintensity; *Wilcoxon signed-rank test; † Fisher's exact test; ‡ Mann-Whitney U test.

The BPs and BP circadian rhythms of both groups at the baseline and 18 months later are shown in Table 2. Mean systolic/diastolic BPs and nighttime diastolic BP in the azilsartan group were significantly decreased at 18 months when compared with those at the

Table 4. Progression of cerebral small vessel disease in the patients with/without dipper-type circadian rhythm of blood pressure.

cSVD	Progression at 18		p-value
	Dipper-type circadian rhythm at 18 months	Other circadian rhythms	
Lacunes	0/40 (0)	0/31(0)	–
Cerebral microbleeds	5/40 (13)	3/31 (10)	1.00*
Fazekas score (PVH)	0/40 (0)	0/31 (0)	–
Fazekas score (DWMH)	0/40 (0)	0/31 (0)	–
WMH volume (cm^3)	0.20 (-4.63–9.62)	1.08 (-4.76–11.14)	0.04 †

Values are expressed as median (range) or number (percentage); cSVD, cerebral small vessel disease; DWMH, deep white matter hyperintensity; PVH, periventricular hyperintensity; WMH, white matter hyperintensity; *Fisher's exact test; † Mann-Whitney U test.

Table 5. Univariate/multivariate logistic regression analyses regarding the WMH volume progression.

	Progression of WMH volume* (more than 10% increase)		Univariate analysis	Multivariate analysis (stepwise)		
	(+) (n = 37)	(−) (n = 34)	p-value	Odds ratio	95% CI	p-value
Age (years old)	73 (52–83)	66 (51–79)	0.021 †	1.07	1.01–1.13	0.028
Men	21 (56.8)	25 (73.5)	0.213 ‡			
Diabetes mellitus	12 (32.4)	11 (32.4)	1.000 ‡			
Dyslipidemia	17 (45.9)	16 (47.1)	1.000 ‡			
CVD	35 (94.6)	30 (88.2)	0.417 ‡			
Heart disease	10 (27.0)	7 (20.6)	0.586 ‡			
PAD	11 (29.7)	10 (29.4)	1.000 ‡			
Antiplatelet drugs	32 (86.5)	24 (70.6)	0.146 ‡			
Anticoagulants	4 (10.8)	3 (8.8)	1.000 ‡			
Azilsartan*	16 (43.2)	19 (55.9)	0.346 ‡			
Dipper rhythm*	18 (48.6)	22 (64.7)	0.232 ‡			
Mean SBP*	117 (100–144)	122 (94–147)	0.997 †			
Mean DBP*	77 (52–91)	78 (64–91)	0.537 †			
Daytime SBP*	122 (105–149)	126 (96–151)	0.588 †			
Daytime DBP*	80 (61–92)	80 (65–95)	0.444 †			
Nighttime SBP*	110 (83–138)	107 (85–142)	0.276 †			
Nighttime DBP*	71 (50–87)	72 (54–83)	0.836 †			

Values are expressed as median (range) or number (percentage); CI, confidence interval; CVD, cerebrovascular disease; DBP, diastolic blood pressure; PAD, peripheral artery disease; SBP, systolic blood pressure; *at 18 months after the baseline; † Mann-Whitney U test; ‡ Fisher's exact test.

baseline, whereas there were no significant differences in these values between the baseline and 18 months later in the control group. In addition, normalization of the BP circadian rhythms to the dipper type were more frequently found in the azilsartan group (52.9%) than in the control group (6.7%).

The temporal changes in the lacunes, CMBs, Fazekas score, and WMH volume are shown in Table 3. There were no apparent changes in the number of the lacunes or Fazekas scores for both groups. Progression of the number of

CMBs were found in five and three patients in the azilsartan group and the control group, respectively; however, there was no significant difference between the groups. In contrast, the WMH volume was significantly increased after 18 months in both groups. The progression volume in the azilsartan group tended to be smaller than that in the control group. However, there was no significant difference between the groups.

To elucidate the relationship between the BP circadian rhythm and cSVD progression, temporal increase in the WMH volume was significantly suppressed in the patients with the dipper-type rhythm after 18 months when compared with those with the other types. In contrast, there was no significant difference in the increase of the CMB number between the patients with the dipper and other types (Table 4). The multivariate logistic regression analysis by a stepwise method revealed that only age was independently related to the progression of WMH volume, which was defined as more than a 10% increase (Table 5).

Regarding intra/interrater agreements in the image interpretations, the kappa coefficient values for intra/interrater agreements of the visual assessments ranged 0.49–0.86 (median: 0.66) / 0.23–0.70 (0.59), while the ICC value for the intrarater agreement of the volume measurement was 0.99.

IV. Discussion

Several clinical trials have been conducted to compare the efficiency of ARBs with those of other antihypertensive agents in terms of stroke prevention. One trial revealed that ARB administration significantly lowered the rate of recurrent stroke compared to a calcium channel blocker [9]. However, in another trial, there were no significant differences between the effects of these two agents [21]. Compared with the ACE inhibitors, a recent trial failed to show the advantages of the ARB [22], although a meta-analysis revealed a significant risk reduction of 8% in incidence rate of stroke in the ARBs group compared with the ACE inhibitor group [23]. Thus, until now, the effects of ARBs in stroke prevention when compared with other agents have been unclear.

Azilsartan, a new ARB, has been reported to exhibit strong antihypertensive effects compared with other ARBs [24-26], because azilsartan tightly binds with angiotensin II type 1 receptor [27, 28] as well as, presumably, suppressing the sympathetic nervous system and increasing urinary sodium excretion [29]. Besides strong antihypertensive effects, azilsartan has been reported to exhibit specific effects in converting pathological BP circadian rhythms that are associated with stroke events [11, 12, 30] into normal rhythms by lowering nighttime BP, which few other ARBs or antihypertensive agents achieved [15, 16]. In this study, the patients administered azilsartan showed significant suppression of BP and significant normalization of the circadian rhythm as compared with those administered other ARBs. These results supported the aforementioned characteristics of azilsartan, which can contribute to stroke prevention.

The cSVD, which is caused by aging, hypertension, and cerebral amyloid angiopathy, is known to be a major risk factor for hemorrhagic and ischemic strokes [1-8]. The lacunes and WMHs have been reported as risk factors for subsequent stroke with hazard ratios of 3.9 and 3.6–4.7, respectively [3],

while the CMBs have been reported as risk factors for ischemic stroke and intracerebral hemorrhage with hazard ratios of 4.5 and 50, respectively [7]. In general, antihypertensive therapies can suppress the progression of cSVD [31, 32], although a recent study showed that telmisartan, a conventional ARB, did not suppress the increase of WMHs mainly because BP lowering was insufficient [33]. Normalization of the BP circadian rhythm can also suppress cSVD progression because high nighttime systolic BP has been reported to be related to large WMH volume [34]. In this study, azilsartan administration normalized BP and its circadian rhythm when compared with other ARBs. In addition, temporal increase in the WMH volume was significantly smaller in the patients with the dipper-type normal circadian rhythm, although there was no significant difference between the azilsartan group and the control group. These results partly support the results of the previous studies indicating that normalization of BP and its circadian rhythm suppresses cSVD progression and can contribute to stroke prevention [31, 32, 34-36].

In this study, although azilsartan could successfully manage BP and its circadian rhythm, we failed to determine substantial effects of azilsartan on suppression of the cSVD progression,presumably due to the following limitations as follows. First, the sample size in this study was too small when compared with the previous studies [33, 37]. Because more than 30% of patients were excluded or dropped out due to various issues, only approximately 35 patients per arm were eligible for further analysis, which appeared barely enough to achieve significant differences. Second, the follow-up period after the randomization, i.e., 1 year, was too short as compared with the previous studies [33, 37]. The number of lacunes and Fazekas scores were unchanged in all the patients and the number of CMBs increased in only eight patients. In addition, stroke events occurred only in one patient in the control group. This issue substantially reduced the accuracy of the analysis. The third limitation involves technical issues related to the WMH volume measurement. The semi-automated method we used showed an excellent Intrarater agreement; however, this may include substantial errors while evaluating subtle longitudinal changes in the WMH volume mainly because we did not perform co-registration, signal normalization, or subtraction between the baseline and follow-up images. More sophisticated methods are needed for accurate evaluation of WMH progression during relatively short periods. Finally, the age of the patients substantially affected the results in this study. Age is known to be a cardinal factor for WMH volume and its progression [32], as our multivariate analysis showed that only age was independently related to the increase in the WMH volume. Differences in WMH volume progression among patients with a relatively varied age distribution could mask the subtle differences between the azilsartan and control groups.

In conclusion, azilsartan significantly normalized BP and its circadian rhythm as compared with other ARBs. In addition, an increase in the WMH volume was significantly suppressed in the patients with the normal, dipper-type circadian rhythm. However, we found no substantial effects of azilsartan on

suppression of cSVD progression. Further studies with a larger sample size, long follow-up period, and sophisticated measurement method are needed to elucidate the role of azilsartan in sSVD prevention.

Conflict of interest: The authors have no conflict of interest to declare.

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高血圧症患者におけるアジルサルタンによる脳小血管病の進行抑制効果の検討

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要旨

近年，血圧日内変動の異常が脳小血管病のリスクであることが報告されている．そこで、血圧日内変動正常化作用を持つ新規 angiotensin II receptor blocker (ARB) アジルサルタンが，従来の ARB と比し脳小血管病の進行抑制に有効か前向きに検討した．

高血圧で従来の ARB 内服中の患者を対象に，登録時に MRI と 24 時間自由行動下血圧測定を施行，6 ヵ月後にアジルサルタンへの変更群と従来 ARB 継続群に割り付け，18 ヵ月後に MRI と自由行動下血圧測定を再施行し，変更群と継続群におけるラクナ梗塞，微小出血，白質病変の変化を比較した．

104 例中 71 例が解析対象となった．変更群では継続群と比し平均収縮期・拡張期血圧の有意な低下と血圧日内変動の有意な正常化を認めたが（$p < 0.05$），脳小血管病の経時的変化に差を認めなかった．しかし，18 ヵ月後血圧日内変動正常例では，白質病変体積の増加が有意に抑制された（$p < 0.05$）．

今回の検討では，アジルサルタンによる脳小血管病の進行抑制は認めなかった．