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ORIGINAL ARTICLE

Stroke patients with cerebral microbleeds on MRI scans have arteriolosclerosis as well as systemic atherosclerosis

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Cerebral microbleeds (CMBs) are recognized as a manifestation of arteriolosclerosis in cerebral small vessels. However, little is known regarding whether stroke patients with CMBs often have systemic atherosclerosis. The aim of the present study was to elucidate this issue using the cardio–ankle vascular index (CAVI), a new index of systemic atherosclerosis, in acute ischemic stroke patients. We prospectively studied 105 patients (71 males, median age = 70.0 years) with acute ischemic stroke. All of the patients were examined using T2*-weighted gradient echo magnetic resonance imaging (MRI) to look for and assess the CMBs and using fluid-attenuated inversion recovery to evaluate white matter hyperintensity (WMH). We assigned the patients into CMB and non-CMB groups and compared the clinical characteristics of these groups. The factors associated with CMBs were investigated using multivariate logistic regression analysis. T2*-weighted gradient echo MRI revealed CMBs in 47 patients (44.8%) and no CMBs in 58 patients (55.2%). The CAVI was significantly higher in the CMBs group (10.5 *vs.* 8.6, $P<0.001$). In the multivariate logistic regression analysis, CAVI per one point increase (odds ratio (OR), 1.50; 95% confidence interval (CI), 1.12–2.00; $P=0.006$), advanced WMH (OR, 4.78; 95% CI, 1.55–14.74; $P=0.006$) and impaired kidney function (OR, 3.31; 95% CI, 1.16–9.81; $P=0.031$) were independent factors associated with the presence of CMBs. A high CAVI was independently associated with CMBs in patients with acute ischemic stroke. Our results indicated that ischemic stroke patients with CMBs may have cerebral arteriolosclerosis as well as systemic atherosclerosis.
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Keywords: arteriolosclerosis; cardio–ankle vascular index; cerebral microbleeds; ischemic stroke; systemic atherosclerosis

INTRODUCTION

Cerebral microbleeds (CMBs), represented on T2*-weighted gradient echo magnetic resonance imaging (MRI) scans as spotty low-intensity areas, are found in 33.5–40.0% of patients with ischemic stroke,[1,2] and the presence of CMBs is recognized as a risk factor for subsequent intracerebral hemorrhage in such patients.[3] Histopathological analyses of the small cerebral vessels associated with CMBs have generally identified vascular pathological changes indicative of hypertensive arteriolosclerosis.[4,5]

Atherosclerosis of the systemic medium or large arteries is caused mainly by aging[6] and hypertensive wall damage.[7] Pulse wave velocity (PWV) is typically determined in the clinical setting to assess the grade of systemic atherosclerosis. Recently, the novel cardio–ankle vascular index (CAVI) was developed as an indicator of atherosclerosis.[8] A previous study showed that a CAVI $\geqslant$9.0 was associated with the presence of carotid plaques, increased intima media thickness and coronary artery disease.[9] Furthermore, Suzuki *et al.*[10] reported that CAVI was statistically greater in ischemic stroke patients with leukoaraiosis and small-vessel occlusion. However, no evidence has yet indicated that CAVI is associated with CMBs in patients with ischemic stroke. The present study examined the association between CMBs and CAVI and determined whether ischemic stroke patients with CMBs exhibited not only cerebral arteriolosclerosis but also systemic atherosclerosis.

METHODS

Patients

We prospectively enrolled consecutive patients with acute cerebral infarction or transient ischemic attack within 7 days after onset between October 2009 and September 2010. All of the patients underwent diffusion-weighted imaging, fluid-attenuated inversion recovery (FLAIR) and T2*-weighted gradient echo MRI imaging. Cerebral infarction was diagnosed as an acute neurological event lasting $\geqslant$24 h, which was explained by representative lesions on the MRI scan, including diffusion-weighted imaging. A transient episode of neurological dysfunction caused by focal brain ischemia lasting $\leqslant$24 h was defined as transient ischemic attack. We examined blood biochemistry, blood count, electrocardiogram, MRI and chest X-rays upon admission, and CAVI was determined within 14 days thereafter. Patients with heart valve replacements,

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pacemakers or clipped cranial arteries were excluded from this study, as MRI is contraindicated for such patients.

The following clinical data were collected from all of the patients: (1) age and gender; (2) National Institutes of Health Stroke Scale (NIHSS) score upon admission; (3) vascular risk factors, including hypertension, diabetes mellitus and hyperlipidemia; (4) atrial fibrillation; (5) impaired kidney function; (6) previous illness, such as stroke, ischemic heart disease or peripheral artery disease; (7) current smoking status and history of alcohol consumption; (8) pre-admission use of antithrombotic agents, such as antiplatelet agents and warfarin; (9) CAVI; and (10) ischemic stroke subtype, using Trial of Org 10172 in the Acute Stroke Treatment (TOAST) criteria.[11]

Risk factors

We assessed vascular risk factors based on the following definitions: (1) hypertension was defined as a history of using antihypertensive agents, a systolic blood pressure >140 mm Hg, or a diastolic blood pressure >90 mm Hg 14 days after the stroke; (2) diabetes mellitus was defined as the use of oral hypoglycemic agents or insulin, a fasting blood glucose of >126 mg dl^{-1}, or a glycosylated hemoglobin level $>6.4\%$; (3) hyperlipidemia was defined as the use of antihyperlipidemic agents or a serum cholesterol level >220 mg dl^{-1}; (4) impaired kidney function was defined as a serum estimated glomerular filtration rate of <60 ml^{-1} min per 1.73 m^2; (5) previous stroke was defined as a history of cerebral infarction or intracranial hemorrhage; (6) previous ischemic heart disease was defined as a history of angina pectoris or myocardial infarction; and (7) peripheral artery disease was defined as an ankle–brachial index of <0.9 on at least one side.

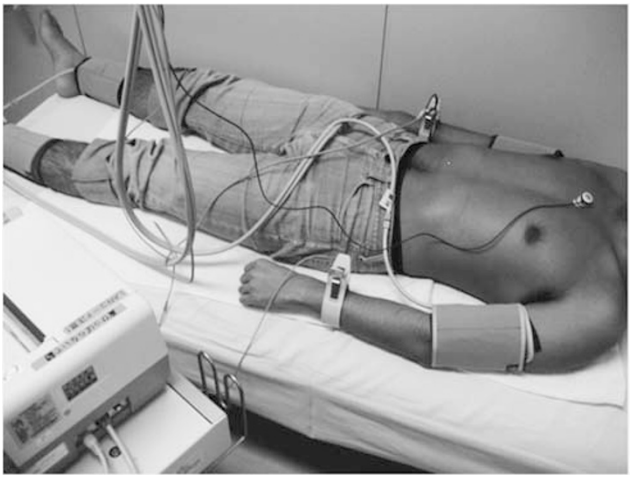

Figure 1 Measurement of the CAVI. The CAVI was automatically calculated from the pulse volume, blood pressure and vascular length from heart to ankle. CAVI, cardio–ankle vascular index.

Measurement of the CAVI

Technologists who were blinded to the clinical data measured the CAVI using an automated Vasera VS-1000 (Fukuda Denshi, Tokyo, Japan). Cuffs were applied to the four extremities, and electrocardiogram electrodes were attached to the upper arm. A microphone was placed on the sternal angle to obtain phonocardiograms. The patients rested in the supine position for 5 min (Figure 1). The PWV was calculated by dividing the distance from the aortic valve to the ankle artery by the sum of the time between the sound of the aortic valve closing and the notch of the brachial pulse wave and the time between the increase in the brachial and ankle pulse waves.

The CAVI was calculated from blood pressure and the PWV using the following equation:

$$\mathrm{CAVI} = 2\rho \times 1/(\mathrm{Ps} - \mathrm{Pd}) \times \ln(\mathrm{Ps}/\mathrm{Pd}) \times \mathrm{PWV}^2$$

(Ps, systolic blood pressure; Pd, diastolic blood pressure; ρ, blood density).

The higher CAVI obtained from either the left or right side was included in the analysis.

Neuroimaging of CMBs and white matter hyperintensity

We examined all of the patients by MRI within 7 days of admission using a Symphony Vision 1.5-T system (Siemens, Munich, Germany). The imaging protocol consisted of T2*-weighted gradient echo sequences (TR/TE, 484 ms/40 ms; field of view, 26 cm; acquisition matrix, 163×260; section thickness, 5.0 mm with a 0.5-mm intersection gap); a FLAIR sequence (TR/TE, 8550 ms/111 ms; field of view, 23 cm; acquisition matrix, 208×230; section thickness, 5.0 mm with a 0.5-mm intersection gap); and a diffusion-weighted imaging sequence (TR/TE, 2600 ms/79 ms; *b* values, 1000 and 50 s mm^{-2}; field of view, 23 cm; acquisition matrix, 230×230; section thickness, 5.0 mm with a 0.5-mm intersection gap). We defined CMBs as hypointense lesions 2–5 mm in diameter in the brain parenchyma identified in T2*-weighted gradient echo images (Figure 2a).

Patients with probable cerebral amyloid angiopathy according to the Boston criteria (multiple CMBs restricted to the cortical/corticosubcortical regions)

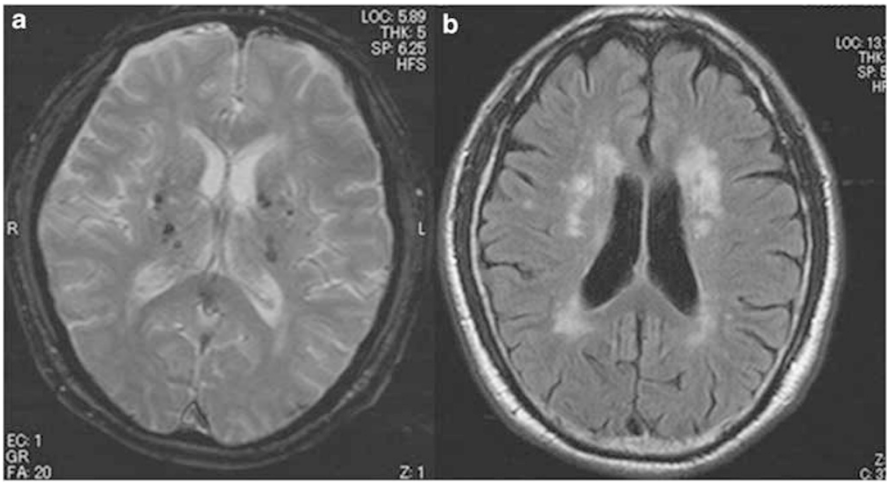

Figure 2 MRI scan of the brain of a 73-year-old male patient with lacunar infarction and a CAVI of 11.5. (**a**) A T2*-weighted gradient echo image shows multiple CMBs in the bilateral basal ganglia. (**b**) A FLAIR image shows advanced WMH. CAVI, cardio–ankle vascular index; CMBs, cerebral microbleeds; FLAIR, fluid-attenuated inversion recovery; WMH, white matter hyperintensity.

Table 1 Baseline clinical background of groups with and without CMBs

	All (n = *105*)	*CMBs* (n = *47*)	*Non-CMBs* (n = *58*)	P-*value*
Age, years; median (IQR)	70.0 (68.0–76.5)	72.0 (65.0–80.0)	66.5 (53.8–76.0)	0.017
Male, *n* (%)	71 (67.6)	36 (76.6)	35 (60.3)	0.095
NIHSS score; median (IQR)	3 (2–8)	3 (2–5)	2 (1–6)	0.461
Classification of stroke, n (%)				
Transient ischemic attack	9 (8.6)	3 (6.4)	6 (10.3)	
Large artery atherosclerosis	23 (21.9)	15 (31.9)	8 (13.8)	
Cardioembolism	26 (24.8)	9 (19.1)	17 (29.3)	
Small-vessel occlusion	18 (17.1)	11 (23.4)	7 (12.1)	
Other or undetermined cause	29 (27.6)	9 (19.1)	20 (34.5)	
Risk factors, n (%)				
Hypertension	79 (75.2)	42 (89.4)	37 (63.8)	0.003
Diabetes mellitus	39 (37.1)	17 (36.2)	22 (37.9)	1.000
Hyperlipidemia	52 (49.5)	21 (44.7)	31 (53.4)	0.434
Atrial fibrillation	21 (20.0)	5 (10.6)	16 (27.6)	0.048
Impaired kidney function	41 (39.0)	24 (51.1)	17 (29.3)	0.028
Previous stroke	24 (22.9)	17 (36.2)	7 (12.1)	0.005
Previous ischemic heart disease	11 (10.5)	7 (14.9)	4 (6.9)	0.213
Peripheral artery disease	23 (21.9)	13 (27.7)	10 (17.2)	0.239
Smoking	54 (51.4)	25 (53.2)	29 (50.0)	0.845
Alcohol	54 (51.4)	24 (51.1)	30 (51.7)	1.000
Antithrombotic agents	45 (42.9)	24 (51.1)	21 (36.2)	0.165
Advanced WMH, *n* (%)	47 (44.8)	32 (68.1)	15 (25.9)	<0.001
CAVI; median (IQR)	9.3 (8.1–10.7)	10.5 (9.2–11.7)	8.6 (7.6–10.2)	<0.001

Abbreviations: CAVI, cardio–ankle vascular index; CMBs, cerebral microbleeds; IQR, interquartile range; NIHSS, National Institute of Health Stroke Scale; WMH, white matter hyperintensity.
Advanced WMH was defined as WMH of grades 2 or 3 using scoring system of Fazekas *et al*.

were excluded from this study.[12] Hypointense lesions within the subarachnoid space were regarded as pial blood vessels. Symmetric hypointense lesions in areas of the globus pallidus were regarded as calcification, and intracerebral lesions with a hemorrhagic component were excluded.

The severity of white matter hyperintensity (WMH) in the FLAIR images was scored as described by Fazekas *et al*.[13] into grades of 0, absent; 1, punctuate; 2, early confluent; and 3, confluent. Grade 2 or 3 WMH was regarded as advanced WMH (Figure 2b). One neurologist (TS) who was blinded to the clinical information evaluated the MRI images. The medical ethics committee of the Jikei University School of Medicine approved the study.

Statistical analysis

All of the patients were assigned to groups based on the presence or absence of CMBs, and their clinical characteristics were compared. Univariate analysis was performed using Fisher's exact test and the Mann–Whitney *U* test. Receiver operating characteristic curves analysis was performed to determine the cut-off values of CAVI to differentiate the two groups. Variables with *P*-values of <0.1 were included in the multivariate logistic regression analyses to determine factors that are independently associated with the presence of CMBs.

Then, linear regression analysis was used to test the association between the number of CMBs and the CAVI. Moreover, we also compared the clinical characteristics between the patients with single and multiple ($\geqslant 2$) CMBs. The data were statistically analyzed using the Statistical Package for the Social Sciences (SPSS ver. 17.0) software for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 113 patients were admitted to the Jikei University Hospital with acute ischemic stroke during the study period. We excluded two patients who were diagnosed with cerebral amyloid angiopathy, three with pacemakers and three who did not undergo CAVI determination because of a leg fracture ($n=1$) or death soon after admission ($n=2$). We therefore enrolled 105 patients (median age, 70.0 years; male, $n=71$; median NIHSS score, 3).

T2*-weighted gradient echo MRI revealed CMBs in 47 patients (44.8%) and no CMBs in 58 patients (55.2%). The characteristics of the two groups are shown in Table 1. The CMB group was significantly older than the non-CMB group (72.0 *vs.* 66.5 years; $P=0.017$). Hypertension, impaired kidney function and advanced WMH were more frequent (89.4% *vs.* 63.8%, $P=0.003$; 51.1% *vs.* 29.3%, $P=0.028$ and 68.1% *vs.* 25.9%, $P<0.001$), whereas atrial fibrillation was less frequent, in the CMB group than in the non-CMB group (10.6% *vs.* 27.6%, $P=0.048$). The use of antithrombotic agents before admission did not significantly differ between the two groups. The CAVI was significantly higher in the CMB group (10.5 *vs.* 8.6, $P<0.001$).

The factors with representative values of $P<0.1$ in the univariate analysis were age per 10 year increase, male sex, hypertension, previous stroke, atrial fibrillation, impaired kidney function, advanced WMH and CAVI per one point increase; these factors were included in the multivariate logistic regression analysis (Table 2, Model 1). CAVI per one point increase (odds ratio (OR), 1.50; 95% confidence interval (CI), 1.12–2.00; $P=0.006$), advanced WMH (OR, 4.78; 95% CI, 1.55–14.74; $P=0.006$) and impaired kidney function (OR, 3.31; 95% CI, 1.16–9.81; $P=0.031$) were independent factors associated with the presence of CMBs. Using receiver operating characteristic curves, the cut-off level for the CAVI in the presence of CMBs was 9.2

Table 2 Multivariate logistic analysis model to evaluate independent factors for the presence of CMBs

	Model 1			*Model 2*		
	OR	*95% CI*	P-*value*	*OR*	*95% CI*	P-*value*
Male	1.15	0.39–3.40	0.806	1.12	0.38–3.32	0.842
Age (per 10 years)	0.98	0.93–1.03	0.806	0.98	0.93–1.03	0.842
Hypertension	1.11	0.29–4.18	0.880	1.28	0.34–4.74	0.715
Impaired kidney function	3.31	1.16–9.81	0.031	2.81	0.97–8.20	0.058
Previous stroke	1.96	0.53–7.24	0.310	1.79	0.50–6.36	0.376
Atrial fibrillation	0.16	0.04–0.70	0.015	0.18	0.05–0.73	0.017
CAVI (per one point increase)	1.50	1.12–2.00	0.006	—	—	—
CAVI $\geqslant$9.2	—	—	—	5.46	1.59–18.75	0.007
Advanced WMH	4.78	1.55–14.74	0.006	3.92	1.30–11.84	0.016

Abbreviations: CAVI, cardio–ankle vascular index; CI, confidence interval; CMBs, cerebral microbleeds; OR, odds ratio; WMH, white matter hyperintensity.
Advanced WMH is defined as grade 2 or 3 WMH using the scoring system of Fazekas *et al*.
Impaired kidney function is defined as serum estimated glomerular filtration rate $<60\,ml^{-1}$ min per $1.73\,m^2$.
Model 1: male, age (per 10 years), hypertension, impaired kidney function, previous stroke, atrial fibrillation, CAVI (per one point increase) and advanced WMH.
Model 2: male, age (per 10 years), hypertension, impaired kidney function, previous stroke, atrial fibrillation, CAVI $\geqslant$9.2 and advanced WMH.

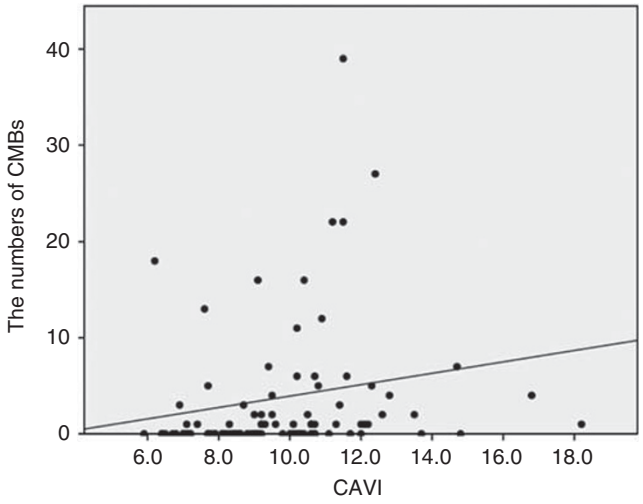

Figure 3 Linear regression analysis of the number of CMBs and the CAVI. There was a weak but statistically significant relationship between the number of CMBs and the CAVI ($R^2 = 0.040$, $P = 0.041$). CAVI, cardio–ankle vascular index; CMBs, cerebral microbleeds.

(sensitivity, 78.7%; specificity, 65.5%). We also tested two categories (CAVI$\geqslant$9.2 or $<$9.2) with the same adjustment applied (Table 2, Model 2). A CAVI$\geqslant$9.2 was independently associated with CMBs (OR, 5.46; 95% CI, 1.59–18.75; $P = 0.007$).

There was a weak but statistically significant relationship between the number of CMBs and the CAVI ($R^2 = 0.040$, $P = 0.041$; Figure 3). Thirty-one patients (29.5%) had multiple CMBs on T2*-weighted gradient echo MRI scans. No significant differences in age, sex or any risk factors were observed between the two groups. There was no difference in the CAVI between the patients with single and multiple CMBs (10.4 *vs.* 10.5, $P = 0.613$).

DISCUSSION

The present study found that the CAVI is independently associated with the presence of CMBs. It also found that advanced WMH and impaired kidney function are associated with the presence of CMBs. However, there was no factor, including the CAVI, that significantly distinguished patients with single CMBs from those with multiple CMBs.

We found a correlation between the CAVI (the new index of atherosclerosis) and CMBs in patients with acute ischemic stroke. Our results were partially in line with the previous findings of a close association between the PWV and CMBs.[14–16] However, the PWV is affected by changes in blood pressure during measurement and might not accurately reflect atherosclerosis in hypertensive patients.[8] In contrast, the CAVI is less influenced by blood pressure during measurement than is the PWV.[8] However, the mechanisms linking the CAVI and CMBs are complex and therefore not well understood. One possibility is that the CAVI reflects atherosclerosis in systemic large arteries, including the carotid, coronary and peripheral arteries.[8] Moreover, atherosclerosis in large extracranial[17] or intracranial arteries[18] also leads to arteriolosclerosis in small cerebral vessels and to the development of CMBs. Thus, systemic atherosclerosis may have a key role in the occurrence of cerebral arteriolosclerosis and CMBs. Indeed, the presence of CMBs is a risk factor not only for subsequent intracerebral hemorrhage in patients with ischemic stroke[3] but also for antithrombotic-related intracerebral hemorrhage.[19,20] Therefore, patients with a history of ischemic stroke and an elevated CAVI should be evaluated for CMBs and appropriately treated with antihypertensive and antithrombotic drugs to avoid intracerebral hemorrhage.

The present study demonstrated a significant relationship between advanced WMH and CMBs, which supports the results of other studies indicating a higher frequency of CMBs in patients with ischemic stroke accompanied by severe leukoaraiosis.[21,22] Pathologically, WMH and CMBs are attributed to cerebral small-vessel disease, such as the loss of smooth muscle cells, lumen restriction, vessel wall thickening, vessel wall damage and microaneurysms.[4,5] Interestingly, Suzuki *et al.*[10] showed that WMH was also correlated with the CAVI in ischemic stroke patients. Moreover, previous studies have established a strong association between the CAVI and small-vessel disease of other organs.[23,24] Kubozono *et al.*[23] reported a relationship between the CAVI and a low estimated glomerular filtration rate. Kim *et al.*[24] identified a correlation between the CAVI and microvascular complications in type 2 diabetes mellitus patients without a history of macrovascular disease. The CAVI may thus be a marker of small-vessel disease of various organs, including the brain.

Impaired kidney function was associated with CMBs in this study, which was in agreement with the finding that a low GFR is associated with CMBs.[25] We postulated that endothelial dysfunction might have a key role in impaired kidney function and in the development of CMBs. The kidneys and the brain are early targets for damage by elevated blood pressure.[26] Blood pressure is the major determinant of arteriosclerosis and endothelial dysfunction in patients with chronic kidney disease,[27] and endothelial dysfunction within capillaries appears to contribute to the development of CMBs.[28] Recent studies have shown that endothelial dysfunction is an important mechanism of cerebrovascular damage in patients with lacunar infarction[29] that is correlated with an increased risk of acute ischemic stroke.[30] However, the exact mechanism remains unclear.

The present study has several limitations. First, measurements of the CAVI might not be accurate in patients with severe aortic stenosis, peripheral arterial disease or atrial fibrillation.[22] Second, antihypertensive agents influence arteriosclerosis, and it cannot be excluded that the CAVI was affected in patients taking such drugs.[31] Finally, we could not find any significant factors, including the CAVI, that distinguish between the patients with single CMBs and those with multiple CMBs. The number of patients in our study was relatively small. Further studies are needed to evaluate the association of the CAVI with systemic atherosclerosis and CMBs.

In conclusion, we found that CMBs are independently associated with a high CAVI. We also found that stroke patients with CMBs more frequently exhibit arteriolosclerosis and systemic atherosclerosis than those without CMBs.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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