Effectiveness of Nonvitamin K Antagonist Oral Anticoagulants and Warfarin for Preventing Further Cerebral Microbleeds in Acute Ischemic Stroke Patients with Nonvalvular Atrial Fibrillation and At Least One Microbleed: CMB-NOW Multisite Pilot Trial

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Background: Nonvitamin K antagonist oral anticoagulants (NOACs) are considered superior, or at least noninferior, to warfarin in preventing stroke or systemic embolism in patients with nonvalvular atrial fibrillation. Here, we recruited acute ischemic stroke patients with nonvalvular atrial fibrillation and at least one cerebral microbleed (CMB), and evaluated the proportion of patients who had an increased number of CMBs (%) after receiving anticoagulant therapy with NOACs or with warfarin for 12 months. *Methods:* This was a multicenter, prospective, observational cohort study at 20 centers, conducted between 2015 and 2017, in which we recruited 85 patients with at least one CMB detected by 1.5T magnetic resonance imaging (T2*WI) at baseline, who received NOACs or warfarin for at least 12 months. We compared the proportions of patients with increased numbers of CMBs in the NOACs and warfarin treatment groups. *Results:* The proportions of patients with increased numbers of CMBs at month 12 of treatment were 28.6% and 66.7% in the NOACs and warfarin groups, respectively. The new CMBs showed no specific regional localization in either group. In the NOACs and warfarin groups, physicians prescribed lower-than-standard dosing in 13.3% and 50% of the cases, respectively. The administration of reduced doses at physicians' discretion did not appear to alter the incidence of new CMBs. *Discussion:* This is the first evidence to suggest

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efficacy of NOACs for preventing further CMBs in patients with at least one CMB, although no statistical evaluation was carried out.

Key Words: Acute ischemic stroke—anticoagulant—cerebral microbleeds—MRI—NOACs—warfarin

Introduction

Anticoagulants, especially warfarin, are generally prescribed to prevent the recurrence of ischemic stroke (IS) in patients with nonvalvular atrial fibrillation (NVAF)[1], but may cause bleeding, particularly intracranial hemorrhage, including intracerebral hemorrhage (ICH).[2] Cerebral microbleeds (CMBs) appear as small round hypointense lesions on T2*-weighted[3] and susceptibility-weighted magnetic resonance imaging (MRI), [4] and were identified as a predictor of future ICH in prospective observational studies of patients with either ICH or IS.[5,6] A high incidence of ICH is reported in patients with multiple CMBs, particularly those with CMBs ≥5.[7] Among CMB-positive patients, a high incidence of intracranial hemorrhage associated with oral anticoagulation therapy has been reported.[8] The incidence and absolute number of CMBs increase in proportion to $CHADS_2$ score in patients with IS accompanied by NVAF.[9] Imaizumi et al.[10] found that warfarin alone did not increase the incidence of ICH in all subjects with CMBs, but subjects with 3 or more deep CMBs did show an increased incidence. A meta-analysis conducted by Lovelock et al.[11] found a higher incidence of CMBs in patients with ICH receiving warfarin than in patients with ICH not receiving antithrombotic therapy. Further, Orken et al.[12] found that patients who had one or more CMBs at baseline developed more additional CMBs after 2 years (26%), compared with patients (12%) who did not have any CMB at baseline ($P = .03$). All these findings strongly suggest a relationship between the occurrence or absolute number of CMBs and the development of intracranial hemorrhage during warfarin therapy. However, there has been no study so far on the progression of CMBs in patients receiving nonvitamin K antagonist oral anticoagulants (NOACs).

Recent studies indicate that NOACs, including dabigatran,[13] rivaroxaban,[14] apixaban,[15] and edoxaban,[16] are superior, or at least noninferior, to warfarin in preventing IS or systemic embolism in patients with NVAF, and they have been reported to significantly reduce the incidence of hemorrhagic stroke. On the other hand, the proportion of patients with at least one CMB was higher in ICH patients than in IS patients receiving NOACs, as was the absolute number of CMBs.[4] In this context, we recruited acute IS patients with NVAF who showed at least one CMB, and we evaluated and compared the proportion of patients with an increased number of CMBs (%) after receiving anticoagulant therapy with NOACs or with warfarin for 12 months.

Methods

Study Design

The Cerebral Microbleeds as a Predictor of Future Intracerebral Hemorrhage during NOACs or Warfarin Therapy in NVAF Patients with Acute Ischemic Stroke (CMB-NOW) study was an investigator-initiated, multicenter, cohort, prospective, observational clinical trial comparing NOACs (dabigatran, rivaroxaban, apixaban, or edoxaban) and warfarin therapy during 12 months.[17] This trial was registered with ClinicalTrials.gov (ClinicalTrials.gov Identifier: NCT02356432), and was approved by each local ethics committee, including that of Tokai University Hospital (No. 14R-155). All patients gave written informed consent, or assent was obtained from relatives of patients who were unable to provide consent.

We recruited acute IS patients with NVAF and at least one CMB detected by 1.5T MRI (T2*WI) at baseline, who were given NOACs or warfarin for at least 12 months. We compared the proportion of patients with an increased number of CMBs at month 12 of treatment with NOACs or warfarin. Trained neurologists, neurosurgeons or nurses in participating hospitals performed clinical assessment at baseline, 6 months, and 12 months after registration. Prior to registration, clinical assessment items included age, gender, height, weight, smoking history, amount of alcohol consumption, pre-existing conditions and co-morbidity, and antithrombotic therapy prior to onset of IS/transient ischemic attack; these data were recorded. For quality assurance, data validation and registry procedures included site monitoring and auditing.

Selection Criteria

Inclusion and exclusion criteria were listed elsewhere.[17] Briefly, medication with NOACs (dabigatran, rivaroxaban, apixaban, or edoxaban) or warfarin, as well as dosing, was prescribed by each attending physician without restriction, based on assessment of the condition of each patient. The physicians' discretion to prescribe appropriate treatment (drugs, regimen, and dosage) for atrial fibrillation, dyslipidemia, diabetes mellitus, and hypertension during the follow-up period was also not restricted in any way. Patients receiving antiplatelet agents were not permitted to receive anticoagulants concomitantly.

Dosing Schedules

Standard anticoagulant treatment schedules were as follows.

Dabigatran: Dabigatran 150 mg was given orally twice daily after meals. For patients meeting any one of the following criteria, the dose was 110 mg orally twice daily after meals: age ≥70 years, moderate renal impairment (CrCL 30-50 mL/min), receiving P-glycoprotein inhibitors, or at increased bleeding risk.

Rivaroxaban: Rivaroxaban 15 mg was given once daily after a meal. For patients with renal impairment (CrCL 30-49 mL/min), the dose was 10 mg orally once daily after a meal.

Apixaban: Apixaban 5 mg was given orally twice daily after meal. For patients meeting any 2 of the following criteria, the dose was 2.5 mg orally twice daily after meals: age ≥80 years, body weight ≤60 kg, and serum creatinine ≥1.5 mg/dL.

Edoxaban: Edoxaban 60 mg was given orally once daily after meals. For patients meeting any one of the following criteria, the dose was 30 mg orally once daily after meals: renal impairment (CrCL 30-50 mL/min), body weight ≤60 kg or receiving P-glycoprotein inhibitors.

Warfarin: Prothrombin time-international normalized ratio (PT-INR) was controlled in accordance with the JCS2008 guideline concerning the drug treatment of atrial fibrillation, that is, INR 2.0 to 3.0 in patients younger than 70 years, or INR 1.6 to 2.6 in patients not younger than 70 years.[18]

Lower doses than those described above were given at the attending physician's discretion, and are described as "reduced doses" in this work.

Imaging Analysis

CMBs were defined as asymptomatic, small, round, hypointense spots with diameter ≤10 mm on a T2*-weighted gradient-echo MR image.[19] Prior to registration, the presence of CMBs was diagnosed by means of 1.5 Tesla MRI by neurologists or neurosurgeons with Japanese Board Certification in Neurology or Neurosurgery, respectively, who are members of the CMB-NOW study. Subsequently, all radiological data including diffusion-, T1-, T2-, and T2*-weighted images was evaluated by neuroradiologists (N.Y. and T.O.) in the Cerebral Microbleeds Evaluation Committee using the assessment scale of Gregoire et al.[19] in a blinded state. White matter lesions were also evaluated according to the classification by Fazekas et al.[20]

Statistical Analysis

Primary endpoint was the proportion of subjects with an increased number of CMBs at month 12 of treatment with NOACs or warfarin. Comparison between the NOACs group and the warfarin group was also made for secondary endpoints (proportion with new CMBs at month 6, number of new CMBs at months 6 and 12, location of CMBs (infratentorial, lobar, and deep described as previous paper[21]), white matter lesions, and the incidence of adverse events).

Data are presented as the mean ± SD (normal continuous distribution data; patients' characteristics) or median with interquartile range (non-normal continuous data; whole counts of CMBs), and as counts or percentages for categorical data. Statistical significance was defined as 2-sided at the 5% level. For normal continuous distribution data, the independent sample t test was employed. When the 2 caudal sides were $P < .05$, the difference was taken as statistically significant. The analysis was done with SPSS Statistics 20.0 software.

Results

Baseline Characteristics of Patients

Between March 30, 2015, and September 26, 2017, 85 potentially eligible patients (75 in the NOACs group and 10 in the warfarin group) at 20 hospitals located mainly in Kanagawa prefecture, Japan (see Supplementary File), were recruited to join the study. After neuroimaging quality assurance, our final analysis included 66 patients at 6 months and 62 patients at 12 months after registration.

Table 1. *Demographic characteristics of patients*

Variable	Total	NOACs group	Warfarin group	*P* value
Number of patients n, (%)	85	75 (88.2)	10 (11.8)	–
Age (y, mean ± Standard deviation)	74.6 ± 7.6	74.8 ± 7.3	73.0 ± 10.1	.60
Sex distribution n, (% men)	60 (70.1)	53 (70.7)	7 (70.0)	1.00
Smoking n, (%)	33 (38.8)	28 (37.3)	5 (50.0)	.64
Alcohol abuse n, (%)	33 (38.8)	28 (37.3)	5 (50.0)	.22
Previous atrial fibrillation n, (%)	62 (72.9)	52 (69.3)	10 (100.0)	.06
Previous paroxysmal atrial fibrillation n, (%)	23 (27.1)	23 (30.7)	0 (0.0)	.06
Previous cerebral infarct n, (%)	18 (21.2)	15 (20.0)	3 (30.0)	.44
Previous transient ischemic attack n, (%)	1 (1.2)	1 (1.3)	0 (0.0)	1.00
Previous anticoagulant medication n, (%)	28 (32.9)	24 (32.0)	4 (40.0)	.72
Hypertension n, (%)	57 (67.1)	50 (66.7)	7 (70.0)	1.00
Diabetes mellitus n, (%)	23 (27.1)	15 (20.0)	8 (80.0)	.44
Dyslipidemia n, (%)	28 (32.9)	22 (29.3)	6 (60.0)	.07

NOACs, Nonvitamin K antagonist oral anticoagulants.

Table 1 summarizes the demographic characteristics of patients in the NOACs and warfarin groups. We found no significant differences in demographics or stroke risk factors between the 2 groups ($P < .05$). The baseline characteristics of patients, including blood pressure, body mass index, and blood chemistry, are summarized in Table 2; there were no significant differences between the 2 groups.

Proportion of Patients with an Increased Number of CMBs

The proportions of patients with an increased number of CMBs at month 12 were 28.6% (16 out of 56 patients) and 66.7% (4 out of 6 patients) in the NOACs and warfarin groups, respectively. The corresponding proportions at 6 months were 22.0% (13 out of 59 patients) and 57.1% (4 out of 7 patients), respectively. The whole number of CMBs was not significantly changed both in NOACs group (median: 3.0 [interquartile range: 8.0] versus 3.0 [7.0]) and in warfarin group (6.0 [5.0] versus 6.0 [7.0]) between 6 months and 12 months. These primary endpoints are summarized in Table 3. We did not carry out statistical comparison, because the numbers of subjects were small.

Locations of CMBs and White Matter Lesions at Month 12

The proportions of patients with an increased number of CMBs (%) in the infratentorial, lobar, and deep white matter regions are summarized in Table 4. There were no clear specific regional differences, although statistical comparison was not carried out. As for white matter lesions, there were no apparent differences according to Fazekas' classification.[20]

Adverse Events in Each Group During 12 Months

Table 5 showed adverse events in each group during 12 months, including death due to cardiovascular events, cerebral infarction, symptomatic intracranial hemorrhage and others. The incidence of adverse events was rare in both groups.

Influence of Reduced Dosing

In this study, doctors' discretion to prescribe appropriate treatment was not restricted, and reduced doses of warfarin and NOACs were prescribed in 50% and 13.3% of the cases, respectively. Reduced dosing did not appear to be related to increased numbers of CMBs. Thus, "real-world" treatment with reduced doses of anticoagulants does not appear to have adverse consequences for patients (Table 6).

Relation Between Increase of CMBs and Blood Chemistry

The low-density lipoprotein (LDL) cholesterol level appeared to be unrelated to increase of CMBs (109.5 ± 29.1 in all patients: 107.1 ± 34.2 in patients with an increased number of CMBs). We also found no relation between

Table 2. *Baseline characteristics of patients at registration*

Variable	Total	NOACs group	Warfarin group	*P* value
Blood pressure				
Systolic pressure (mmHg)	144.4 (25.4)	144.4 (26.3)	144.8 (17.5)	.96
Dyastolic pressure (mmHg)	83.1 (16.8)	82.7 (16.9)	86.6 (16.7)	.49
Pulse rate (min)	75.5 (20.1)	75.7(19.1)	74.6 (28.0)	.88
BMI	23.7 (4.2)	23.5 (4.1)	25.1 (4.7)	.25
Hemoglobin (gram/dL)	13.7 (1.8)	13.7 (1.8)	13.5 (1.4)	.67
Ht (%)	41.2 (5.2)	41.2 (5.3)	41.0 (4.5)	.90
PT-INR	1.9 (0.3)	-	1.9 (0.3)	-
AST (U/L)	26.1 (13.8)	26.5 (14.4)	23.7 (7.1)	.33
ALT (U/L)	21.2 (27.2)	21.7 (28.8)	16.9 (8.3)	.26
Blood urea nitrogen (mg/dL)	16.5 (5.8)	16.5 (5.7)	17.2 (6.6)	.70
T-Bil (mg/dL)	0.9 (0.4)	0.9 (0.4)	0.7 (0.2)	.08
Creatinine (mg/dL)	0.9 (0.3)	0.9 (0.3)	1.0 (0.4)	.46
Ccr (mL/min)	64.3 (23.0)	64.0 (22.4)	66.6 (28.4)	.73
T-Chol (mg/dL)	181.2 (33.7)	182.2 (32.5)	172.7 (45.3)	.52
LDL-Chol (mg/dL)	109.5 (29.1)	110.4 (27.4)	102.0 (40.8)	.42
HDL-Chol (mg/dL)	53.3 (14.1)	53.1 (13.9)	55.5 (16.6)	.65
Triglyceride (mg/dL)	106.2 (52.5)	105.9 (53.7)	108.8 (45.2)	.88
Fasting glucose (mg/dL)	126.0 (43.4)	123.6 (42.2)	142.7 (50.0)	.19
HbA1c (%)	6.2 (1.1)	6.2 (1.2)	6.4 (1.1)	.53
BNP (pg/mL)	219.8 (235.8)	219.4 (249.3)	222.3 (150.2)	.97

AST, aspartate transminase; ALT, Alanine aminotransferase; BNP, brain natriuretic peptide; HbA1c, Hemoglobin A1C; HDL Chol, high-density lipoprotein; LDL Chol, low-density lipoprotein; NOACs, Nonvitamin K antagonist oral anticoagulants.

Table 3. *CMBs at months 6 and 12 of treatment with NOACs or warfarin*

Proportion of patients with increased number of CMBs at month 12			
	Total group	NOACs group	Warfarin group
Total patients (n)	62	56	6
Patients with increased number of CMBs (n)	20	16	4
Proportion of patients with increased number of CMBs (%)	32.3	28.6	66.7

Proportion of patients with increased number of CMBs at month 6			
	Total group	NOACs group	Warfarin group
Total patients (n)	66	59	7
Patients with increased number of CMBs (n)	17	13	4
Proportion of patients with increased number of CMBs (%)	25.8	22.0	57.1

Whole counts of CMBs in patients treated with in NOACs and warfarin (median (IQR))			
	Total group	NOACs group	Warfarin group
Baseline	3.0 (7.0)	2.0 (6.0)	6.5 (7.0)
At 6 months	3.0 (6.0)	3.0 (8.0)	6.0 (5.0)
At 12 months	3.5 (7.0)	3.0 (7.0)	6.0 (7.0)

CMBs, Cerebral microbleeds; IQR, Interquartile Range; NOACs, Nonvitamin K antagonist oral anticoagulants.

increase of CMBs and abnormalities of blood chemistry, including hemoglobin, PT-INR, aspartate transminase, alanine aminotransferase, urea nitrogen, total bilirubin, creatinine, total cholesterol, high-density lipoprotein cholesterol, triglyceride, glucose, HbA1c, and brain natriuretic peptide (data not shown).

Discussion

This is the first study of the efficacy of NOACs for preventing increase of CMBs in acute IS patients with NVAF and at least one CMB, although the number of patients was too small for statistical evaluation to be carried out. NOACs have been reported to show secondary preventive effects against hemorrhagic transformation depending on age, body weight, and renal function in several large clinical trials and also in postmarketing research.[22,23] Soo et al.[24] reported that NOACs exposure was unrelated to the development of new CMBs. However, the duration of NOACs exposure was variable, and no comparison with warfarin was made.[24] Further, NOACs have been also started prior to recruitment in about 40% of IS patients,[24] which is different from our study protocol that NOACs was started after recruitment. Interestingly, we found that new CMBs developed in 6 months after given not only warfarin (57.1%), but also NOACs (22.0%)

Table 4. *Proportion of subjects with increased numbers of CMBs in each brain region at 12 months*

CMBs		Total	NOACs group	Warfarin group
Infratentorial	Patients with increased number of CMBs (n)	9	8	1
	Proportion of patients with increased number of CMBs (%)	14.5	12.9	16.7
Lobar	Patients with increased number of CMBs (n)	15	13	2
	Proportion of patients with increased number of CMBs (%)	24.2	23.2	33.3
Deep	Patients with increased number of CMBs (n)	16	15	2
	Proportion of patients with increased number of CMBs (%)	25.8	26.8	33.3
White matter changes		Total	NOACs group	Warfarin group
Deep and periventricular white matter lesion (Fazekas et al, Ref 21)	Patients with increased grade of Fazekas classification (n)	0	0	0
	Proportion of patients with increased grade of Fazekas classification (%)	0.0	0.0	0.0

CMBs, Cerebral microbleeds; NOACs, Nonvitamin K antagonist oral anticoagulants.

Table 5. *Adverse events in each group during 12 months*

	Total	NOACs group	Warfarin group
Death due to cardiovascular events n, (%)	1 (1.2)	1 (1.3)	0 (0.0)
Reccurrence of cerebral infarction n, (%)	2 (2.4)	2 (2.7)	0 (0.0)
Occuurence of symptomatic intracranial hemorrhage n, (%)	2 (2.4)	2 (2.7)	0 (0.0)
Others*	5 (5.9)	3 (4.0)	2 (20.0)

NOACs, Nonvitamin K antagonist oral anticoagulants.
*Death due to unknown etiology (2 patients), Admission due to pneumonia (1 patient), lung carcinoma (1 patient) and mammary carcinoma (1 patient)

treatments, in patients with at least one CMB. We believe our present results will be helpful in selecting the appropriate anti-coagulant for patients with at least one CMB.

It has been suggested that NOACs could be a risk factor for cerebral hemorrhage in CMB-positive patients, compared to CMB-negative patients.[25] In the present study, anticoagulants were chosen at the discretion of the attending clinicians, so there is a possibility of selection bias. Nevertheless, patients with an increase in the number of CMBs were more frequently seen in the warfarin group than in the NOAC group at both 6 and 12 months after starting treatment in our study. Although we cannot conclude the superiority of NOACs for CMB-positive patients because of the small numbers of patients, we can at least say that NOACs appear to be safe and noninferior to warfarin in these patients. Increases of CMBs counts were seen equally in both lobar and deep white matter regions, regardless of the anticoagulant used. Lee et al.[8] reported a higher prevalence of CMBs in lobar regions after anticoagulation, which was suggestive of amyloid angiopathy. On the other hand, Romero et al.[21] reported that hypertension, lower total cholesterol, and use of statins were related to the incidence of CMBs in both lobar and deep white matter, which was different from our results. Marinescu et al.[26] reported that anticoagulation with warfarin or dabigatran did not influence the increase of CMB counts in amyloid precursor protein 23 mice, which developed CMBs in both lobar and deep brain lesions. Thus, the increase of CMBs counts due to anticoagulants might be promoted by atherosclerotic factors including hypertension, but not amyloid angiopathy. Further, the increase of CMBs counts were frequently seen in first 6 months rather than after 6 months. Several factors might be associated as follows: initially, blood pressure could fluctuate largely in early phase of ischemic stroke. Subsequently, vascular endothelial dysfunction leading to CMB appearance could not recover in first 6 months. In addition, disappearance of CMBs due to phagocytosis by microglia

Table 6. *Patients receiving reduced doses of each anticoagulant*

Anticogulants		Number of patients, n	Number of patients receiving normal dose, n (%)	Number of patients receiving underdose, n (%)
Warfarin	Total patients	10	5 (50.0)	5 (50.0)
	Patients with increased number of CMBs	4	2 (50.0)	2 (50.0)
	% of patients with increased number of CMBs		40%	40%
NOACs	Total patients (edoxaban, dabigatran, rivaroxaban, apixaban)	75	65 (86.7)	10 (13.3)
	Patients with increased number of CMBs	16	14 (87.5)	2 (87.5)
	% of patients with increased number of CMBs		21.5%	20.0%
Edoxaban	Total patients	11	9 (81.1)	2 (18.2)
	Patients with increased number of CMBs	1	1 (100)	0 (0.0)
Dabigatran	Total patients	6	4 (66.7)	2 (33.3)
	Patients with increased number of CMBs	0	0 (0.0)	0 (0.0)
Rivaroxaban	Total patients	28	26 (92.9)	2 (7.1)
	Patients with increased number of CMBs	8	7 (87.5)	1 (12.5)
Apixaban	Total patients	30	26 (86.7)	4 (13.3)
	Patients with increased number of CMBs	7	6 (85.7)	1 (14.3)

CMBs, Cerebral microbleeds; NOACs, Nonvitamin K antagonist oral anticoagulants.

and oligodendrocyte[27] has gradually occurred depends on the duration after the stroke onset, which might affect the changes in CMBs.

As regards the dose of anticoagulant, reduced-dose treatment was given in 50.0% of the warfarin group and 13.3% of the NOAC group. Pharithi et al.[28] reported reduced dosing of NOAC in about 19.0% of recruited patients. In general, warfarin treatment in CMB-positive patients is well known as a risk factor of hemorrhagic transformation, and thus CMB-positive patients are often given a reduced dose of warfarin. Interestingly, reduced-dose treatment did not appear to alter the efficacy of treatment for preventing increase of CMB counts among our patients. Recently, Sato et al.[29] has reported that inappropriate low dose NOAC treatment could not reduce the incidence of major bleeding, compared to appropriate dose NOAC treatment, suggesting that hemorrhagic transformation through vascular endothelial dysfunction may be induced by NOACs treatments, regardless of these dosages. Apart from anticoagulant and dosing, Lee et al.[30] reported that higher LDL-C was associated with a decrease of CMB counts. In contrast, we found no significant relationship between LDL-C and CMB counts. However, hydroxymethylglutaryl-CoA reductase was more frequently used in the NOACs group (88.2%) compared to the warfarin group (11.8%) before starting anti-coagulant (Supplementary File 2), and this could have affected the baseline LDL-C.

Finally, our study has various limitations. In particular, the number of patients was small, because only acute IS patients with NVAF who showed at least one CMB were entered into this study. In addition, selection bias arising from the judgment of the attending physicians and nonrandomization could have influenced the outcome. In fact, the number of recruited patients was 7.5% (52 of 693 NVAF patients) of all cardiogenic cerebral infarct patients in the 5 major hospitals in our study. This is fewer than in previous studies[4,9,25], which may mean that severely ill patients had been excluded. Further, 3.0 T MRI and susceptibility-weighted imaging sequences have been used for detection of CMB in some studies, and so the detection sensitivity might be different among the studies.[4,9,25]

In conclusion, the results of this pilot study suggest that the incidence of hemorrhagic stroke may be lower in patients treated with NOACs than in those treated with warfarin, and this difference may be due to a difference in the effects of warfarin and NOACs on the progression of CMBs in patients with at least one CMB. A further study is planned to test this hypothesis.

Study Organization

The CMB-NOW study was organized by a central coordinating center located at the Department of Neurology, Tokai University School of Medicine, and was conducted at approximately 20 centers, located mainly in Kanagawa Prefecture, Japan.

Conflicts of Interest

Authors have received funds from the following companies.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2019.03.050.

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