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Effect of direct oral anticoagulant for acute major cerebral artery occlusion in cardioembolic stroke/transient ischemic attack patients with non-valvular atrial fibrillation

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ABSTRACT

Background: Direct oral anticoagulants (DOACs) can reduce the frequency of cardioembolic stroke with non-valvular atrial fibrillation as well as or better compared to vitamin K antagonists (VKAs). However, whether taking DOACs prior to stroke can prevent acute major cerebral artery occlusion (MCAO) has not been fully elucidated.
Methods: We enrolled patients who underwent cardioembolic stroke or transient ischemic attack with non-valvular atrial fibrillation who were admitted to our hospital between April 2011 and February 2017. The patients were classified into four groups based on anticoagulant medications prior to stroke: no oral anticoagulant (No OAC), VKA below therapeutic range on admission, VKA within therapeutic range on admission, and the DOAC group. We compared clinical backgrounds, National Institutes of Health Stroke Scale (NIHSS) scores, and MCAO prevalence on admission. We identified those patients with MCAO and investigated factors related to MCAO.
Results: A total of 287 patients were enrolled in the study (200 No OAC; 49 VKA below therapeutic range; 21 VKA within therapeutic range; and 17 DOAC). Median and interquartile range of NIHSS scores for each group were 10.5 (4–22) for No OAC; 14 (4–22) for VKA below therapeutic range; 8 (6–17) for VKA within therapeutic range; and 3 (1–9) for DOAC ($P = 0.041$). The prevalence of MCAO in each group was 40% in No OAC; 35% in VKA below therapeutic range; 29% in VKA within therapeutic range; and 6% in DOAC ($P = 0.040$). In total, 103 patients were identified with MCAO on admission. Multivariate analysis revealed that taking DOACs prior to stroke was significantly associated with MCAO (OR, 0.09; 95% CI, 0.004–0.75; $P = 0.023$).
Conclusions: DOACs were an independent factor negatively correlated with MCAO in acute cardioembolic stroke with non-valvular atrial fibrillation.

1. Introduction

Cardioemboic stroke with atrial fibrillation can result in severe outcome [1–3]. Vitamin K antagonists (VKAs) within the therapeutic range can reduce the formation of atrial thrombi [4–6] and decrease infarction volume [7,8], thereby reducing not only the frequency of ischemic stroke but also its severity and risk of death from stroke [9,10]. Direct oral anticoagulants (DOACs) can reduce the incidence of cardioembolic stroke with non-valvular atrial fibrillation as well as or better compared to VKAs [11–14].

Some patients have cardioembolic stroke even after receiving DOACs. Previous studies have shown that patients who received DOACs prior to stroke had lower National Institutes of Health Stroke Scale (NIHSS) scores on admission and improved modified Rankin Scale scores at discharge than those who were not taking anticoagulants and those with VKA below the therapeutic range [15–17]. However, the mechanism by which DOACs reduce stroke severity is not completely known. Cardioembolic stroke with atrial fibrillation often causes acute major cerebral artery occlusion (MCAO), which correlates with poor outcome [18]. Based on our results, we believe that administration of DOACs prior to stroke can prevent MCAO and reduce stroke severity. This hospital-based retrospective study aimed to evaluate the clinical characteristics in patients who received DOACs prior to stroke and investigate whether DOACs could prevent MCAO in acute cardioembolic

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Table 1
Comparison of clinical characteristics of enrolled patients.

	No OAC N = 200	VKA		DOAC N = 17	P Value
		Below therapeutic range N = 49	Within therapeutic range N = 21		
Age, years	80.2 ± 10.4	81.6 ± 9.6	82.4 ± 7.9	81.5 ± 5.2	0.78
Sex, Female	116 (58)	23 (47)	10 (48)	8 (47)	0.41
Body weight, kg	53 ± 13.9	50.7 ± 10.5	49.1 ± 10.0	53.8 ± 12.4	0.58
Creatinie clearance, ml/min	51.8 ± 29.7	43.2 ± 22.6	38.7 ± 20.5	51.4 ± 17.8	0.12
Hypertension	155 (78)	41 (84)	16 (76)	15 (88)	0.59
Dyslipidemia	44 (22)	10 (20)	2 (10)	5 (29)	0.48
Diabetes mellitus	42 (21)	9 (18)	3 (14)	4 (24)	0.86
Chronic heart failure	111 (56)	12 (24)	6 (29)	5 (29)	< 0.001
Prior stroke or transient ischemic attack	33 (17)	22 (45)	10 (48)	9 (53)	< 0.001
Vascular disease	28 (14)	8 (16)	2 (10)	4 (24)	0.64
$CHADS_2$ score	2 [2–3]	3 [2–5]	3 [2–4]	3 [3–4]	0.025
CHA_2DS_2-VASc score	4 [3–5]	5 [3–6]	5 [4–5]	5 [4–6]	0.12
Combination with an antiplatelet drug	11 (5.5)	3 (6.1)	2 (10)	4 (24)	0.044
Premorbid mRS (0–2)	118 (59)	25 (51)	11 (48)	12 (71)	0.47

Data are presented as mean ± standard deviation, median [interquartile range] or absolute (percentage) values.
DOAC, direct oral anticoagulant; mRS, modified Rankin Scale; OAC, oral anticoagulant; VKA, vitamin K antagonist.

stroke/transient ischemic attack patients with non-valvular atrial fibrillation.

2. Patients and methods

2.1. Subjects

We retrospectively evaluated patients with cardioembolic stroke or transient ischemic attack with non-valvular atrial fibrillation who were admitted to our hospital between April 2011 and February 2017. Patients with mechanical heart valve and those with > 1 week after stroke onset were excluded. We categorized the patients into four groups based on status of anticoagulant medications prior to stroke, including (1) No oral anticoagulant (No OAC), (2) VKA below therapeutic range on admission, (3) VKA within therapeutic range on admission, and (4) the DOAC group. Japanese patients are recommended to have VKA within the therapeutic range, a prothrombin time/international normalized ratio (PT-INR) 1.6–2.6 in patients aged ≥70 years, and PT-INR 2.0–3.0 in patients aged < 70 years [19]. The requirement for informed consent was waived because all of the data were anonymized before the analysis. This study was approved by the institutional ethics committee.

2.2. Clinical characteristics

We compared the pre-admission clinical characteristics of patients including age, sex, body weight, creatinine clearance, hypertension, dyslipidemia, diabetes mellitus, chronic heart failure, prior stroke or transient ischemic attack, vascular disease, $CHADS_2$ and CHA_2DS_2-VASc score, combination with an antiplatelet drug (aspirin, clopidogrel or cilostazol), and premorbid modified Rankin Scale score (0–2) and evaluated NIHSS scores and MCAO prevalence at the time of admission. Subsequently, we investigated the factors related to MCAO. MCAO was diagnosed by stroke neurologists based on magnetic resonance angiography (Philips Ingenia 3.0 T, Amsterdam, Netherlands) or computed tomography angiography findings. Occlusions of the internal carotid, anterior cerebral (A1 or A2 segment), middle cerebral (M1 or M2 segment), posterior cerebral (P1 or P2 segment) and basilar arteries were identified as MCAO, and preexisting occlusions were excluded.

2.3. Statistical analysis

Continuous variables were presented as mean and standard deviation or median and interquartile range. Differences in clinical demographics and continuous and categorical variables among the four groups were evaluated using the Kruskal Wallis test and Fisher exact test, respectively. In addition, NIHSS scores were evaluated by the Kruskal Wallis test, followed by the Wilcoxon test, and the prevalence of MCAO was assessed using the Fisher exact test, followed by Bonferroni correction. Differences between the groups with and without MCAO were evaluated using the Chi-squared test. Variables associated with $P < 0.1$ on Chi-squared test were selected as input valuables for multivariate logistic regression analysis. All statistical tests were two-sided, and p-values < 0.05 were considered statistically significant. All statistical analyses were performed using JMP software, Version 11 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Study population and clinical characteristics in all groups

A total of 287 consecutive patients were enrolled between April 2011 and February 2017 (157 women, mean age 80.7 ± 9.9 years; 200 No OAC; 49 VKA below therapeutic range; 21 VKA within therapeutic range; and 17 DOAC). There was no patient with VKA above the therapeutic range. All patients underwent magnetic resonance angiography or computed tomography angiography. The DOAC group comprised 5 dabigatran (all cases 220 mg/day), 6 rivaroxaban (all cases 10 mg/day), 5 apixaban (10 mg/day, 3; 5 mg/day, 2) and 1 edoxaban (30 mg/day) cases. There were no cases of inappropriate dosage. Patients aged ≥70 years accounted for 84% (81% No OAC, 90% VKA below therapeutic range, 90% VKA within therapeutic range, and 94% DOAC; P = 0.18). Transient ischemic attack occurred in 11 patients (8 No OAC, 1 VKA below therapeutic range, 1 VKA within therapeutic range, and 1 DOAC; P = 0.87), and 23 patients underwent hemodialysis treatment (15 No OAC, 6 VKA below therapeutic range, 2 VKA within therapeutic range, and 0 DOAC; P = 0.42). Table 1 summarizes a comparison of clinical characteristics in all groups. The No OAC group had a higher rate of chronic heart failure, a lower rate of prior stroke or transient ischemic attack, and a lower $CHADS_2$ score compared with those in other groups. The DOAC group had a higher rate of being combined with an antiplatelet drug.

3.2. NIHSS scores and MCAO prevalence on admission

The NIHSS scores on admission for the four groups are shown in Fig. 1 A. The median and interquartile range of the four groups was 10.5 (4–22) for No OAC; 14 (4–22) for VKA below therapeutic range; 8 (6–17) for VKA within therapeutic range; and 3 (1–9) for DOAC (P = 0.041). The NIHSS scores for the DOAC group were commonly

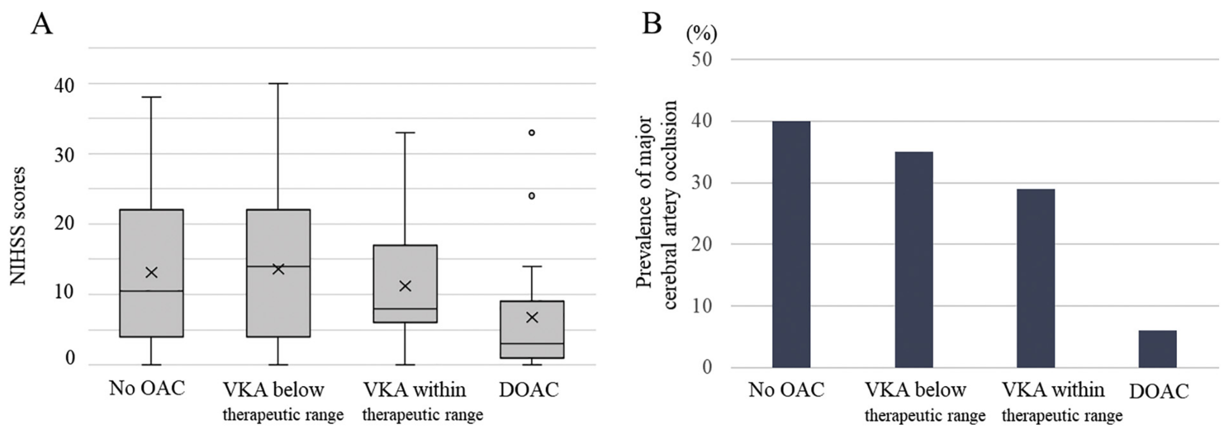

Fig. 1. National Institutes of Health Stroke Scale (NIHSS) scores and prevalence of major cerebral artery occlusion at the time of admission in acute cardioemboic stroke/transient ischemic attack patients with non-valvular atrial fibrillation.

lower when compared with those of the other groups (vs. No OAC, p = 0.0055; vs. VKA below therapeutic range, p = 0.014; vs. VKA within therapeutic range, p = 0.039). The prevalence of MCAO in all of the groups is shown in Fig. 1 B (40% No OAC, 35% VKA below therapeutic range, 29% VKA within therapeutic range, and 6% DOAC; P = 0.040). The locations of the occluded artery in the groups were as follows. No OAC — 8% internal carotid, 27% middle cerebral, 1.5% posterior cerebral, 3% basilar, and 0.5% contemporaneous middle and posterior cerebral artery; VKA below therapeutic range, 4% internal carotid, 29% middle cerebral, 2% basilar artery; VKA within therapeutic range, 24% internal carotid, 5% middle cerebral artery; DOAC, and 6% internal carotid artery. The prevalence of MCAO in the DOAC group was typically lower than in the other groups (vs. No OAC, p = 0.028; vs. VKA below therapeutic range, p = 0.11; vs. VKA within therapeutic range, p = 0.40).

A: NIHSS scores.

B: Prevalence of major cerebral artery occlusion.

DOAC, direct oral anticoagulant; NIHSS, National Institutes of Health Stroke Scale; OAC, oral anticoagulant; VKA, vitamin K antagonist.

3.3. Comparison of clinical characteristics between patients with and without MCAO

Table 2 shows a comparison of clinical characteristics between patients with and without MCAO. Those with MCAO had higher creatinine clearance (P = 0.032), higher NIHSS scores on admission ($P < 0.001$), and lower rates of DOAC prior to stroke (P = 0.0075) compared to those without MCAO. Logistic regression analyses are shown in Table 3. Creatinine clearance (OR, 1.02; 95% CI, 1.01–1.04; P = 0.0023), NIHSS scores on admission (OR, 1.17; 95% CI, 1.12–1.21; $P < 0.001$), and DOAC prior to stroke (OR, 0.09; 95% CI, 0.004–0.75; P = 0.023) were significantly associated with MCAO.

4. Discussion

In the present study, NIHSS scores on admission in the DOAC group were lower compared to those in the other groups. Prior stroke and premorbid modified Rankin Scale score influenced NIHSS scores, but they were not much different between the DOAC and the other groups. Previous studies concluded that rivaroxaban could reduce stroke severity because it leads to loose fibrin clot structure [15], reduces ischemic brain damage through its anti-inflammatory mechanism, and reduces thrombus load, thereby increasing the patency of cerebral microvasculature [20]. We believe that lower NIHSS scores in the DOAC

Table 2
Comparison of clinical characteristics between patients with and without major cerebral artery occlusion.

	Major cerebral artery occlusion (+), N = 103	Major cerebral artery occlusion (−), N = 184	P Value
Age, years	81.2 ± 9.2	80.4 ± 10.3	0.63
Sex, Female	59 (57)	98 (53)	0.54
Body weight, kg	52.3 ± 12.9	52.3 ± 13.1	0.95
Creatinie clearance, ml/min	54.0 ± 28.0	46.8 ± 27.2	0.032
Hypertension	78 (76)	149 (81)	0.29
Dyslipidemia	18 (17)	43 (23)	0.29
Diabetes mellitus	24 (23)	34 (18)	0.36
Chronic heart failure	56 (54)	78 (42)	0.06
Prior stroke or transient ischemic attack	23 (22)	51 (28)	0.33
Vascular disease	14 (14)	28 (15)	0.86
$CHADS_2$ score	3 [2–3]	3 [2–4]	0.91
CHA_2DS_2-VASc score	4 [3–6]	4 [3–5]	0.71
Combination with an antiplatelet drug	3 (2.9)	17 (9.2)	0.053
Premorbid mRS (0–2)	60 (58)	107 (58)	1.00
NIHSS on admission	22 [14–27]	6 [2−13]	< 0.001
No OAC	79 (77)	121 (66)	0.06
VKA below therapeutic range	17 (17)	32 (17)	1.00
VKA within therapeutic range	6 (5.8)	15 (8.2)	0.64
DOAC	1 (0.9)	16 (8.7)	0.0075

Data are presented as mean ± standard deviation, median [interquartile range] or absolute (percentage) values.
DOAC, direct oral anticoagulant; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OAC, oral anticoagulant; VKA, vitamin K antagonist.

Table 3
Multivariate logistic regression model of major cerebral artery occlusion.

	OR	95% CI	P Value
Age (per one year increase)	1.00	0.96–1.05	0.83
Sex, Female	0.87	0.44–1.76	0.72
Cretinine clearance (per 1.0 ml/min)	1.02	1.01–1.04	0.0023
Chronic heart failure	1.27	0.65–2.50	0.48
Combination with an antiplatelet drug	1.04	0.20–4.09	0.95
NIHSS scores on admission (per 1 point)	1.17	1.12–1.21	< 0.001
Anticoagulant status prior to stroke			
No OAC	1.00	Ref.	
VKA below therapeutic range	0.82	0.34–1.96	0.67
VKA within therapeutic range	0.99	0.28–3.22	0.98
DOAC	0.09	0.004–0.75	0.023

CI, confidence interval; DOAC, direct oral anticoagulant; NIHSS, National. Institutes of Health Stroke Scale; OR, odds ratio; OAC, oral anticoagulant.

group correlated with a lower prevalence of MCAO, because NIHSS scores are reported to have a strong association with MCAO in acute ischemic stroke patients [21,22].

In the present study, the prevalence of MCAO in the DOAC group was lower than in the other groups, and DOAC was significant negatively correlated with MCAO in cardioembolic stroke patients. A previous study showed that > 90% of stroke incidence in patients with non-valvular atrial fibrillation was due to left atrial appendage thrombus [23]. In particular, a large left atrial thrombus could lead to MCAO. DOACs were reported to resolve left atrial appendage thrombi, including giant thrombus [24–28]. DOACs exert anticoagulation effect as a thrombin inhibitor or Factor Xa inhibitors and strongly suppress thrombus formation under sufficient anticoagulant conditions. As mentioned above, loose fibrin clot and thrombus load reduction could minimize left atrial appendage thrombus. Further, fewer food or drug interactions and better adherence in patients compared to those taking VKAs [29,30] could contribute to persistent anticoagulation of DOACs. Therefore, DOACs could prevent MCAO in acute cardioembolic stroke patients.

In patients taking DOACs, the appropriate dosage regimen is essential to maintain sufficient anticoagulation and suppress left atrial appendage thrombus. However, a previous study reported that 13% of DOAC-treated patients were dosed inappropriately (9.4% under- and 3.4% overdosed) [31]. In Japan, the rate of underdosed patients is 18.4% [32]. Our study had no cases of inappropriate DOAC prescriptions, which could contribute to a favorable outcome.

The present study had some limitations, which must be addressed. First, we did not evaluate D-dimers, which measure thrombus formation. Second, transthoracic and/or transesophageal echocardiography was not evaluated for the detection of atrial appendage thrombus. Data from D-dimers and echocardiography could lead to a relevant association between DOAC and MCAO. Third, in patients with MCAO, we could not exclude the possibility of preexisting intracranial or cervical artery stenosis prior to stroke. Patients with these stenoses, even those with small thrombi, could have MCAO. Fourth, the study was at risk of being statistically underpowered due to the small number of study subjects (in particular, patients with prior anticoagulant use). Fifth, the results of the study may be specific to Japanese patients because the therapeutic range of VKA in Japan differs from that in other countries (patients aged < 70 years, INR 2.0–3.0; patients aged ≥70 years, INR 1.6–2.6). Finally, we did not have information regarding DOAC adherence. To assess the effect of DOAC-anticoagulant use in practice, adherence information is essential because of the lack of markers such as PT-INR in VKA therapy. Thus, the severity in the DOAC group (NIHSS and prevalence of MCAO) might have been underestimated. These limitations are associated with the retrospective nature of the study. A prospective examination is needed to validate the findings of the present study.

5. Conclusions

The patients taking DOACs prior to stroke had lower NIHSS scores and a lower prevalence of MCAO on admission compared to the other groups. DOAC was an independent factor negatively correlated with MCAO in acute cardioembolic stroke with non-valvular atrial fibrillation.

Disclosures

None.

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