Journal of Stroke and Cerebrovascular Diseases (2015.6) 24(6):1373-1377.

Non-Vitamin K Antagonist Oral Anticoagulants Do Not Increase Cerebral Microbleeds

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Background: Atrial fibrillation (AF) is a cardiac arrhythmia that frequently induces ischemic strokes. Nowadays, non-vitamin K antagonist oral anticoagulants (NOACs) have come into widespread use for cardiogenic embolism prevention in place of warfarin. Recently, cerebral microbleeds (CMBs) have been noticed for their potential implication in cerebral small vessel disease. We hypothesized that NOACs do not have an unfavorable influence over cerebral small vessels and investigated whether NOACs increase CMBs in AF patients in a prospective manner. *Methods:* We performed baseline magnetic resonance imaging (MRI) examinations on the 69 enrolled AF patients and re-examined second round of MRI 1 year later. The enrolled patients continued the same anticoagulation therapy during the meantime. *Results:* CMBs did not develop in the 23 patients with NOACs for 1 year. Nine patients with antiplatelets also did not develop CMBs. On the other hand, 3 of 21 patients continued on warfarin and 3 of 9 with warfarin and antiplatelets had CMBs. When divided into 2 groups according to whether the CMBs developed, significant differences in the incidence of using NOACs were observed between the 2 groups ($P = .02$). A multivariate regression analysis showed that warfarin was independently related to the new development of CMBs (hazard ratio, 10.75; 95% confidence interval, 1.22-94.99; $P = .03$). *Conclusions:* This is the first report to clarify that NOACs do not increase CMBs in AF patients longitudinally in 1 year. Further consideration will be continued with a much longer follow-up in large samples. **Key Words:** NOAC—warfarin—cerebral microbleeds—atrial fibrillation.

Introduction

Atrial fibrillation (AF) is a cardiac arrhythmia that frequently induces ischemic strokes because of hemostasis or excessive blood clotting being prone to promote left atrial thrombosis. Heretofore, warfarin as an anticoagulant has been used to prevent cardiogenic embolism in AF patients. Nowadays, non-vitamin K antagonist oral anticoagulants (NOACs), formerly stood for "novel oral anticoagulants" and redefined recently as "non-vitamin K antagonist oral anticoagulants", not only rival or surpass warfarin in the efficacy but also excel in safety over warfarin[1-3] and are coming into widespread use for cardiogenic embolism prevention.

The CHA_2DS_2-VASc (1 point for congestive heart failure or left ventricular dysfunction, hypertension, age 65 to 74 years, diabetes mellitus, vascular disease [prior

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Received January 27, 2015; revision received February 16, 2015; accepted February 24, 2015.

Grant support/conflict of interest: None declared.

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1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2015.02.018

myocardial infarction, peripheral artery disease, or aortic plaque], sex category [ie, female sex] and 2 points for a prior stroke or transient ischemic attack or thromboembolism and an age ≥75 years) score[4-6] has come into general use for the risk assessment in nonvalvular AF patients because CHA_2DS_2-VASc score predicts future cardiogenic embolisms more accurately than the formerly used $CHADS_2$ score.[7] The CHA_2DS_2-VASc score makes us aware that some of its components also play a key role in focal cerebral microangiopathy.

Cerebral microbleeds (CMBs) are seen as small, from 2 to 5 mm in diameter, round foci with hypointensity on the gradient echo T2*-weighted magnetic resonance imaging (MRI).[8,9] CMBs are believed to represent perivascular accumulation of hemosiderin-containing macrophages on histopathologic examinations,[10-12] and therefore, they are considered to suggest the existence of vulnerability of the cerebral small vessels. We indicated the possibility that AF itself aggravates cerebral small vessels and significantly encompasses an increase in the CMBs as a consequence,[13] whereas only a few reports have addressed focal cerebral microangiopathy in AF patients.

The incidence of intracranial bleeding during NOAC treatment is uniformly lower than that during warfarin treatment.[1-3] Furthermore, there is a report that a hematoma that arises because of acute intracranial bleeding during dabigatran treatment tends to remain small and hard to expand.[14] We hypothesized that NOACs do not have an unfavorable influence over cerebral small vessels. Under this hypothesis, we defined that the goal in the present study was to prove that NOACs do not increase CMBs in AF patients in a prospective manner while considering the association of the CHA_2DS_2-VASc.

Methods

The entire study protocol was approved by the Ethical Review Board of the Asahikawa Medical University, and all patients gave their written informed consent for the study.

Patient Enrollment and the Longitudinal Study

A brain MRI assessment was performed on the outpatients older than 45 years with AF who visited the Cardiovascular, Respiratory, and Neurology Divisions of Asahikawa Medical University Hospital, and they were consecutively enrolled in the study. Valvular AF patients were excluded. A baseline MRI examination was performed on the patients enrolled, and 1 year later, a second round of MRI examinations were performed and analyzed changes in the number of CMBs with informed consent. The enrolled patients continued the same anticoagulation therapy for the prevention of cardiogenic embolism in the study period.

Definition of the Variables

Hypertension was defined as a systolic blood pressure of 140 mm Hg or more and/or diastolic blood pressure of 90 mm Hg or more in subjects who were not taking antihypertensive medications or continuously receiving antihypertensive treatment on an outpatient basis. Diabetes mellitus was defined as a Japan Diabetes Society hemoglobin A1c value of 6.1 or more (corresponds approximately to the National Glycohemoglobin Standardization Program hemoglobin A1c value of ≥6.5) or any continuous antidiabetic treatment on an outpatient basis. Chronic kidney disease was defined as an estimated glomerular filtration rate level of less than 60 ml/min/1.73 m^2 and/or overt albuminuria continuing longer than 3 months. Congestive heart failure was defined as that previously diagnosed by a cardiovascular specialist.

MRI Assessment

The MRI assessments were performed by trained observers who were blinded to the clinical information (J.S. and T.K.). We adopted the recommended criteria for the identification of CMBs proposed by Greenberg et al[8] to precisely assess the number of CMBs: (1) a black lesion on the T2*-weighted MRI, (2) round or ovoid lesions (rather than linear), (3) a blooming effect of the T2*-weighted MRI, (4) signals devoid of hyperintensity on the T1-weighted or T2-weighted sequences, (5) at least half of the lesion surrounded by brain parenchyma, (6) distinct from other potential mimicking conditions such as iron or calcium deposits, bone, or vessel flow voids, and (7) a clinical history excluding any traumatic diffuse axonal injury. CMBs were categorized into 2 groups: lobar (cortex, subcortex, and white matter) CMBs and deep or infratentorial CMBs. A cerebral infarction was defined as a focal lesion with a hypointense lesion with a hyperintense rim in the fluid-attenuated inversion recovery sequence images, with a corresponding hyperintensity on the T2-weighted images and corresponding hypointensity on the T1-weighted images. Cerebral infarctions with no plausible clinical history were defined as asymptomatic cerebral infarctions.

MRI Protocol

The image protocol included T1-weighted, fluid-attenuated inversion recovery, T2-weighted, and gradient echo T2*-weighted MRI. Imaging of the brain was performed on three 1.5 T MRI scanners at our hospital, the Signa Excite (General Electric Medical Systems, Waukesha, WI), Magnetom Sonata (Siemens Medical Solutions, Munich, Germany), and Achieva MR (Philips Healthcare, Bothell, WA) scanners. The gradient echo sequence parameters for the Signa Excite were as follows: 22 axial images; field of view, 220 mm; slice thickness, 5.5 mm;

Table 1. *Profiles of patients assorted according to the medications used against cardiogenic embolism*

Characteristic	NOAC N = 23	Warfarin N = 21	Warfarin + AP N = 9	AP N = 9	None N = 7
Congestive heart failure	10 (43.5%)	8 (38.1%)	6 (66.7%)	5 (55.6%)	1 (14.3%)
Hypertension	15 (65.2%)	11 (52.4%)	7 (77.8%)	5 (55.6%)	3 (42.9%)
Age ≥ 75 y	11 (47.8%)	11 (52.4%)	5 (55.6%)	4 (44.4%)	2 (28.6%)
Diabetes mellitus	3 (13.0%)	7 (33.3%)	2 (22.2%)	3 (33.3%)	1 (14.3%)
Stroke/TIA	3 (13.0%)	3 (14.3%)	1 (11.1%)	0	2 (28.6%)
Vascular disease	3 (13.0%)	4 (19.0%)	3 (33.3%)	3 (33.3%)	1 (14.3%)
Age 65 to 74 y	16 (70.0%)	17 (81.0%)	9 (100.0%)	6 (66.7%)	5 (71.4%)
Sc (female sex)	6 (26.1%)	8 (38.1%)	2 (22.2%)	3 (33.3%)	1 (14.3%)
Chronic kidney disease	7 (30.4%)	12 (57.1%)	7 (77.8%)	3 (33.3%)	1 (14.3%)
Baseline CMBs	8 (34.8%)	12 (57.1%)	3 (33.3%)	2 (22.2%)	2 (28.6%)
Baseline ACIs	5 (21.7%)	8 (38.1%)	4 (44.4%)	1 (11.1%)	3 (42.9%)
Development of CMBs	0	5 (23.8%)	3 (33.3%)	0	1 (14.3%)
Development of ACIs	2 (8.7%)	2 (9.5%)	1 (11.1%)	0	0

Abbreviations: NOAC, non-vitamin K antagonist oral anticoagulants; AP, antiplatelets; Sc, sex category; TIA, transient ischemic attack; CMBs, cerebral microbleeds; ACIs, asymptomatic cerebral infarcts.

interslice gap, 1.0 mm; 256 × 256 matrix; echo time, 20 ms; repetition time, 640 ms; and flip angle, 20°. For the Magnetom Sonata, the parameters were 22 axial images; repetition time, 600 ms; echo time, 18 ms; slice thickness, 5.5 mm; interslice gap, 1.0 mm; field of view, 175 × 200 mm; and flip angle, 20°; and for the Achieva MR scanner, the parameters were repetition time, 700 ms; echo time, 20 ms; slice thickness, 5.5 mm; interslice gap, 1.0 mm; field of view, 210 mm; and flip angle, 20°.

Statistical Analysis

Statistical analyses were performed using SPSS, version 11.0 software (SPSS Inc., Chicago, IL). The Fisher exact test, chi-square test for dichotomous variables, or the Kruskal-Wallis test for ranked data were used for the group comparisons. The hazard ratio and 95% confidence interval (CI) of the development of the CMBs was obtained using a logistic regression analysis with the forced entry method. In this regard, the clinical variables with a P less than .10 in the univariate analysis were entered into the multivariate analysis. Finally, we considered a P less than .05 statistically significant.

Results

Sixty-nine patients were enrolled and repeated MRI examinations at 1-year interval (Table 1). There were 23 AF patients with NOACs including 1 with apixaban 10 mg, 1 with apixaban 5 mg, 1 with dabigatran 300 mg, 11 with dabigatran 220 mg, 5 with rivaroxaban 15 mg, and 4 with rivaroxaban 10 mg. CMBs newly developed in 13.0% of the whole patients (9 of 69). Among the 9 CMBs, 6 were lobar CMBs and 3 were deep or infratentorial CMBs.

No CMBs developed in the 23 patients with NOACs for a year. Nine patients with antiplatelets also did not develop any CMBs. On the other hand, among the 21 patients with warfarin, 3 had newly developed CMBs. Moreover, 3 of 9 patients with warfarin and antiplatelets incurred CMBs. The incidence of CMBs significantly differed among the groups (P = .04). The proportion of patients with chronic kidney disease and paroxysmal AF differed significantly among the groups, respectively. On the other hand, the duration of AF and the number of baseline CMBs did not differ significantly among each group. The duration of taking warfarin before this study among the groups of NOACs, warfarin, and warfarin with antiplatelets also did not differ significantly.

When divided into 2 groups according to whether the CMBs developed, significant differences in the incidence of the use of NOACs and warfarin were observed between the 2 groups (Table 2). Because there were no AF patients with NOACs who developed CMBs, the hazard ratios of NOACs were impossible to calculate based on either a univariate or multivariate analysis. A multivariate regression analysis showed that only warfarin was independently related to the new development of CMBs (hazard ratio, 10.75; 95% CI, 1.22-94.99; P = .03; Table 2). No symptomatic CIs were observed in either group during the follow-up duration.

Discussion

The present findings demonstrated the possibility that NOACs do not increase CMBs in AF patients in a prospective manner.

Table 2. *Statistical analysis of 69 patients and the variates appertaining to the development of CMBs*

				Logistic regression analysis			
		Fisher's exact test		Univariate		Multivariate	
Variates	n = 9	*P*	OR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)
Congestive heart failure	4	1.00	1.05 (.28-4.00)	.95	1.05 (.26-4.29)		
Hypertension	5	1.00	.83 (.22-3.18)	.80	.83 (.20-3.42)		
Age ≥75 y	6	.29	2.44 (.60-9.76)	.24	2.44 (.56-10.70)		
Diabetes mellitus	4	.20	3.20 (.80-12.95)	.12	3.20 (.74-13.77)		
Stroke/TIA	1	1.00	1.13 (.16-8.41)	.85	.81 (.09-7.39)		
Vascular disease	2	1.00	.67 (.15-3.17)	.88	1.14 (.21-6.22)		
Age 65-74 y	8	.67	2.67 (.39-17.45)	.37	2.67 (.31-23.11)		
Sc (female sex)	2	1.00	.67 (.15-3.17)	.63	.87 (.13-3.53)		
Chronic kidney disease	4	1.00	1.05 (.28-4.00)	.95	1.05 (.26-4.29)		
NOAC	0	.02	NA	1.00	NA		
Warfarin	8	.01	13.82 (2.05-89.48)	.02	13.82 (1.62-117.93)	.03	10.75 (1.22-94.99)
Antiplatelets	3	.69	1.50 (.37-6.28)	.60	1.50 (.33-6.75)		
Baseline CMBs	5	.14	3.71 (.91-14.96)	.08	3.71 (.84-16.38)	.30	2.38 (.47-12.00)
Baseline ACIs	6	.12	3.44 (.88-13.45)	.09	3.44 (.82-14.42)	.34	2.12 (.45-10.62)

Abbreviations: ACIs, asymptomatic cerebral infarcts; CI, confidence interval; CMBs, cerebral microbleeds; HR, hazard ratio; NA, not applicable; NOAC, non-vitamin K antagonist oral anticoagulants; OR, odds ratio; TIA, transient ischemic attack.

The table is divided into 3 broad parts according to the type of analytical method.

Relationship between AF and CMBs

One of the most important findings of this study was the fact that no AF patients with NOACs developed CMBs in the space of a year. CMBs have been considered to represent perivascular accumulation of hemosiderin-containing macrophages as a corollary of extravasated erythrocytes from cerebral small vessels.[15] We prospectively clarified that patients with AF showed a significantly higher prevalence of CMBs, but the presence of CMBs in the baseline MRI was highly predictive of the consequent onset of an asymptomatic cerebral infarction and an increase in CMBs in patients with AF.[13] CMBs have been described in association with a number of conditions reflecting the vulnerability of cerebral small vessels and that overlap with the CHA_2DS_2-VASc score: an older age, hypertension, smoking, lacunar infarcts, prior ischemic strokes or intracranial hemorrhages, white matter disease, and Alzheimer disease.[16] However, each element of the CHA_2DS_2-VASc score was not associated with the new onset of CMBs in the present study. Despite some pathophysiological mechanism of AF itself enhancing the vulnerability of cerebral small vessels, the AF patients with NOACs did not develop CMBs for 1 year in the present study. We continue further consideration in the future study with a much longer follow-up and accumulation of cases.

CMBs were categorized by their location based on presumed differences in the underlying etiology: deep or infratentorial CMBs were thought to represent hypertensive arteriopathy, whereas lobar CMBs pointed toward cerebral amyloid angiopathy.[17] In the present study, CMBs were found more often in lobar areas than deep or infratentorial areas. Lobar CMBs are detected in a significant proportion of the AF patients according to a recent report.[18] We considered the influence of CMBs in the 2 categories together because of the moderate cases this time.

Relationship between NOACs and CMBs

In the present study, NOACs were significantly negatively associated with the development of CMBs by a Fisher's exact test; however, they were not considered significant according to a multivariate regression analysis because of the statistical nature. On the one hand, as mentioned earlier, warfarin was significantly related to the development of CMBs in the present study. If warfarin increases CMBs, the difference in the preliminary warfarin exposure might affect the development of CMBs during this study period. However, we clarified that the advance duration of taking warfarin did not differ among the groups.

Warfarin exerts an anticoagulation effect by the inhibition of the vitamin K–dependent synthesis of coagulation factors II, VII, IX, and X and regulatory factor proteins C and S. NOACs, including the direct thrombin inhibitor (dabigatran) and factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban), do not influence factor VII. A complex formation of the tissue factor and activated coagulation factor VII is an important initiator of the coagulation cascade. The tissue factor is at a high concentration in the brain and, thereby, is thought to be a protective factor against cerebral hemorrhages.[19] In

fact, it has been reported that NOACs do not increase symptomatic cerebral hemorrhages.[1-3] It is also well known that the presence of CMBs predicts future cerebral hemorrhages. In line with this, it may be highly possible that NOACs do not harm the cerebral small vessels and, therefore, can cause less CMBs. Furthermore, the performance of NOACs is independent of prior warfarin exposure.

Whether antiplatelets increase CMBs is a disputed question. The CMBs seemed to have statistically been unaffected by the antiplatelets alone in this study; however; a remarkable 3 of 9 patients with both warfarin and antiplatelets had CMBs. The result agrees with the well-known clinical fact that the combination use of warfarin and antiplatelets significantly augments intracerebral hemorrhages.[20] Although the duration of AF and number of baseline CMBs also hold the potential to affect the development of CMBs pathologically as mentioned earlier, a comparison among the groups did not show any significant differences. It is true that the proportion of patients with paroxysmal AF significantly differed among the 5 groups; however, there did not seem to be a difference among the groups of NOACs, warfarin, and warfarin with antiplatelets.

This study had several limitations. First, the results of this preliminary challenging report have limited effectiveness because of the small number of cases and short period of follow-up. However, the practical use of NOACs has not been for long yet. To determine the association between CMBs and AF with a sufficient statistical power, more patients must be studied for a longer duration as a large clinical trial. Second, we employed 3 types of MRI systems in the present study. Ideally, all the imaging should have been processed by a single MRI system. Accordingly, we very cautiously performed a comparative review of the MR images.

Acknowledgments: We thank Eitaro Sugiyama, Akiho Minoshima, Kohei Shimamura, Takeshi Nishiura, Yasuko Tanabe, Naka Sakamoto, Toshiharu Takeuchi, Kazumi Akasaka, Kazuhiro Sumitomo, and Jun-ichi Kawabe, the cardiovascular specialists of our department, for their actual management of the subjects.

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