Adequate Adherence to Direct Oral Anticoagulant is Associated with Reduced Ischemic Stroke Severity in Patients with Atrial Fibrillation

Kazuo Yamashiro, MD,* Naohide Kurita, MD,* Ryota Tanaka, MD,† Yuji Ueno, MD,* Nobukazu Miyamoto, MD,* Kenichiro Hira, MD,‡ Sho Nakajima, MD,* Takao Urabe, MD,‡ and Nobutaka Hattori, MD*

Background: The impact of adherence to direct oral anticoagulants (DOACs) is unknown. We aimed to assess the effects of preceding anticoagulation treatment on neurologic severity at admission and functional outcomes at discharge in patients with atrial fibrillation (AF) who developed acute ischemic stroke. *Methods:* We retrospectively assessed consecutive patients with acute ischemic stroke and AF. Adherence to DOACs was assessed using the 4-item Morisky Medication Adherence Scale. Associations between preceding DOAC treatment and stroke severity at admission and functional outcomes at hospital discharge were examined. *Results:* Of 387 patients with AF and acute ischemic stroke, 248 (64.1%) were not administered an anticoagulant before stroke onset, 95 (24.5%) had subtherapeutic warfarin with an international normalized ratio less than 2 at the time of stroke, 16 (4.1%) had therapeutic warfarin, 6 (1.6%) had DOACs with nonadherence, and 22 (5.7%) had DOACs with adequate adherence. Multivariate analysis showed that DOAC treatment with adequate adherence was associated with lower odds of severe stroke (National Institute of Health Stroke Scale $\geq$10 at admission) (odds ratio, .24; 95% confidence interval, .03-.98; P = .04) and higher odds of excellent recovery (modified Rankin Scale score, 0-1 at discharge) (odds ratio, 4.89; 95% confidence interval, 1.51-20.6; P < .01) compared with no anticoagulation therapy. *Conclusions:* Preceding DOAC treatment with adequate adherence has beneficial effects on stroke severity at admission and functional outcome at discharge in patients with AF. Hence, our results encourage an increased effort to bolster adherence to DOACs in patients with AF.

Key Words: Ischemic stroke—atrial fibrillation—direct oral anticoagulant—medication adherence

Introduction

Atrial fibrillation (AF) is a common cardiac arrhythmia. In 2010, the estimated number of individuals with AF globally was 33.5 million, and the incidence and prevalence progressively increase, with approximately 5 million new cases annually.[1] Advancing age, cardiovascular disease, and increased levels of obesity/metabolic disorders are associated with AF risk.[2] The inpatient care database in the United States showed that the AF prevalence in acute ischemic stroke has continued to increase from 19.7% in 2004 to 24.0% in 2013.[3] The Framingham study reported that AF is associated with a 5-fold increased risk

From the *Department of Neurology, Juntendo University School of Medicine, Tokyo, Japan; †Division of Neurology, Department of Internal Medicine, Jichi Medical University, Tochigi, Japan; and ‡Department of Neurology, Juntendo University Urayasu Hospital, Chiba, Japan.

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Address correspondence to Ryota Tanaka, MD, Division of Neurology, Department of Internal Medicine, Jichi Medical University, 3311-1 Yakushiji, Shimono, Tochigi 329-0498, Japan. E-mail: rtanaka@jichi.ac.jp.

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of stroke.[4] Furthermore, AF is associated with severe disability and mortality in patients with acute ischemic stroke.[5,6]

A meta-analysis of randomized trials showed that adjusted-dose warfarin reduces stroke risk by approximately 60% compared with a placebo in patients with AF.[7] In addition, a preceding therapeutic warfarin treatment with an international normalized ratio (INR) greater than equal to 2.0 has been associated with reduced stroke disability and mortality in patients with AF.[8-11] However, maintaining stable therapeutic levels of anticoagulation using warfarin is challenging. One third of patients had difficulties maintaining their target INR ranges, which was reflected in a time in therapeutic range of less than 60% in community-based studies.[12,13]

Recently, nonvitamin-K-dependent direct oral anticoagulants (DOACs) have become available for the prevention of stroke and systemic embolism in patients with AF. One of the potential advantages of DOACs compared with warfarin is the dosing, which is fixed according to the indication and specific patient risk factor. Moreover, routine coagulation monitoring is not required. A recent meta-analysis of phase 3 studies demonstrated that DOACs have a favorable risk-benefit profile with significant reductions in stroke, intracranial hemorrhage, and mortality, and with similar major bleeding as for warfarin.[14] In addition, some studies showed that preadmission DOAC treatment improves stroke severity in patients with AF and acute ischemic stroke.[15-18] However, the impact of adherence to DOACs, which could affect patient outcomes,[19,20] remains to be established. In this study, we aimed to assess the effects of preceding anticoagulation treatment, including warfarin with therapeutic or subtherapeutic range and DOACs with or without adequate adherence, on neurologic severity at admission and functional outcomes at discharge in patients with AF who developed acute ischemic stroke.

Materials and Methods

Subjects

Consecutive patients with nonvalvular AF who developed acute ischemic stroke or transient ischemic attack (TIA) and who were admitted from January 2008 to December 2016 to the Department of Neurology, Juntendo University School of Medicine were retrospectively examined. Patients with prosthetic mechanical heart valves were excluded. This study was approved by the institutional review board of Juntendo University Hospital. All patients provided informed consent in compliance with institutional guidelines.

All patients underwent brain computed tomography or magnetic resonance imaging (or both) on admission. Acute lacunar infarct was defined as the presence of a single high intensity area in the perforating artery territory and a maximum infarct diameter less than 15 mm on diffusion-weight magnetic resonance imaging. Major artery occlusion (MAO) was defined as occlusion of the internal carotid artery, middle cerebral artery horizontal segment, or basilar artery on magnetic resonance angiography. Information on clinical variables, including age, sex, body mass index, past medical history, and medications prior to the index stroke, was obtained from medical charts. Hypertension was defined as a systolic blood pressure greater than equal to 140 mm Hg and/or a diastolic blood pressure greater than equal to 90 mm Hg or treatment with antihypertensive medications before stroke onset. Dyslipidemia was defined as total cholesterol level greater than equal to 220 mg/dL, triglyceride level greater than equal to 150 mg/dL, or the use of lipid-lowering medications. Diabetes mellitus was defined as glycated hemoglobin (HbA1c) level greater than equal to 6.5% on admission or the use of insulin or oral hypoglycemic agents. The subjects were considered current smokers if they had at least one cigarette a day within the previous year. The $CHADS_2$ and CHA_2DS_2-VASc scores[21] before the index stroke or TIA were calculated for each patient.

Adherence to DOACs was assessed using the 4-item Morisky Medication Adherence Scale,[22] which has the following 4 "yes"/"no" items: (1) Do you ever forget to take your medicine? (2) Are you careless at times about taking your medicine? (3) When you feel better, do you sometimes stop taking your medicine? (4) Sometimes if you feel worse when you take the medicine, do you stop taking it? Adequate adherence was defined as a response of "no" to all four questions and nonadherence as a "yes" response to any of the 4 questions. The scale was used previously to assess adherence to warfarin[23] and DOACs.[24]

Outcomes

Patients were divided into 5 groups based on the anticoagulation therapy prior to the index event[1]: no anticoagulation therapy[2]; subtherapeutic warfarin with an admission INR less than 2[3]; therapeutic warfarin with an INR greater than equal to 2[4]; nonadherence to DOACs (dabigatran, rivaroxaban, or apixaban); and[5] adequate adherence to DOACs.

Stroke severity was assessed using the National Institute of Stroke Scale (NIHSS) score at admission, ranging from 0 to 42, with a higher score indicating greater stroke severity. Patients with an NIHSS score greater than equal to 10 were classified as having severe stroke.[15] Functional outcome was assessed using the modified Rankin Scale (mRS) score at discharge, ranging from 0 (no symptoms) to 6 (death). Patients with an mRS score of 0 or 1 were classified as having excellent recovery, whereas those with an mRS score of 0-2 were classified as having functional independence.[17]

Statistical Analysis

Medians (interquartile ranges) and numbers (percentages) were used to describe the distribution of continuous and categorical variables, respectively. Baseline characteristics were compared using the Kruskal-Wallis test for continuous variables and Pearson χ^2 test for categorical variables across 5 preceding anticoagulation therapy groups. Multivariate logistic regression analyses were performed to investigate the relationships between preceding anticoagulation therapies and each clinical outcome measure: stroke severity at admission and functional outcome at discharge. The relationship between preceding anticoagulation therapies and MAO was also analyzed. Only patients without MAO prior to the admission were included. Backward stepwise elimination was used to select the independent variables. Preceding anticoagulation therapy was included as an independent variable; no anticoagulation therapy was the reference group. All statistical analyses were performed using JMP 12.0.1 software (SAS Inc., Cary, NC). A P value less than .05 was considered statistically significant.

Results

During the study period, 2171 patients with acute ischemic stroke were admitted. Among these patients, 387 had nonvalvular AF (median age, 77 years; 35% women), 248 (64.1%) were not administered any anticoagulant prior to stroke onset, 95 (24.5%) had a subtherapeutic warfarin with an INR less than 2 at the time of stroke, 16 (4.1%) had therapeutic warfarin, 6 (1.6%) were nonadherent to DOACs, and 22 (5.7%) had DOACs with adequate adherence. Of the 28 patients receiving DOACs, 18 (64.3%) were administered lower doses. Age ($P < .01$), sex ($P = .01$), frequency of chronic AF ($P < .01$), diabetes mellitus ($P = .01$), congestive heart failure ($P < .01$), previous stroke/TIA ($P < .01$), $CHADS_2$ ($P < .01$), CHA_2DS_2-VASc ($P < .01$), and modified Rankin scale ($P < .01$) scores prior to the index event; and levels of estimated glomerular filtration rate ($P = .02$), B-type natriuretic peptide ($P < .01$), PT−INR ($P < .01$), and D-dimer ($P = .04$) were different among the groups. The prevalence of acute lacunar infarct was not statistically different among the groups (Table 1).

The median NIHSS score at admission was different among the groups ($P < .01$; Table 1). Multivariate regression analysis showed that DOAC treatment with adequate adherence is associated with lower odds of severe stroke (NIHSS greater than equal to 10 at admission) compared with no anticoagulation therapy (odds ratio [OR], .24; 95% confidence interval [CI], .03-.98; $P = .04$; Table 2).

Functional outcome at discharge as assessed by mRS score was different among groups ($P < .01$; Table 1, Fig 1). Multivariate regression analysis showed that patients administered DOACs with adequate adherence is associated with excellent recovery (mRS score, 0-1; OR, 4.89; 95% CI, 1.51-20.6; $P < .01$) and functional independence (mRS score, 0-2; OR, 3.86; 95% CI, 1.08-20.1; $P = .04$) at discharge compared with those without anticoagulation therapy (Table 3).

MAO was found in 1 of 22 patients administered DOACs with adequate adherence, and its prevalence (4.6%) was lowest among the groups (Table 1). Multivariate regression analysis showed that DOAC treatment with adequate adherence was independently associated with lower odds of MAO (OR, .07; 95% CI, .003-.45; $P < .01$; Table 4).

Among the 28 patients administered DOACs, 5 (17.9%) had a dose lower than the recommended dose. NIHSS score at admission and mRS score at discharge were not different between the groups (Table 5).

Discussion

This study showed that a preceding DOAC treatment with adequate adherence is associated with reduced odds of severe stroke at admission and with increased odds of excellent recovery and functional independence at hospital discharge in patients with AF compared with no anticoagulation therapy.

Anticoagulation therapy has been demonstrated to reduce not only stroke risk but also stroke severity in patients with AF who developed ischemic stroke. Therapeutic warfarin with an INR greater than equal to 2 at onset was associated with less severe stroke and fewer deaths in previous studies.[8-10] DOACs have been approved for patients with AF in Japan since 2011. Recently, 2 studies in Japan have investigated the association between stroke severity and preceding anticoagulation therapy including warfarin and DOACs in patients with acute ischemic stroke and AF. They showed that DOACs, not therapeutic warfarin, were associated with less severe stroke at admission,[15,16] one of these studies has reported a significant association between therapeutic warfarin and a favorable outcome at hospital discharge.[16] Therapeutic warfarin was defined as an INR greater than equal to 2 for patients aged less than 70 years and an INR greater than equal to 1.6 for patients aged greater than equal to 70 years in one study,[15] and as an INR greater than equal to 1.6 for all patients in another study.[16] The Fukuoka Stroke Registry showed that an INR greater than equal to 2 is associated with both less severe neurological deficits on admission and less poor functional outcome at discharge in Japanese patients.[11] The inconsistent outcomes in the previous studies could be attributed to the definition of therapeutic warfarin. In our study, we found that DOAC treatment, rather than therapeutic warfarin with an INR greater than equal to 2, was associated with less severe stroke at admission and favorable outcomes at discharge in our patients. Therefore, DOACs may have a greater effect in reducing stroke severity than therapeutic warfarin in Japanese patients. In contrast, studies from the United States[17] and Germany[18]

Table 1. *Baseline characteristics according to preceding anticoagulant treatment among patients with AF who had acute ischemic stroke*

	None N = 248	Warfarin, PT-INR <2.0 N = 95	Warfarin, PT-INR ≥2.0 N = 16	DOACs, non-adherence N = 6	DOACs, adequate adherence N = 22	*P* value
Age (years)	74 (67-82)	80 (72-85)	80(73-84)	81 (72-83)	71 (63-81)	<.01
Female	91 (36.7)	37 (39.0)	5 (31.3)	0 (0)	1 (4.6)	.01
BMI (kg/m^2)	23 (20-26)	23 (21-25)	22 (18-24)	24 (22-29)	24 (21-26)	.29
Chronic AF	170 (68.6)	92 (96.8)	15 (93.8)	6 (100)	20 (90.9)	<.01
Hypertension	161 (64.9)	64 (67.4)	14 (87.5)	5 (83.3)	17 (77.3)	.26
Dyslipidemia	91 (36.7)	37 (39.0)	7 (43.8)	1 (16.7)	10 (45.5)	.72
Diabetes mellitus	50 (20.2)	34 (35.8)	6 (37.5)	2 (33.3)	10 (45.5)	.01
Congestive heart failure	34 (13.7)	35 (36.8)	9 (56.3)	1 (16.7)	2 (9.1)	<.01
Current smoking	50 (24.3)	21 (25.6)	4 (28.6)	3 (50.0)	2 (10.5)	.37
Antiplatelet therapy	77 (31.1)	38 (40.0)	8 (50.0)	3 (50.0)	6 (27.3)	.25
Previous stroke/TIA	22 (8.9)	30 (31.6)	7 (43.8)	1 (16.7)	4 (18.2)	<.01
$CHADS_2$ score	2.0 (1.0-2.0)	2.0 (2.0-3.0)	3.0 (2.3-4.0)	3.5 (1.5-4.0)	2.0 (1.0-3.3)	<.01
CHA_2DS_2-VASc score	3 (2.0-4.0)	4 (4.0-5.0)	4.5 (4.0-5.8)	4.5 (2.3-5.3)	3 (2.0-5.0)	<.01
Pre-admission mRS score	0 (0-0)	0 (0-0)	0 (0-1.5)	0 (0-.5)	0 (0-0)	<.01
NIHSS at admission	4.0 (1.0-11.0)	6.0 (2.0-15.0)	4.5 (2.0-14.8)	5.0 (1.0-19.0)	2.0 (.8-4.0)	<.01
Acute lacunar lesion*	10/225 (4.4)	4/86 (4.7)	1/10 (10.0)	0/6 (0)	2/22 (9.1)	.80
MAO at admission†	55/225 (24.0)	18/86 (20.9)	3/10 (30.0)	2/6 (33.3)	1/22 (4.6)	.25
Laboratory data						
Glucose (mg/dL)	113 (99-139)	125 (105-156)	110 (95-126)	118 (92-156)	108 (96-145)	.08
eGFR (mL/min/1.73 m^2)	68 (56-85)	59 (41-77)	57 (40-75)	63 (52-77)	69 (53-89)	.02
BNP (pg/mL)	158 (75-278)	274 (187-464)	137 (50-362)	126 (98-561)	78 (56-151)	<.01
PT−INR	1.1 (1.0-1.1)	1.3 (1.2-1.5)	2.2 (2.1-2.5)	1.3 (1.1-1.7)	1.2 (1.1-1.4)	<.01
D-dimer (μg/mL)	1.6 (1.2-2.8)	1.8 (1.2-3.7)	1.2 (1.0-2.6)	1.4 (1.1-3.7)	1.3 (0-1.8)	.04
Reperfusion therapy	17 (6.9)	13 (13.7)	0 (0)	0 (0)	1 (4.6)	.14
mRS score at discharge	1.0 (0-4)	2.0 (1-4)	2.5 (.3-4)	3.0 (1-5)	1.0 (0-1)	<.01

Data are median (interquartile range) or number (%). AF = atrial fibrillation; BNP = B-type natriuretic peptide; DOAC = direct oral anticoagulant; eGFR = estimated glomerular filtration rate; MAO = major artery occlusion; mRS = modified Rankin Scale; NIHSS = National Institute of Health Stroke Scale; PT−INR = prothrombin time−international normalized ratio; TIA = transient ischemic attack.

*Number of patients with acute lacunar infarct/number of total patients (%).

†Number of patients with MAO/number of total patients (%).

Table 2. *Multivariable regression analysis for severe stroke (National Institute of Health Stroke Scale score ≥10) at admission*

	Odds ratio	95% CI	*P* value
Age	1.02	.99-1.05	.15
Female	.81	.47-1.40	.47
Chronic AF (versus paroxysmal)	1.32	.71-2.56	.39
Congestive heart failure	1.79	.98-3.29	.06
$CHADS_2$ score	1.02	.81-1.28	.87
Glucose (per 10 mg/dL)	1.06	1.01-1.12	.02
Pre-morbid mRS (per 1 point)	1.34	1.08-1.68	<.01
Anticoagulant status prior to the event			
No anticoagulation therapy	1 (ref)		
Warfarin, PT−INR <2.0	.95	.52-1.72	.88
Warfarin, PT−INR ≥2.0	.77	.22-2.41	.66
DOACs, nonadherence	1.08	.14-6.19	.93
DOACs, adequate adherence	.24	.03-.98	.04

Abbreviations: AF, atrial fibrillation; CI, confidence interval; DOAC, direct oral anticoagulant; mRS, modified Rankin Scale; PT−INR, prothrombin time−international normalized ratio.

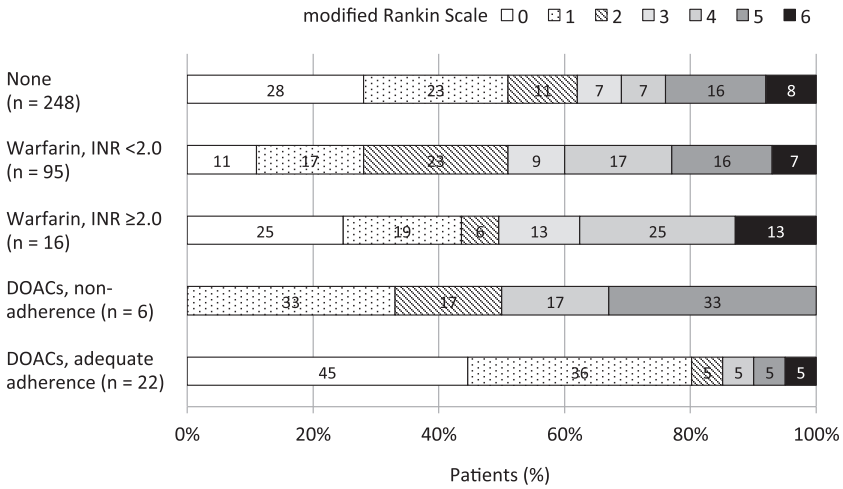

Figure 1. *Scores on the modified Rankin Scale at discharge.*

Table 3. *Multivariable regression analysis for outcomes at discharge*

	mRS score of 0-1			mRS score of 0-2		
	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value
Age	.96	.93-.99	<.01	.95	.92-.98	<.01
Female	.72	.43-1.21	.22	.65	.38-1.09	.10
Chronic AF (versus paroxysmal)	.88	.49-1.56	.66	.74	.40-1.37	.34
Congestive heart failure	.73	.37-1.42	.35	.55	.29-1.04	.07
$CHADS_2$ score	1.05	.83-1.33	.67	1.07	.85-1.35	.58
Glucose (per 10 mg/dL)	.91	.85-.96	<.01	.92	.86-.97	<.01
Pre-morbid mRS (per 1 point)	.34	.12-.60	<.01	.49	.32-.68	<.01
Reperfusion therapy	.20	.06-.54	<.01	.20	.06-.54	<.01
Anticoagulant status prior to the event						
No anticoagulation therapy	1 (ref)					
Warfarin, PT−INR <2.0	.63	.34-1.17	.15	1.43	.78-2.67	.25
Warfarin, PT−INR ≥2.0	1.20	.34-4.32	.78	1.05	.31-3.63	.94
DOACs, nonadherence	.47	.06-3.01	.43	.60	.09-3.89	.58
DOACs, adequate adherence	4.89	1.51-20.7	<.01	3.86	1.08-20.1	.04

Abbreviations: AF, atrial fibrillation; CI, confidence interval; DOAC, direct oral anticoagulant; mRS, modified Rankin Scale; PT−INR, prothrombin time−international normalized ratio.

Table 4. *Multivariable regression analysis for major artery occlusion*

	Odds ratio	95% CI	*P* value
Age	1.02	.99-1.05	.28
$CHADS_2$ score	1.23	.97-1.57	.08
Glucose (per 10 mg/dL)	1.10	1.03-1.18	<.01
Anticoagulant status prior to the event			
No anticoagulation therapy	1 (ref)		
Warfarin, PT−INR <2.0	.57	.29-1.08	.08
Warfarin, PT−INR ≥2.0	1.09	.22-4.30	.90
DOACs, non-adherence	1.15	.15-6.55	.88
DOACs, adequate adherence	.07	.003-.45	<.01

Abbreviations: CI, confidence interval; DOAC, direct oral anticoagulant; PT−INR, prothrombin time−international normalized ratio.

demonstrated that both DOACs and therapeutic warfarin are associated with less severe stroke at admission and poor functional outcomes. A further study investigating whether this difference is due to ethnicity or study scale (relatively small in Japanese studies) is required.

Our study showed for the first time that adequate adherence, rather than nonadherence, to DOAC treatment is associated with less severe stroke at admission and a better functional outcome at hospital discharge. Lower adherence to DOACs was associated with an increased risk of mortality and stroke in patients with AF.[19,20] Monitoring the INR, which is useful in assessing the anticoagulant effect of warfarin, could not be adapted for DOACs. However, DOACs could exert appropriate anticoagulant

Table 5. *Clinical background characteristics of patients with the recommended dose of DOACs and those with underdosed DOACs*

	Recommended dose N = 23	Underdosed N = 5	*P* value
Age (years)	77 (63-81)	72 (60-84)	.81
Female	1 (4.4)	0 (0)	.63
BMI (kg/m^2)	23.8 (21.5-25.8)	24.0 (21.5-35.1)	.49
Chronic AF	21 (91.3)	5 (100)	.49
Hypertension	4 (17.4)	2 (40.0)	.26
Dyslipidemia	8 (34.8)	3 (60.0)	.30
Diabetes mellitus	9 (39.1)	3 (60.0)	.39
Congestive heart failure	1 (4.4)	2 (40.0)	.02
Current smoking	5 (25.0)	0 (0)	.21
Antiplatelet therapy	7 (30.4)	2 (40.0)	.68
Previous stroke/TIA	4 (17.4)	1 (20.0)	.89
CHADS2 score	2.0 (1-4)	3.0 (1-4.5)	.50
CHA_2DS_2-VASc score	3.0 (2-5)	5.0 (2-6)	.44
Pre-admission mRS score	1.0 (0-2)	1.0 (.5-3.5)	.64
NIHSS at admission	2.0 (1-5)	2.0 (1-7)	.69
Acute lacunar lesion*	2/23 (8.7)	0/5 (0)	.49
MAO at admission†	2/23 (8.7)	1 (20.0)	.46
Laboratory data			
Glucose (mg/dL)	111 (92-144)	108 (95.5-314.5)	.57
eGFR ($mL/min/1.73\ m^2$)	65.6 (55.7-79.2)	89.6 (46.5-132.9)	.36
BNP (pg/mL)	82.6 (73.4-125.8)	259.2 (128.5-397.8)	.05
PT−INR	1.2 (1.1-1.5)	1.2 (1.1-1.9)	.75
D-dimer (μg/mL)	1.2 (0-1.7)	1.6 (1.3-3.1)	.11
Reperfusion therapy	1 (4.4)	0 (0)	.63
mRS score at discharge	1.0 (0-2)	1.0 (.5-3.5)	.64

Data are median (interquartile range) or number (%).

Abbreviations: AF, atrial fibrillation; BNP, B-type natriuretic peptide; DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate; MAO, major artery occlusion; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; PT−INR, prothrombin time−international normalized ratio; TIA, transient ischemic attack.

*Number of patients with acute lacunar infarct/number of total patients (%).

†Number of patients with MAO/number of total patients (%).

actions even without laboratory monitoring. Thus, adequate adherence is essential for maintaining the efficacy of DOACs. We found that DOACs with adequate adherence was associated with less MAO. Thus, the reduced severity and good functional outcome in patients administered DOACs with adequate adherence may be explained by the smaller atrial clot formation. A relatively higher proportion of patients with potential noncardioembolic stroke, such as lacunar infarct, may contribute to the reduced severity in patients administered DOACs.[15] However, there was no significant difference in the prevalence of acute lacunar infarct among groups.

We used the Morisky Medication Adherent Scale[22] to assess the adherence to DOAC treatment and found that 21% of patients were nonadherent prior to the ischemic events. Casstellucci et al evaluated anticoagulation adherence using the same scale and reported that 42.9% of patients administered DOACs over a median follow-up of 24 months were nonadherent.[24] Predictors of anticoagulation adherence were age, female sex, and use of other oral medications. Moreover, they found no significant difference between once-daily and twice-daily dose regimens of DOACs. An observational study using a large database reported significantly higher adherence in once-daily dose regimens of rivaroxaban than in twice-daily dose regimens of dabigatran or apixaban.[25] In contrast, rivaroxaban and apixaban showed similar high adherence when initiated in a well-structured AF clinic, suggesting the importance of patient education and closer follow-up for medication adherence.[26]

DOACs require dose adjustments based on patient factors or concomitant medications. The ORBIT-AF II registry reported that 9.4% of DOAC-treated patients were underdosed and 3.4% were overdosed. Moreover, such off-label dose was associated with increased risk of adverse events.[27] In our study, 17.9% were underdosed and none was overdosed. Although we did not find an association between underdosed DOACs and stroke severity or functional outcome, further research with larger samples is needed.

This study has some limitations. First, this is a retrospective study, and unmeasured factors possibly confounded our results. In particular, we had no data on the duration of the anticoagulant therapy, which might have affected the incidence and severity of stroke. Second, we analyzed hospital-based data, which might have caused a selection bias. Third, the number or patients was small in each anticoagulation treatment group, which in turn reduced the statistical power. However, when we combined patients with adequate adherence to DOACs and those with nonadherence to DOACs, the treatment was no longer significantly associated with reduced stroke severity or functional outcomes (data not shown). Thus, adherence to DOACs possibly has a certain impact on stroke outcomes.

In conclusion, our study showed that a preceding DOAC treatment with adequate adherence has a beneficial effect on stroke severity at admission and functional outcome at discharge in patients with AF and acute ischemic stroke. Our results encourage an increased effort to bolster adherence to DOACs in patients with AF.

Disclosure Statement

K.Y., N.K., R.T., Y.U., N.M., K.H., S.N., T.U., and N.H. report no conflicts of interest.

References

1. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. Circulation 2014;129:837-847.
2. Ball J, Carrington MJ, McMurray JJ, et al. Atrial fibrillation: profile and burden of an evolving epidemic in the 21st century. Int J Cardiol 2013;167:1807-1824.
3. Otite FO, Khandelwal P, Chaturvedi S, et al. Increasing atrial fibrillation prevalence in acute ischemic stroke and TIA. Neurology 2016;87:2034-2042.
4. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 1991;22:983-988.
5. Kimura K, Minematsu K, Yamaguchi T. Japan Multicenter Stroke Investigators' Collaboration (J-MUSIC). Atrial fibrillation as a predictive factor for severe stroke and early death in 15,831 patients with acute ischaemic stroke. J Neurol Neurosurg Psychiatry 2005;76:679-683.
6. Hannon N, Sheehan O, Kelly L, et al. Stroke associated with atrial fibrillation—incidence and early outcomes in the north Dublin population stroke study. Cerebrovasc Dis 2010;29:43-49.
7. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007;146:857-867.
8. Hylek EM, Go AS, Chang Y, et al. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. N Engl J Med 2003;349:1019-1026.
9. O'Donnell M, Oczkowski W, Fang J, et al. on behalf of the Investigators of the Registry of the Canadian Stroke Network. Preadmission antithrombotic treatment and stroke severity in patients with atrial fibrillation and acute ischaemic stroke: an observational study. Lancet Neurol 2006;5:749-754.
10. Ay H, Arsava EM, Gungor L, et al. Admission international normalized ratio and acute infarct volume in ischemic stroke. Ann Neurol 2008;64:499-506.
11. Nakamura A, Ago T, Kamouchi M, et al. on behalf of the Fukuoka Stroke Registry Investigators. Intensity of anticoagulation and clinical outcomes in acute cardioembolic stroke: the Fukuoka Stroke Registry. Stroke 2013;44:3239-3242.
12. Rose AJ, Ozonoff A, Henault LE, et al. Warfarin for atrial fibrillation in community-based practice. J Thromb Haemost 2008;6:1647-1654.
13. Hallinen T, Soini EJ, Asseburg C, et al. Warfarin treatment among Finnish patients with atrial fibrillation: retrospective registry study based on primary healthcare data. BMJ Open 2014;4:e004071.

14. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014;383:955-962.
15. Sakamoto Y, Okubo S, Nito C, et al. The relationship between stroke severity and prior direct oral anticoagulant therapy in patients with acute ischaemic stroke and non-valvular atrial fibrillation. Eur J Neurol 2017;24:1399-1406.
16. Tomita H, Hagii J, Metoki N, et al. Severity and functional outcome of patients with cardioembolic stroke occurring during non-vitamin Kantagonist oral anticoagulant treatment. J Stroke Cerebrovasc Dis 2015;24:1430-1437.
17. Xian Y, O'Brien EC, Liang L, et al. Association of preceding antithrombotic treatment with acute ischemic stroke severity and in-hospital outcomes among patients with atrial fibrillation. JAMA 2017;317:1057-1067.
18. Hellwig S, Grittner U, Audebert H, et al. Non-vitamin K-dependent oral anticoagulants have a positive impact on ischaemic stroke severity in patients with atrial fibrillation. Europace 2017;20:569-574.
19. Shore S, Carey EP, Turakhia MP, et al. Adherence to dabigatran therapy and longitudinal patient outcomes: insights from the veterans health administration. Am Heart J 2014;167:810-817.
20. Borne RT, O'Donnell C, Turakhia MP, et al. Adherence and outcomes to direct oral anticoagulants among patients with atrial fibrillation: findings from the veterans health administration. BMC Cardiovasc Disord 2017;17:236.
21. Camm AJ, Kirchhof P, Lip GY, et al. Guidelines for the management of atrial fibrillation: the task force for the management of atrial fibrillation of the European Society of Cardiology (ESC). Eur Heart J 2010;31:2369-2429.
22. Morisky DE, Green LW, Levine DM, et al. Concurrent and predictive validity of a self-reported measure of medication adherence. Med Care 1986;24:67-74.
23. Davis NJ, Billett HH, Cohen HW, et al. Impact of adherence, knowledge, and quality of life on anticoagulation control. Ann Pharmacother 2005;39:632-636.
24. Castellucci LA, Shaw J, van der Salm K, et al. Self-reported adherence to anticoagulation and its determinants using the Morisky medication adherence scale. Thromb Res 2015;136:727-731.
25. McHorney CA, Crivera C, Laliberte F, et al. Adherence to non-vitamin-K-antagonist oral anticoagulant medications based on the Pharmacy Quality Alliance measure. Curr Med Res Opin 2015;31:2167-2173.
26. Al-Khalili F, Lindstrom C, Benson L. Adherence to anticoagulant treatment with apixaban and rivaroxaban in a real-world setting. Clin Trials Regul Sci Cardiol 2016;18:1-4.
27. Steinberg BA, Shrader P, Thomas L, et al. for the ORBIT-AF Investigators and Patients: Off-label dosing of non-vitamin Kantagonist oral anticoagulants and adverse outcomes: the ORBIT-AF II Registry. J Am Coll Cardiol 2016;68:2597-2604.