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ORIGINAL COMMUNICATION

Evolution of acute lacunar lesions in terms of size and shape: a PICASSO sub-study

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Abstract

The imaging definition of lacunar infarcts is variable, particularly regarding their size and the presence of cavitation. We investigated the changes of diameter and evolution pattern of acute lacunar infarcts, and the factors associated with the evolution pattern. Patients with acute single subcortical hemispheric or brainstem ischemic lesions of penetrating arterial territories were included. Maximal diameters on initial diffusion-weighted image (DWI) and follow-up fluid-attenuated inversion recovery image (FLAIR), which performed > 12 months after initial DWI, were semi-automatically measured. Clinical characteristics were compared according to evolution patterns on follow-up FLAIR, classified as cavitated, focal lesion without cavitation, and disappeared. Five hundred nine patients were included. Mean time to follow-up was 31.3 ± 13.7 months. Mean diameter of acute lacunar lesions decreased from 12.9 ± 4.4 to 8.5 ± 4.8 mm during follow-up. Lesions of 58.2% patients remained as cavitated, 18.3% as focal lesion without cavitation, and 23.6% disappeared. Initial NIHSS score ($p = 0.005$), diameter of initial lesion ($p < 0.001$), number of slices showing acute lesion on DWI ($p < 0.001$), progression of white matter lesion ($p < 0.001$), number of acute lesions involving gray matter ($p = 0.008$) and lesion location ($p < 0.001$) were different among three groups. After adjustment for covariates, diameter of the acute lesion, initial number of old lacunes, and anterior lesion location were associated with the appearance of cavitation. Initial lesion diameter and posterior lesion location were associated with the disappearance. We observed reduction of the acute lacunar lesion diameter in 86%. There were predictive factors of disappearance and cavitation of acute lacunar infarction.

Keywords Lacunar infarction · Cavitation · Size criteria

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Introduction

Lacunar infarcts from small vessel occlusion comprise 15–26% of all ischemic strokes [1–3]. The conventional definition of a lacunar infarct is a subcortical lesion with a cerebrospinal fluid (CSF)-filled cavity measuring less than 15 mm, which means most lacunar infarcts require cavitation [4]. However, acute lacunar infarcts detected by imaging are variably described, and there are fewer agreements on lacunar lesion size criteria and the presence of cavitation on follow-up imaging [5]. According to a recent study, three evolution patterns of acute lacunar lesions were observed such as infarcts with cavitation, the lesions progressed to focal white matter lesions, and non-visualization [6]. The appearance of cavitation, a central CSF-like hypointensity, was reported diversely from 28 to 76.5% in recent studies [7, 8].

With regard to lesion size, diffusion-weighted magnetic resonance imaging (MRI) mostly overestimates the actual infarct size because it may include vasogenic edema and possible ischemic penumbra [9, 10].

The imaging evolution pattern in terms of size and cavitation of acute lacunar infarcts during their chronic period after sufficient reorganization is still unclear and needs to be identified. Knowing how acute lacunar infarcts evolve over time and how they can be detected long after an acute stroke event are important for making an exact diagnosis of chronic lacunar infarcts and secondary stroke prevention. Some previous studies attempted to investigate this issue, but their small study population, short time interval, and without monitoring vascular risk factors and use of medications remained as limitations [6, 8, 11]. Therefore, we aimed to investigate the evolution pattern of acute lacunar infarcts and the factors associated with each evolution pattern in prospectively enrolled subjects with long-term follow-up. During which time their vascular risk factors and compliance to medications were monitored.

Methods

Patients

This study was performed by analyzing data of participants in the PreventIon of CArdiovascular events in iSchemic Stroke patients with high risk of cerebral hemOrrhage (PICASSO) trial. The eligible patients for the PICASSO study were those with noncardioembolic ischemic stroke or transient ischemic attack within 180 days and with a history of intracerebral hemorrhage or the presence of multiple cerebral microbleeds [12]. The design and methods of the PICASSO study have been described elsewhere [13]. Patients were randomly assigned to receive cilostazol, aspirin, cilostazol plus probucol, or aspirin plus probucol. Among them, patients with acute single subcortical hemispheric or brainstem ischemic lesion of penetrating arterial territories without a definite cause of cardioembolism and large vessel disease, and with initial and follow-up MRI were included in the present study. There were no other exclusion criteria. Electrocardiography and clinical history of all patients were collected more than two times and Holter monitoring was performed. Echocardiography was performed by clinician's decision.

Clinical information was collected at baseline. The data included age, sex, use of medication (antiplatelet and statin drugs), risk factors for stroke (the presence of hypertension, diabetes, hyperlipidemia and smoking status), initial National Institutes of Health stroke scale (NIHSS) score, and radiologic findings. Smoking habits were categorized on admission as non-smoker and smoker (current or former). The study was approved by the ethics committee of each participating center and all participants were enrolled after a written informed consent was obtained.

Imaging analysis

MRIs including initial diffusion-weighted imaging (DWI), gradient echo image (GRE) and fluid attenuated inversion recovery (FLAIR) at the end of the clinical trial within a time interval of more than 12 months were mandatary.

MRI was performed according to the protocol of each participating center (slice thickness of DWI, 2–6 mm). DWI was performed at median 1 day after symptom onset (interquartile range 0–1). All MRI scans were collected from individual centers in digital format and rated centrally in each analysis by two neurologists who were blinded to patients' baseline and outcome information (white matter lesions [WMLs], and lacunes were rated by H.S.K. and M.W.L.; and cerebral microbleeds [CMBs] by C.C. and J-W.J.). WMLs were defined as punctuate, early confluent, or confluent abnormalities based on FLAIR images. Initial and follow-up WMLs were coded according to the modified Fazekas scale [14] and age-related white matter change rating scale [15]. In addition, the modified Rotterdam Progression Scale (mRPS) score was measured to visualize the change of WMLs [16]. Advanced WMLs were defined as grades 2 and 3 according to modified Fazekas grading. CMBs were defined as focal homogenous areas with diameters of 2–10 mm and coded according to the microbleed anatomical rating scale [17]. Only definite CMBs were analyzed in this study. Old lacunes were characterized as round or ovoid subcortical lesions measuring 3–20 mm in diameter with signal intensities corresponding to liquor [7]. Maximal diameters (by axial and saggital)

on DWI and follow-up FLAIR images were semi-automatically measured using Petavision (Asan Medical Center, Seoul, Republic of Korea) or YAMAKI DICOM Tools (Kyoto University, Kyoto, Japan). The change in lesion diameter over time was analyzed. Index lacunar lesions on follow-up were classified as cavitated, focal lesion without cavitation and disappeared (Fig. 1). The presence of a cavity was defined as the appearance of a CSF signal on a FLAIR image within the original area of acute lacunar lesions. Lesions at thalamus, brain stem, occipital lobe, or cerebellum were regarded as posterior circulation.

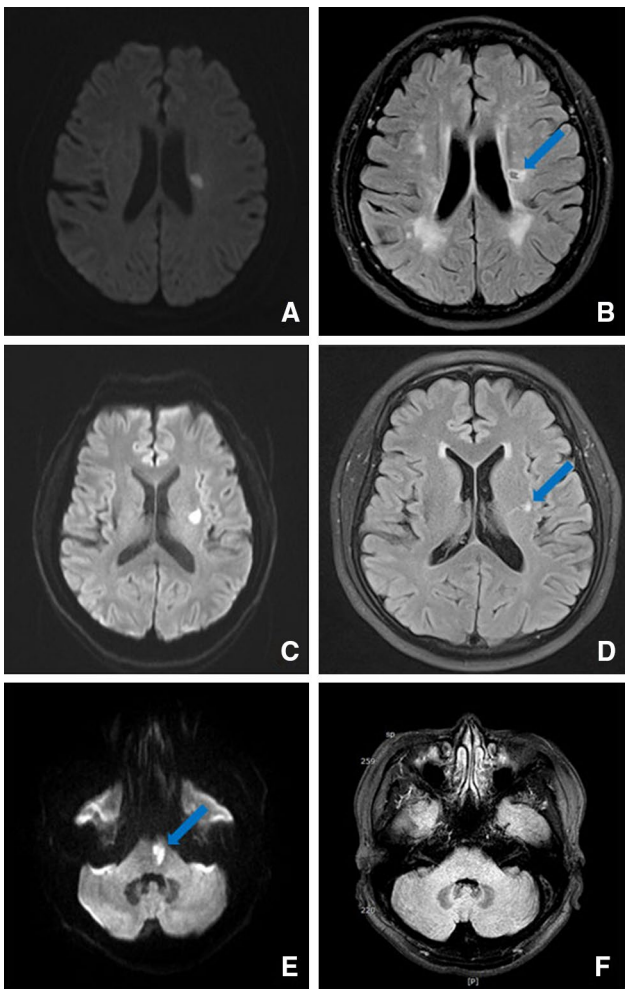

Fig. 1 **a** An acute ischemic lesion is showing at left corona radiata. The lesion diameter is 10.5 mm on DWI. **b** On follow-up FLAIR, it became cavitated lacunar infarct (arrow) with similar diameter after 13 months. **c** An acute ischemic lesion is showing at left basal ganglia. The initial lesion diameter is 16 mm on DWI. **d** It shrank to 8.5-mm-sized focal lesion on follow-up FLAIR (arrow) after 25 months. **e** A 3-mm-sized acute ischemic lesion is showing at pons (arrow). **f** It disappeared on follow-up FLAIR after 13 months. *DWI* diffusion-weighted imaging, *FLAIR* fluid attenuation inversion recovery

Statistical analyses

Descriptive analysis for the change in lesion size and appearance of cavitation over time was used. Group comparisons of continuous variables were performed using the ANOVA or Student *t* test for normally distributed data and the Kruskal–Wallis test or Mann–Whitney *U* test for non-normally distributed data. The Pearson chi-square test or Fisher exact test was used to compare categorical variables. To determine independent factors of the presence of cavitation, we performed multivariate logistic regression analysis. All models were adjusted for age, sex, the type of antiplatelet drug, use of statin, presence of diabetes mellitus, presence of hypertension, which were believed to be potential cofounding factors and factors selected from the results of the univariate analysis with $p < 0.05$. Two-sided values of $p < 0.05$ were considered significant, and all statistical analyses were performed using SPSS 21.0 package for Windows (SPSS Inc., Chicago, IL, USA).

Results

During the study period (between August 1, 2009 and August 31, 2015), 1534 patients were enrolled in the PICASSO trial. Among them, 509 patients with acute lacunar infarcts on initial MRI and with follow-up FLAIR images were analyzed in the present study.

Patients' mean age (± standard deviation) was 63.7 (± 10.5) years and 334 (65.6%) were men. The index of high-risk cerebral hemorrhage for enrollment was macrohemorrhage in 175 (34.4%) patients and multiple microbleeds in 334 (65.6%). The acute lacunar lesion was located in anterior circulation in 298 (58.5%) patients and posterior circulation in 211 (41.5%).

Median time interval between initial and follow-up imaging was 31 months (range 12–64 months, interquartile range 19–40 months). Mean diameter of acute lacunar lesions was 12.9 ± 4.4 mm. At follow-up, mean lesion diameter decreased to 8.5 ± 4.8 mm. Mean percentage of the decrease in the final lesion diameter compared with the initial lesion diameter was 66.2 ± 33.7%. The diameter of lacunar lesions was decreased in 440 (86.4%), same in 42 (8.3%) and increased in 27 (5.3%).

Regarding the lesion shape at follow-up, lesions of 296 (58.2%) patients remained as cavitated, 93 (18.3%) as focal WMLs, and 120 (23.6%) disappeared.

Clinical characteristics and radiologic findings according to the evolution pattern are described in Table 1. In addition, mean systolic blood pressure ($p = 0.482$), glucose level ($p = 0.460$), and adherence to medications ($p = 0.549$) during follow-up period did not differ among three groups.

Table 1 Characteristics of patients according to the evolution pattern of lacunar stroke detected by follow-up MRI

	Total ($n=509$)	Cavitated ($n=296$)	Focal lesion without cavitation ($n=93$)	Disappeared ($n=120$)	p value
Demographic characteristics					
Age, years	63.7 ± 10.5	64.1 ± 10.5	63.8 ± 9.7	62.8 ± 11.1	0.540
Sex, male (%)	334 (65.3)	197 (66.7)	65 (69.9)	72 (60.0)	0.280
Medication					
Cilostazol (%)	247 (48.5)	147 (49.7)	43 (46.2)	57 (47.5)	0.819
Probucol (%)	261 (51.3)	150 (50.7)	44 (47.3)	67 (55.8)	0.444
Clinical finding					
Initial NIHSS score (IQR)	1 (1–3)	2 (1–3)[a]	1 (0–2)[ab]	1 (0–2)[b]	0.005
Initial MRS, score (IQR)	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–2)	0.444
Presence of hypertension, number (%)	455 (89.4)	263 (88.9)	80 (86.0)	112 (93.3)	0.205
Presence of diabetes mellitus, number (%)	152 (29.9)	87 (29.4)	32 (34.4)	33 (27.5)	0.530
Presence of hyperlipidemia, number (%)	228 (44.8)	131 (44.3)	39 (41.9)	58 (48.3)	0.622
Smoker, number (%)	240 (47.2)	142 (48.0)	45 (48.4)	53 (44.2)	0.754
Index of high risk of ICH					0.440
History of ICH, number (%)	77 (15.1)	44 (14.9)	14 (15.1)	19 (15.8)	
Radiologic findings of ICH, number (%)	98 (19.3)	61 (20.6)	21 (22.6)	16 (13.3)	
Multiple microbleeds, number (%)	334 (65.6)	191 (64.5)	58 (62.4)	85 (70.8)	
Radiologic findings					
Index event to screening MRI, days (IQR)	0 (0–1)	0 (0–2)	0 (0–1)	0 (0–1)	0.421
MRI time interval, months (IQR)	31 (19–40)	31 (19–40)	36 (21–46)	31 (17–39)	0.658
Initial diameter, mm	12.9 ± 4.4	13.8 ± 4.4[a]	11.7 ± 4.0[a]	11.8 ± 4.4[b]	< 0.001
Follow-up diameter, mm	8.5 ± 4.8	10.8 ± 3.4	8.8 ± 3.5	N/C	
Number of slices showing acute lesion on DWI					< 0.001
1	214 (21.9)	96 (32.4)	46 (49.5)	72 (60.0)	
2	170 (17.4)	107 (36.1)	32 (34.4)	31 (25.8)	
3 or more	125 (12.8)	93 (31.4)	15 (16.1)	17 (14.2)	
Initial advanced WMH, number (%)	342 (67.2)	199 (67.2)	64 (68.8)	79 (65.8)	0.899
Follow-up advanced WMH, number (%)	343 (67.4)	201 (67.9)	63 (67.7)	79 (65.8)	0.917
Initial ARWMC scale score	11.6 ± 5.0	11.8 ± 5.1	11.8 ± 4.9	11.0 ± 4.8	0.352
Follow-up ARWMC scale score	11.6 ± 5.0	11.8 ± 5.0	12.0 ± 5.0	10.8 ± 4.8	0.1188
Modified RPS score	1.1 ± 1.4	1.3 ± 1.6[a]	1.0 ± 1.3[ab]	0.7 ± 1.0[b]	< 0.001
Initial microbleeds, number	5.9 ± 12.9	6.5 ± 15.7	4.2 ± 6.3	5.8 ± 8.0	0.258
Follow-up microbleeds, number	7.6 ± 14.1	8.2 ± 16.9	6.4 ± 9.4	7.0 ± 8.3	0.576
Initial lacune, number	2.7 ± 2.5	2.9 ± 2.7	2.3 ± 2.3	2.5 ± 2.1	0.067
Follow-up lacune, number	3.5 ± 2.8	4.0 ± 2.9[a]	2.8 ± 2.5[b]	2.9 ± 2.3[b]	< 0.001
Lesion location, number (%)					
Corona radiata	240 (47.2)	177 (59.8)[a]	46 (49.5)[a]	17 (14.2)[b]	< 0.001
Internal capsule	75 (14.7)	31 (10.5)[b]	24 (25.8)[a]	20 (16.7)[ab]	0.001
Basal ganglia	83 (16.3)	62 (20.9)[a]	14 (15.1)[b]	7 (5.8)[b]	0.001
Thalamus	50 (9.8)	26 (8.8)	11 (11.8)	13 (10.8)	0.631
Midbrain	5 (1.0)	3 (1.0)	0 (0.0)	2 (1.7)	0.472
Pons	140 (27.5)	66 (22.3)[b]	12 (12.9)[b]	62 (51.7)[a]	< 0.001
Medulla	12 (2.4)	4 (1.4)[b]	1 (1.1)[ab]	7 (5.8)[a]	0.016
Cerebellum	5 (1.0)	2 (0.7)	0 (0.0)	3 (2.5)	0.132
Acute lesion involving gray matter, number	246 (48.3)	144 (49.0)[ab]	33 (35.5)[a]	68 (56.7)[b]	0.008
Lesions located in anterior circulation, number (%)	298 (58.5)	196 (66.2)[a]	69 (74.2)[a]	33 (27.5)[b]	< 0.001
Baseline MMSE score[‡]	24.6 ± 5.2	24.5 ± 5.1	25.1 ± 4.8	24.6 ± 5.6	0.642

Table 1 (continued)

Data are presented as mean ± SD, median (IQR) or number (%)

Advanced white matter lesions were defined as those with a Fazekas score ≥ 2

WML white matter lesion, *NIHSS* National Institute of Health Stroke scale, *MRS* modified Rankin scale, *ICH* intracerebral hemorrhage, *WMH* white matter hyperintensities, *N/C* not checked, *ARWMC* age-related white matter changes, *RPS* Rotterdam Progression Scale, *MRI* magnetic resonance imaging, *IQR* interquartile range, *SD* standard deviation, *MMSE* Mini-mental status examination

[a > b]Tukey's multiple comparison test and Bonferroni-adjusted chi-square test were performed for post hoc analysis

[‡]MMSE was performed in 263 (88.9%) of cavitated, 79 (84.5%) of focal lesion without cavitated, and 106 (88.3%) of disappeared patient group

[†]*p* value for over all comparison by ANOVA, Kruskal–wallis test, chi-square test and Fisher's exact

Initial NIHSS score ($p = 0.005$), diameter of initial lesion ($p < 0.001$), number of slices showing acute lesion on DWI ($p < 0.001$), progression of white matter lesion ($p < 0.001$), number of acute lesions involving gray matter ($p = 0.008$) and lesion location ($p < 0.001$) were different among three groups.

In multivariate analysis, initial diameter of the lesion detected by DWI, initial count of old lacunes, and location of lesions were independently associated with the appearance of cavitation, after adjusting for covariates (Table 2). Regarding the disappeared pattern, small lesion size (per 1 mm increase of diameter, Odds ratio: 0.918, 95% CI 0.870–0.970, $p = 0.002$) and posterior lesion location (posterior versus anterior lesion location, Odds ratio: 7.428, 95% CI 4.241–13.010, $p < 0.001$) were predictive factors according to multivariate analysis (Table 3).

Discussion

During the 31-month follow-up, we observed an 86.4% decrease and 5.3% increase of the acute lacunar lesion diameter when comparing the initial DWI and follow-up FLAIR imaging. Regarding the evolution pattern, 58.2% showed cavitation, 18.3% showed focal lesion without cavitation, and 23.6% disappeared. The initial lesion diameter, number of old lacune, and anterior lesion location were the predictive factors of cavitary change. The initial lesion diameter and posterior lesion location were the predictive factors of disappearance.

In this study, mean lesion diameter changed from 12.9 mm to 8.5 mm, and this finding is similar to that of previous studies (13.5–8.2 mm and 14.1–7.76 mm) [6, 11]. Acute lesions detected by DWI include vasogenic edema

Table 2 Multivariate logistic regression analysis of cavitation of acute lacunar infarcts

	Unadjusted OR	Adjusted	*p* value
Initial NIHSS score, per 1 point increase	1.108 (1.013–1.212)	1.082 (0.987–1.186)	0.094
Initial diameter, per 1 mm increase	1.123 (1.074–1.175)	1.130 (1.078–1.184)	< 0.001
Initial number of lacunes, per 1 increase	1.109 (1.023–1.202)	1.092 (1.006–1.185)	0.031
Lesion location, anterior	2.133 (1.487–3.060)	2.117 (1.441–3.110)	< 0.001

The *p* value shown is from multivariate models

Data are presented as ORs (95% confidence intervals)

Data were adjusted for age, sex, the type of antiplatelet drug, use of statin, presence of diabetes mellitus, presence of hypertension, initial NIHSS score, initial diameter of the acute lacunar infarct, initial number of old lacunes and lesion location

NIHSS National Institute of Health Stroke scale, *OR* odds ratio

Table 3 Multivariate logistic regression analysis of disappearance of acute lacunar infarcts

	Unadjusted OR	Adjusted	*p* value
Initial diameter, per 1 mm increase	0.919 (0.873–0.967)	0.918 (0.870–0.970)	0.002
Lesion location, involving gray matter	1.550 (1.026–2.342)	1.114 (0.372–1.112)	0.114
Lesion location, posterior	5.634 (3.578–8.871)	7.428 (4.241–13.010)	< 0.001

The *p* value shown is from multivariate models

Data are presented as ORs (95% confidence intervals)

Data were adjusted for age, sex, the type of antiplatelet drug, use of statin, presence of diabetes mellitus, presence of hypertension, initial diameter of the acute lacunar infarct and lesion locations

OR odds ratio, *WML* white matter lesion

that resolves after an acute period, and subsequent gliotic change makes the lesion shrink on follow-up FLAIR images.

Cavitation was observed in lesions of 58.2% patients, which is consistent with that reported in previous studies (61% and 51.6%) [6, 11]. The pathological definition of lacunar infarcts requires a subcortical lesion with complete or partial cavitation with a maximal diameter of 15 or 20 mm [18]. Several studies have suggested that not all acute lacunar strokes remain cavitated [6–8, 11]. Therefore, the idea that acute symptomatic small vessel occlusion (lacunar infarct) goes to the lacuna with cavitation should be reconsidered. Focal lesion without cavitation could be the sequela of acute symptomatic lacunar infarcts, or they could disappear.

What kind of acute lacunar infarcts become cavitated? First, according to our results, acute lesions with a larger initial diameter evolved to cavitation more frequently. A larger infarct core with more neuronal cell loss may cause empty spaces such as a cavity during gliosis. Second, a higher number of old lacunes were correlated with cavitation. A higher risk of small vessel disease may affect cavitary change. Previous studies showed that the Fazekas score and periventricular WMLs were associated with cavitation [8, 11]. According to our univariate analysis, patients with cavitated lesions had more progression to WMLs compared to those without. Third, anterior lesion location was a predictive factor for cavitation even after adjusting for other factors. Acute lacunar infarcts in anterior circulation occur in the corona radiata, internal capsule, and basal ganglia, which mainly consist of white matter and tracts (myelinated axons). In posterior circulation, the thalamus, brainstem, and cerebellum, at which the compact presence of cell bodies and tracts are observed, are the main locations for lacunar infarcts. These pathologic differences may explain the significantly different proportion of lesions with cavitation. When they proceed to gliosis following ischemic insult and finally develop an empty space, the cavity would easily be made in anterior circulation with sparse density of cell body tissue. Another explanation for this finding is the less accurate FLAIR image, particularly of the brainstem, as there is the possibility of underestimation of the cavitary lesion.

Some may argue that the proportion of lesions with cavitation would increase over time even after this study period. One report showed that the time to follow-up affected the occurrence of cavitation [7]. However, the median follow-up of that study was only 8 months. We think our study's follow-up period is sufficient for including gliosis after ischemic injury. Additionally, analysis of the effect of the time interval on the development of cavitation did not show statistical significance. We could barely assume that the cavitation rate would increase thereafter.

In 23.6% of patients, acute lacunar infarcts could not be observed on follow-up FLAIR images, i.e., they disappeared. This finding was also reported in a previous study (26.6%) [6]. Patients with disappeared acute lacunar infarct had smaller diameter of acute lesion and lesser number of slices showing high signal on initial axial DWI. Lesion located at posterior circulation was predictive factors for disappearance. Small lesions could not be detected because of the inter-slice gap of conventional MRI. Also, patients with disappeared lesion had lesser mRPS. Lower small vessel disease burden during follow-up period might be attributed to disappearance of acute lacunar lesion. The proportion of the disappeared lesions is not negligible. The patients with a definite clinical symptom previously but without radiological evidence long after the symptom event should be candidates for secondary stroke prevention even though there is no MRI evidence of acute lacunar infarcts.

This study has some limitations. First, it was a sub-study of the PICASSO trial, which included Asian patients with a high risk of hemorrhagic stroke. Thus, the findings cannot be generalized to all patients with stroke. However, there were a sufficient number of patients to show a difference between those with and without cavitated lesions at follow-up. Our preliminary study showed a similar proportion of cavitated lesions and decrease in the diameter of acute lacunar lesions even in the general stroke population from a single center [6]. Second, we used only FLAIR imaging for follow-up. High-resolution T1-weighted MRI might show more cavitated lesions, but our result seems to be more pragmatic. Finally, we used a visual scale for rating WMLs, CMBs, and lacune. Volumetry methods might provide a more precise result; however, a visual scale is reliable and well correlated with results of volumetry methods [19] and it might be more practical to clinicians. Fourth, slice thickness of DWI was ranged from 3 to 6 mm and two magnetic field strengths (both 1.5T and 3T) were used in this study. However, about 80% of DWI showed a slice thickness of 5 mm. Fifth, as high-resolution MRI (HR-MRI) was not performed in this study, we could not identify the presence of branch atheromatous plaque. Further study with HR-MRI will give us more information about association between pathophysiology of lacune and their fate. Sixth, although initial NIHSS score was different among three groups, clinical lacunar syndromes (pure motor stroke, pure sensory stroke, sensorimotor stroke, ataxic hemiparesis, dysarthria clumsy hand syndrome and atypical lacunar syndrome) were not evaluated. As atypical lacunar syndrome is known to be associated with favorable outcome, future study is needed to evaluate an association between clinical lacunar syndrome and evolution pattern of lacunar infarct [20]. Finally, detailed neuropsychological tests were not performed. In this study, only baseline MMSE score was analyzed and it was not different among three groups. As mild neuropsychological abnormalities are known to be associated with presence of multiple old lacunes in patients with a first-ever lacunar infarct [21], detailed

neuropsychological tests might reveal difference among three groups. Future studies should include these data.

In conclusion, we observed a reduction of the acute lacunar lesion diameter in 86%. On follow-up FLAIR image, 58.2% showed cavitation and 28.6% disappeared. The initial lesion diameter, number of old lacunes, and anterior lesion location were the predictive factors of cavitary change, and the initial lesion diameter and posterior lesion location were the predictive factors of disappearance.

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Compliance with ethical standards

Conflicts of interest The authors have no conflicts of interest to report.

Ethical standards This study was approved by the ethics committee of each participating center and all participants were enrolled after written informed consent was obtained.

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