Journal of Arrhythmia 33 (2017) 475–482

Contents lists available at ScienceDirect

Journal of Arrhythmia

journal homepage: www.elsevier.com/locate/joa

Original Article

Indications for suboptimal low-dose direct oral anticoagulants for non-valvular atrial fibrillation patients

Masahiko Umei, MD*, Mikio Kishi, MD, Takahiro Sato, MD, PhD, Akito Shindo, MD, Masayuki Toyoda, MD, Masaaki Yokoyama, MD, Masashiro Matsushita, MD, Satoshi Ohnishi, MD, Masao Yamasaki, MD, PhD*

Department of Cardiology, NTT Medical Center Tokyo, Tokyo, Japan

ARTICLE INFO

Article history:
Received 28 March 2017
Received in revised form
16 May 2017
Accepted 30 May 2017
Available online 30 June 2017

Keywords:
Atrial fibrillation
Direct oral anticoagulants
Bleeding
Thromboembolism
Suboptimal dose

ABSTRACT

Background: Direct oral anticoagulants (DOACs) have been developed for stroke prevention in patients with non-valvular atrial fibrillation (NVAF). We conducted a retrospective cohort study of patients with NVAF who were newly treated with DOACs in a real-world clinical setting.
Methods: We retrospectively analyzed patients with NVAF newly treated with one of three DOACs—dabigatran, rivaroxaban, or apixaban—between January 1, 2013, and December 31, 2015.
Results: A total of 670 patients with NVAF who were newly prescribed one of the three DOACs were analyzed; 74 patients (10.9%) received dabigatran, 290 (43.3%) received rivaroxaban, and 306 (45.8%) received apixaban. Fifteen patients had thromboembolic events, almost half of which were due to discontinuation of DOACs. Six patients had major bleeding, although almost all were discharged with good neurological prognoses. A total of 129 patients were treated with a suboptimal low-dose DOAC; none experienced a thromboembolic event as long as the DOAC was taken regularly, and none of the patients in any of the three DOAC groups had major bleeding events.
Conclusions: With good adherence, the clinical course associated with DOACs is comparatively good. In the future, suboptimal low-dose DOAC therapy may serve as an appropriate choice for some patients with a high risk of stroke and bleeding.

1. Introduction

Atrial fibrillation (AF) is associated with an increased risk of stroke and death. In patients who are newly diagnosed with AF, the mortality risk is especially high during the first 4 months [1]. In order to prevent devastating thromboembolic events, anticoagulants are initiated as soon as possible among high-risk patients. However, while anticoagulants can effectively prevent thromboembolism, they may also trigger bleeding events. Therefore, whether patients with a high risk of bleeding should be prescribed anticoagulants remains controversial.

Warfarin and other vitamin K antagonists have long been known to be effective anticoagulants in preventing stroke among patients with non-valvular atrial fibrillation (NVAF), and are recommended for patients with a high risk of stroke [2]. Nevertheless, their use may be troublesome because of their slow onset and their interactions with several foods and drugs, requiring close monitoring of the international normalized ratio (INR) [3]. These disadvantages, as well as others, sometimes lead to poor medication adherence and thus ineffective prevention of stroke [4].

Direct oral anticoagulants (DOACs) were developed to provide an effective and prompt anticoagulant regimen that does not require frequent drug monitoring [5]. Four DOACs have hitherto been found to be at least as effective and safe as warfarin in the prevention of stroke among patients with NVAF [6–9]. Moreover, many studies and reports have compared the efficacy and safety of warfarin and DOACs [10–13]. However, in current clinical practice, concerns persist regarding which DOAC to prescribe and whether they should be continued in patients who have had bleeding events or who are at a high risk of bleeding. These patients are often prescribed suboptimal low-dose DOACs (lower than the recommended dose); however, the efficacy of suboptimal low-dose DOACs has not been established.

Therefore, we compared the baseline characteristics, medication persistence, efficacy, and safety outcomes of patients with NVAF

* Correspondence to: Department of Cardiology, NTT Medical Center Tokyo, 5-9-22 Higashi-Gotanda, Shinagawa-ku, Tokyo, 141-8625, Japan.
E-mail addresses: m-umei@umin.org (M. Umei), yamasaki.masao@east.ntt.co.jp (M. Yamasaki).

http://dx.doi.org/10.1016/j.joa.2017.05.008
1880-4276/

who were newly treated with one of three DOACs: dabigatran, rivaroxaban, or apixaban. In addition, we analyzed the clinical time course of patients who were prescribed suboptimal low-dose DOACs in a real-world clinical practice setting.

2. Materials and methods

2.1. Subjects

This was a retrospective cohort study of patients with NVAF who were newly treated with DOACs—dabigatran, rivaroxaban, or apixaban— between January 1, 2013, and December 31, 2015. Since the baseline characteristics of patients prescribed warfarin can be expected to be completely different from those of patients treated with DOACs, patients who were prescribed warfarin were excluded from the present study. In addition, edoxaban was introduced in our hospital at the end of 2014 and only a small number of patients had been prescribed it at the time the present study was started; thus, we also excluded these patients from the present study. All patients were treated in the Department of Cardiology at the NTT Medical Center in Tokyo. Patients who did not return to our center after being prescribed a DOAC (for reasons such as being referred to the local doctor, etc.) were excluded. The study was registered as a retrospective study under the Protocol Registration System of the UMIN Clinical Trials Registry (UMIN000025009). We combined covariate information with the CHA_2DS_2 [14] and CHA_2DS_2-VASc scores [15] to assess stroke risk and the HAS-BLED score [16] as a measure of the risk of bleeding.

2.2. Medication

Decisions regarding prescription and dosages were left to the discretion of the treating physicians, who in principle abided by the drug package insert. Lower-dose DOACs are recommended for elderly patients with chronic kidney disease (CKD) and for those with a high risk of bleeding. In Japan, lower doses of dabigatran should be considered for elderly patients (age $\geq$ 70 years), patients with moderate renal impairment (creatinine clearance 30–49 mL/min), those with concomitant use of interacting drugs (e.g., verapamil), or those with a high risk of bleeding. Lower doses of rivaroxaban should be considered for patients with moderate renal impairment (creatinine clearance 30–49 mL/min), while low-dose apixaban is recommended in patients with at least two of the following: age $\geq$ 80 years, weight $\leq$ 60 kg, or serum creatinine $\geq$ 1.5 mg/dL.

The Rely study [6] demonstrated that, compared with warfarin, low-dose dabigatran was associated with lower rates of major hemorrhage, while high-dose dabigatran was associated with lower rates of stroke and systemic embolism; this indicated that low-dose dabigatran may not be “suboptimal” treatment. However, in the present study, we defined “suboptimal low-dose DOAC” as low-dose DOAC prescribed without an indication for a low dose, according to the drug package insert in Japan; this is because physicians usually abide by current guidelines and drug package inserts in real-world clinical practice.

2.3. Follow-up

Follow-up data were obtained at routine or additional visits to our hospital. The patients were followed until the end of the specified period (2 years after the first prescription, until March 30, 2016), or until discontinuation of anticoagulants (loss to follow-up). In patients who discontinued therapy before the end of the 2-year follow-up, the observation period ended 1 month after the last dose of medication.

2.4. Outcomes

Information regarding the discontinuation of anticoagulants, thromboembolic events, bleeding, and all-cause mortality was obtained from the medical records. Discontinuation events were defined as the cessation of anticoagulants and/or a switch to a different anticoagulant. Temporary discontinuation for reasons such as surgery was not considered as a discontinuation event. Thromboembolic events were diagnosed by doctors in the Department of Neurosurgery and the Stroke Unit at our hospital, and were classified as ischemic stroke, transient ischemic attack (TIA), or systemic embolism. Ischemic stroke was defined as a sudden loss of neurological function lasting more than 24 hours. TIA was defined as a transient episode of neurological dysfunction lasting for less than 24 hours without acute infarction. Bleeding events included major bleeding, clinically-relevant non-major bleeding (CRNM bleeding), and minor bleeding. Major bleeding was defined according to the criteria of the International Society on Thrombosis and Haemostasis as clinically overt bleeding accompanied by a decrease in hemoglobin level of at least 2 g per deciliter, or the requirement of a transfusion of at least 2 units of packed red cells, occurring at a critical site. CRNM bleeding was defined as visible bleeding that did not meet the criteria for major bleeding, but which led to a medical intervention or unscheduled contact with a physician and temporary cessation of treatment. All clinically overt bleeding not meeting the criteria for either major or CRNM bleeding was defined as minor bleeding.

2.5. Statistical analysis

Statistical analyses were performed using SPSS® Statistics version 21 (IBM Corp, Armonk, NY). Data are expressed as mean $\pm$ standard deviation (SD) for continuous variables and as percentages for categorical variables. Student's t-tests were performed for continuous variables and chi-square tests were performed for categorical variables. *P*-values < 0.05 were considered statistically significant. Event curves were created using the Kaplan–Meier method.

3. Results

Between January 1, 2013 and December 31, 2015, a total of 683 patients with NVAF were newly prescribed one of the three DOACs under investigation (dabigatran, rivaroxaban, and apixaban). Approximately 44% of the patients had previously received warfarin. A total of 13 patients never visited our hospital after receiving the DOAC prescription, and were thus excluded from analysis. Therefore, we retrospectively analyzed 670 patients; 74 (10.9%) received dabigatran, 290 (43.3%) received rivaroxaban, and 306 (45.8%) received apixaban.

Baseline characteristics are shown in Table 1. The mean follow-up period was 15.2, 19.6, and 13.4 months in the dabigatran, rivaroxaban, and apixaban groups, respectively. Patients in the apixaban group were older, had a higher proportion of females, and had more CKD than those in the other two DOAC groups. Patients prescribed apixaban had the highest $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores (2.3 ± 1.3, 3.7 ± 1.7, 2.7 ± 1.3, respectively), followed by patients in the rivaroxaban (2.1 ± 1.3, 3.2 ± 1.7, 2.5 ± 1.3, respectively) and dabigatran groups (1.2 ± 1.0, 2.1 ± 1.5, 1.7 ± 1.1, respectively). Overall, 14 patients in the dabigatran group, 27 patients in the rivaroxaban group, and 23 patients in the apixaban group had 0 points on the $CHADS_2$ score; 6 patients in the dabigatran group, 9 patients in the rivaroxaban group, and 7 patients in the apixaban group had 0 points on the CHA_2DS_2-VASc score (data not shown). Patients who were taking

Table 1
Baseline characteristics.

	Dabigatran	Rivaroxaban	Apixaban	Dabigatran-Rivaroxaban	Dabigatran-Apixaban	Rivaroxaban-Apixaban
	N=74	*N*=290	*N*=306	*P*-value		
Follow-up period (month)	15.2 ± 8.4	19.6 ± 7.6	13.4 ± 7.5	< 0.001	0.101	< 0.001
Age	65 (± 9.6)	70 (± 10.0)	75 (± 11.5)	< 0.001	< 0.001	< 0.001
Sex (male)	54 (74.0%)	222 (76.5%)	188 (61.2%)	0.522	0.030	< 0.001
Male weight (kg)	68.7 (± 11.1)	69.6 (± 12.5)	64.9 (± 13.5)	0.651	0.064	< 0.001
Female weight (kg)	54.8 (± 17.4)	51.6 (± 8.4)	49.6 (± 11.2)	0.468	0.106	0.209
Systolic blood pressure (mmHg)	139 (± 20)	130 (± 18)	130 (± 21)	< 0.001	< 0.001	0.753
eGFR (mL/min/1.73m^2)	66.7 (± 13.2)	62.5 (± 15.0)	58.9 (± 15.3)	0.031	< 0.001	0.004
CrCl (mL/min)	78.5 (± 23.4)	72.5 (± 52.0)	58.1 (± 24.4)	0.378	< 0.001	< 0.001
CrCl (mL/min), n(%)						
≥ 50	56 (75.7)	223 (76.9)	168 (54.9)			
≥ 30 to 50	8 (10.8)	40 (13.8)	100 (32.7)			
< 30	0 (0)	3 (1.0)	23 (7.5)			
Missing	10 (13.5)	24 (8.3)	15 (4.9)			
Paroxysmal, n(%)	43 (58.1)	114 (39.3)	144 (47.6)	0.003	0.089	0.056
Existing comorbidities, n(%)						
CKD	21 (28.8%)	122 (42.1%)	170 (55.4%)	0.030	< 0.001	0.001
Heart failure	7 (9.6%)	78 (26.9%)	95 (30.9%)	< 0.001	< 0.001	0.265
Hypertension	50 (68.5%)	217 (74.8%)	225 (73.3%)	0.305	0.411	0.652
Diabetes mellitus	16 (21.9%)	83 (28.6%)	76 (24.8%)	0.206	0.612	0.298
Prior stroke / TIA / thromboembolism	3 (4.1%)	60 (20.7%)	61 (19.9%)	< 0.001	< 0.001	0.743
Vascular disease	5 (6.8%)	45 (15.5%)	49 (16.0%)	0.017	0.013	0.868
$CHADS_2$ score	1.2 (± 1.0)	2.1 (± 1.3)	2.3 (± 1.3)	< 0.001	< 0.001	0.062
CHA_2DS_2-VASc score	2.1 (± 1.5)	3.2 (± 1.7)	3.7 (± 1.7)	< 0.001	< 0.001	0.003
HAS-BLED score	1.7 (± 1.1)	2.5 (± 1.3)	2.7 (± 1.3)	< 0.001	< 0.001	0.333
Medical treatment, n (%)						
Antiplatelet	5 (6.8%)	34 (11.7%)	42 (13.7%)	0.029	0.010	0.633
PPI	12 (16.4%)	73 (25.2%)	81 (26.4%)	0.076	0.051	0.718
B-blocker	42 (57.5%)	121 (41.7%)	120 (39.1%)	0.011	0.003	0.481
ACEI / ARB	36 (49.3%)	158 (54.5%)	130 (42.3%)	0.491	0.282	0.003
Ca blocker	30 (41.1%)	157 (54.1%)	136 (44.3%)	0.060	0.621	0.014
Statin	15 (20.5%)	103 (35.5%)	106 (34.5%)	0.006	0.012	0.823
Digoxin	14 (19.2%)	117 (40.3%)	105 (34.2%)	< 0.001	0.006	0.128
Amiodarone	1 (1.4%)	7 (2.4%)	8 (2.6%)	0.579	0.534	0.876

Data shown as n (%) and mean ± SD. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CrCl, creatinine clearance; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; PPI, proton pump inhibitor; TIA, transient ischemic attack
$CHADS_2$ = Congestive heart failure, Hypertension (blood pressure consistently above 140/90 mmHg or treated hypertension on medication), Age ≥ 75 years, Diabetes mellitus, prior Stroke/TIA/thromboembolic event (doubled).
CHA_2DS_2-VASc = Congestive heart failure (or left ventricular systolic dysfunction), Hypertension (blood pressure consistently above 140/90 mmHg or treated hypertension on medication), Age ≥ 75 years (doubled), Diabetes mellitus, prior Stroke/TIA/thromboembolic event (doubled), Vascular disease, Age 65–74 years, Female sex.
HAS-BLED = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (> 65years), Drugs/alcohol use.

antiplatelet medications and/or were on statin drugs were prescribed rivaroxaban or apixaban more often than dabigatran.

Among the 670 patients, 43 (58.1%) in the dabigatran group, 131 (45.2%) in the rivaroxaban group, and 146 (47.7%) in the apixaban group were prescribed lower doses of the respective DOACs. A total of 129 patients were treated with suboptimal low-dose DOACs (dabigatran, 9 patients; rivaroxaban, 75 patients; apixaban, 45 patients). Table 2 shows the baseline characteristics of patients prescribed each of the suboptimal low-dose DOACs. Compared with patients treated with the recommended high-dose DOACs, patients prescribed suboptimal low-doses were significantly older, more often with moderate renal impairment, and with concomitant use of antiplatelet drugs in the rivaroxaban and apixaban groups. Patients in the rivaroxaban group who had a higher risk of bleeding (higher HAS-BLED score) were prescribed suboptimal low-dose DOACs. Patients with prior strokes in the apixaban group were more likely to be prescribed the recommended high-dose than the suboptimal low-dose regimen (P=0.009).

During the follow-up period, 192 patients (28.7%) had discontinuation events. Of these patients, 29 were on dabigatran, 93 on rivaroxaban, and 70 on apixaban (Table 3). Discontinuation events were divided into three groups: temporary cessation, switch to other anticoagulants, and complete cessation. Apart from adverse events, other reasons for discontinuation included deterioration in renal function, maintenance of sinus rhythm after AF ablation, surgical/interventional procedures such as aortic valve replacement, patient's desire, and patients' own initiative without consulting a physician. Among patients prescribed dabigatran, the most common reason for discontinuation was digestive symptoms, such as upset stomach, nausea, and vomiting (10 patients; 34.5%). Among patients prescribed rivaroxaban, deterioration in renal function was the most common reason for discontinuation (21 patients; 22.3%), followed by bleeding events (18 patients; 19.1%). Among patients prescribed apixaban, the most common reason for discontinuation was bleeding (20 patients; 28.6%). Some patients discontinued the DOAC because their sinus rhythm was maintained after AF ablation, and/or they had a $CHADS_2$ score of 0 since the initiation of the DOAC. Approximately 3% of the patients discontinued DOAC without consulting a doctor, pharmacist, or any other healthcare worker. Most of the patients who had CRNM bleeding events had some desire to stop anticoagulants completely after the bleeding events (dabigatran 1 patient, rivaroxaban 2 patients, apixaban 6 patients) (data not shown). In addition to bleeding events, maintenance of sinus rhythm, and patients' desire, reasons for complete cessation included difficulty in oral

Table 2
Baseline characteristics of patients receiving recommended high-dose and suboptimal low-dose medications.

	Dabigatran			**Rivaroxaban**			**Apixaban**		
	Recommended high-dose ***N*=24**	Suboptimal low-dose ***N*=9**	*P*-value	Recommended high-dose ***N*=153**	Suboptimal low-dose ***N*=75**	*P*-value	Recommended high-dose ***N*=156**	Suboptimal low-dose ***N*=45**	*P*-value
Age	59 (±8.9)	61 (±6.6)	0.408	66 (±9.0)	73 (±8.3)	<0.001	69 (±10.1)	75 (±8.9)	<0.001
Sex (male)	21 (87.5 %)	5 (55.6 %)	0.120	130 (84.4 %)	58 (73.4 %)	0.063	(74.0 %)	(76.5 %)	0.192
Weight (kg)	65.3 (±10.9)	74.0 (±17.8)	0.081	69.1 (±13.9)	64.9 (±12.4)	0.024	65.0 (±12.7)	61.5 (±18.2)	0.151
Cre (mg/dL)	0.89 (±0.17)	0.81 (±0.16)	0.080	0.88 (±1.73)	0.91 (±0.23)	0.222	0.92 (±0.21)	1.02 (±0.35)	0.081
CrCl (mL/min)	85.3 (±24.4)	93.9 (±16.1)	0.327	81.4 (±22.6)	65.1 (±13.8)	<0.001	70.2 (±23.2)	54.8 (±21.6)	<0.001
CrCl (mL/min), n(%)									
≥ 60	21 (87.5 %)	9 (100 %)		132 (86.3 %)	40 (53.3 %)		100 (64.1 %)	15 (33.3 %)	
≥ 50 to 60	3 (12.5 %)	0 (0 %)		21 (13.7 %)	35 (46.7 %)		28 (17.9 %)	9 (20 %)	
< 50							28 (17.9 %)	21 (46.7 %)	
$CHADS_2$ score	0.8 (±0.7)	1.4 (±1.1)	0.038	1.8 (±1.2)	2.3 (±1.3)	0.003	2.0 (±1.3)	2.0 (±1.2)	0.061
CHA_2DS_2-VASc score	1.3 (±1.0)	2.2 (±1.6)	0.050	2.7 (±1.6)	3.6 (±1.6)	<0.001	3.1 (±1.6)	3.5 (±1.6)	0.139
HAS-BLED score	1.2 (±1.0)	1.4 (±1.1)	0.569	2.2 (±1.2)	2.9 (±1.3)	<0.001	2.4 (±1.4)	2.6 (±1.1)	0.306
Prior stroke / TIA / thromboembolism	0 (0 %)	1 (11.1 %)	0.347	28 (18.3%)	16 (21.3 %)	0.588	31 (19.9 %)	3 (6.7 %)	0.009
Previous bleeding events	2 (8.3%)	0 (0 %)	0.387	15 (9.8 %)	9 (12.0 %)	0.614	13 (8.3 %)	2 (4.4 %)	0.311
Medical treatment, n(%)									
Antiplatelet	1 (4.2 %)	0 (0 %)	0.042	12 (7.8%)	14 (18.7%)	0.041	18 (11.5 %)	13 (28.9 %)	0.014

Data shown as n (%) and mean ± SD. CrCl, creatinine clearance; CKD, chronic kidney disease; TIA, transient ischemic attack
$CHADS_2$ = Congestive heart failure, Hypertension (blood pressure consistently above 140/90 mmHg or treated hypertension on medication), Age ≥75 years, Diabetes mellitus, prior Stroke/TIA/thromboembolic event (doubled).
CHA_2DS_2-VASc = Congestive heart failure (or left ventricular systolic dysfunction), Hypertension (blood pressure consistently above 140/90 mmHg or treated hypertension on medication), Age ≥75 years (doubled), Diabetes mellitus, prior Stroke/TIA/thromboembolic event (doubled), Vascular disease, Age 65–74 years, Female sex.
HAS-BLED = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (>65years), Drugs/alcohol use.

Table 3
Discontinuation of DOAC and the reasons for discontinuation.

	Dabigatran *N*=74	Rivaroxaban *N*=290	Apixaban *N*=306
Discontinuation events (%)	29 (39.2)	93 (32.1)	70 (22.9)
Temporary cessation(%[a])	0 (0)	3 (3.2)	9 (12.9)
Switch to other anticoagulants (%[a])	25 (86.2)	66 (71.0)	40 (57.1)
Complete cessation(%[a])	4 (13.8)	24 (25.8)	21 (30)
Adverse events	12 (41.3)	31 (33.3)	36 (51.4)
Digestive symptom	10	0	1
Bleeding	1	18	20
Abnormality in laboratory data	0	4	5
Other	1	9	10
Reason for discontinuation			
Deterioration in renal function	2 (6.9)	21 (22.6)	0 (0)
Maintenance of sinus rhythm	4 (13.8)	7 (7.5)	10 (14.3)
Surgical/interventional procedures	0 (0)	4 (4.3)	8 (11.4)
Patient's desire	4 (13.8)	12 (12.9)	5 (7.1)
Of the patient's own initiative	1 (3.4)	5 (5.4)	3 (4.3)
Other	6 (9.5)	13 (14.0)	8 (11.4)

[a] As a percentage of the total discontinuation events.

Table 4
Thromboembolic, bleeding, and all-cause mortality events: (A) all patients; (B) suboptimal low-dose patients.

A	**Variables : Events (%)**	**Dabigatran (*N*=74)**	**Rivaroxaban (*N*=290)**	**Apixaban (*N*=306)**
	Thromboembolism	0 (0)	8 (2.8)	7 (2.3)
	Ischemic stroke	0 (0)	7 (2.4)	5 (2.0)
	TIA	0 (0)	0 (0)	1 (0.3)
	Systemic embolism	0 (0)	1 (0.3)	1 (0.3)
	Any bleeding	8 (10.7)	57 (19.7)	51 (16.7)
	Major bleeding	0 (0)	2 (0.7)	4 (1.3)
	CRNM bleeding	1 (1.3)	7 (2.4)	10 (3.3)
	All-cause mortality	0 (0)	4 (1.4)	12 (3.9)
B	**Variables : Events (%), sub-optimal low-dose**	**Dabigatran (*N*=9)**	**Rivaroxaban (*N*=75)**	**Apixaban (*N*=45)**
	Thromboembolism	0 (0)	1 (1.3)	1 (2.2)
	Ischemic stroke	0 (0)	1 (1.3)	1 (2.2)
	TIA	0 (0)	0 (0)	0 (0)
	Systemic embolism	0 (0)	0 (0)	0 (0)
	Any bleeding	3 (33.3)	12 (16.5)	2 (4.4)
	Major bleeding	0 (0)	0 (0)	0 (0)
	CRNM bleeding	0 (0)	3 (4.0)	0 (0)
	All-cause mortality	0 (0)	2 (2.7)	0 (0)

TIA, transient ischemic attack; CRNM bleeding, clinically-relevant non-major bleeding

administration of the medicine due to worsening underlying disease. Cumulative rates (Kaplan–Meier) for discontinuation events were significantly different between the dabigatran and rivaroxaban groups (P=0.015), and between the dabigatran and apixaban groups (P=0.002).

The number of thromboembolic events in each DOAC group is shown in Table 4A, while the number of thromboembolic events with suboptimal low-dose DOACs is shown in Table 4B. A total of 15 patients had a thromboembolic event; Table 5 describes all of these patients. Systemic embolism occurred in one patient in the rivaroxaban group (involving a limb arterial embolism) 3 days after DOAC discontinuation due to minor bleeding (No. 8), and in 1 patient in the apixaban group (involving a limb arterial embolism) 14 days after DOAC discontinuation due to major bleeding (No. 15). Among the 8 patients prescribed rivaroxaban who had a thromboembolic event (Nos. 1–8), 3 patients discontinued treatment on their own initiative (Nos. 5, 6, and 7). In addition, 3 patients were diagnosed with or suspected of a lacunar infarction and continued taking rivaroxaban; 2 patients were discharged with the addition of aspirin (Nos. 2 and 3), and one was discharged with the addition of clopidogrel (No. 4). Another patient was diagnosed with a cardiogenic embolism due to NVAF and was prescribed warfarin instead of rivaroxaban (No. 1). Among the

Table 5
Clinical features of patients with thromboembolism.

Patient	DOAC	Dose (mg)	Age	$CHADS_2$ score	$CHADS_2VASc$ score	HASBLED score	Prior Stroke	Antiplatelet	Type of Thromboembolism	DOAC persistence at the onset of thromboembolism	Medication after intensive treatment
No.1	Rivaroxaban	10	71	3	4	4	+	None	Ischemic stroke	Continued	Warfarin
No.2		15	72	2	3	2	–	None	Ischemic stroke	Continued	Rivaroxaban + aspirin
No.3		15	79	3	5	2	–	None	Ischemic stroke	Continued	Rivaroxaban + aspirin
No.4		15	79	5	6	4	+	None	Ischemic stroke	Continued	Rivaroxaban + clopidogrel
No.5		15	67	4	6	4	+	None	Ischemic stroke	Cessation by the patient's own initiative	Rivaroxaban
No.6		10 (suboptimal low-dose)	76	2	3	3	–	None	Ischemic stroke	Cessation by the patient's own initiative	Rivaroxaban
No.7		15	68	4	7	4	+	Aspirin + clopidogrel	Ischemic stroke	Cessation by the patient's own initiative	Rivaroxaban + aspirin + clopidogrel
No.8		15	64	4	4	3	+	None	Systemic embolism	Cessation due to minor bleeding	Apixaban
No.9	Apixaban	5	93	5	7	6	+	None	Ischemic stroke	Continued	Warfarin
No.10		5	83	2	5	3	–	Aspirin + clopidogrel	Ischemic stroke	Continued	Warfarin + aspirin + clopidogrel
No.11		10	78	5	6	5	+	None	Ischemic stroke	Uncertain	Warfarin
No.12		5 (suboptimal low-dose)	78	4	6	4	–	Aspirin + prasugrel	Ischemic stroke	Cessation by the patient's own initiative	Apixaban+ Aspirin + prasugrel
No.13		10	63	4	4	4	+	None	Ischemic stroke	Cessation by the patient's own initiative	Edoxaban
No.14		5	81	5	7	5	+	Aspirin + clopidogrel	TIA	Continued	Apixaban + aspirin + clopidogrel
No.15		5	93	2	5	5	–	None	Systemic embolism	Cessation due to major bleeding	Apixaban

Abbreviations as in Table 1.

Table 6
Clinical features of patients with major bleeding events.

Patient	DOAC	Dose (mg)	Age	$CHADS_2$ score	$CHADS_2$-VASc score	HASBLED score	Prior stroke	Antiplatelet	Type of bleeding	Medication after intensive treatment
No.1	Rivaroxaban	15	79	3	5	2	–	Aspirin	Lower gastrointestinal bleeding	Apixaban 5 mg+ Clopidogrel
No.2		10	81	4	6	4	+	Aspirin + Prasugrel	Gastrointestinal hemorrhage	Aspirin+ Prasugrel
No.3	Apixaban	10	58	4	4	2	+	None	Subcortical cerebral hemorrhage	Apixaban 10 mg
No.4		10	77	3	5	3	–	Aspirin + Clopidogrel	Thalamic hemorrhage	Edoxaban 30 mg+ Aspirin + clopidgrel
No.5		10	66	3	4	6	+	Aspirin	Chronic subdural hematoma	Apixaban 10 mg+ Aspirin
No.6		5	90	3	4	3	–	None	Lower gastrointestinal bleeding	None

The doses for aspirin, clopidogrel, and prasugrel are 100 mg, 75 mg, and 3.75 mg, respectively.
Abbreviations as in Table 1.

7 patients prescribed apixaban who had a thromboembolic event (Nos. 9–15), two patients discontinued apixaban on their own initiative (Nos. 12 and 13), and 1 patient discontinued apixaban because of a major bleeding event (lower gastrointestinal bleeding) (No. 15). One patient had a history of medication failures due to higher brain dysfunction after intracranial bleeding events; however, there were no medical record descriptions indicating DOAC discontinuation (No. 11). Three patients were diagnosed with or suspected of a cardiogenic cerebral embolism and were prescribed warfarin instead of apixaban (Nos. 9, 10, and 11). Another patient was diagnosed with a TIA and continued medication. One patient in each of the rivaroxaban (No. 6) and apixaban (No. 12) groups was prescribed suboptimal low-dose DOACs. In the following period, 33 out of 670 patients underwent catheter ablation, and none of them developed any stroke (data not shown).

Bleeding events are also shown in Table 4. A total of 116 patients (17.3%) experienced a bleeding event during the follow-up period. Two patients in the rivaroxaban group and 4 patients in the apixaban group experienced major bleeding. In addition, 1 patient in the dabigatran group, 7 patients in the rivaroxaban group, and 10 patients in the apixaban group experienced CRNM bleeding. No intracranial hemorrhages occurred in the patients prescribed dabigatran or rivaroxaban. One of the 2 major bleeding events in the rivaroxaban group involved upper gastrointestinal bleedings, while 1 involved lower gastrointestinal bleeding; all required blood transfusions. Major bleeding events in the apixaban group involved 1 subdural hematoma, 1 thalamic hemorrhage, 1 subcortical cerebral and 1 lower gastrointestinal bleeding from stage IV colon cancer (Table 6). Among patients prescribed the suboptimal low doses, none had major bleeding events in any of the 3 DOAC groups (Table 4B). The incidence of any bleeding event among patients receiving suboptimal doses of apixaban was significantly lower than that in those recommended high-dose apixaban ($P=0.031$); however, no significant difference was found in the rivaroxaban group ($P=0.142$).

All-cause mortality is also shown in Table 4. There were no deaths in the dabigatran group, 4 deaths (1.4%) in the rivaroxaban group, and 12 deaths (3.9%) in the apixaban group. However, no patients in the rivaroxaban and apixaban groups died because of a thromboembolic or bleeding event. In the rivaroxaban group, all deaths were related to various cancers, while in the apixaban group 4 patients died from heart failure, 4 from pneumonia, 3 from cancers, and 1 from senile decay. Two patients in the rivaroxaban group were prescribed a suboptimal low dose, compared to none in the apixaban group.

4. Discussion

4.1. Major findings and important points

In the present study, our findings can be summarized into 6 main points as follows.

1) Patients with a comparatively high risk of stroke and bleeding tended to be prescribed apixaban or rivaroxaban in our hospital. Patients prescribed suboptimal low-dose were significantly older, more often with moderate renal impairment and with concomitant use of antiplatelet drugs than high dose of DOAC in the rivaroxaban and apixaban group.
2) Patients prescribed dabigatran discontinued the medication significantly more often than did those prescribed rivaroxaban or apixaban, with the main reason for discontinuation being digestive symptoms.
3) The incidence of thromboembolic events was more or less similar to that reported in previous clinical trials, demonstrating the considerable efficacy of the examined DOACs.
4) Given that 7 out of 15 patients had a stroke or systemic embolism following DOAC discontinuation, and 5 of them stopped taking the medication on their own initiative, without consulting a physician, adherence to anticoagulants is one of the most important issues in improving their efficacy of anticoagulants.
5) Bleeding events occurred in all three DOAC groups; however, major bleeding (including intracranial hemorrhage) occurred in only a very small proportion in this study, with no mortality.
6) No patient on suboptimal low-dose DOAC had an ischemic stroke, as long as the DOAC was taken regularly. Patients often desire cessation of anticoagulants after even minor bleedings; however, maintaining a low-dose DOAC may be important for patients who have a higher risk of stroke and bleeding in such situations.

4.2. Baseline characteristics

We retrospectively analyzed patients with NVAF who were prescribed one of 3 DOACs—dabigatran, rivaroxaban, or apixaban—in a real-world clinical setting. Specifically, we investigated medication details, such as whether patients continued the DOAC or switched to another anticoagulant during the follow-up period, the reason for discontinuation, and whether patients who developed thromboembolic events had been taking the DOAC correctly at the time of event onset. Numerous studies have already compared the efficacy and safety outcomes of DOACs and warfarin

[17,18]. DOACs have been preferred over warfarin by the physicians in our hospital ever since dabigatran was introduced in 2012 (except in cases such as patients with decreased renal function or post-valve surgery).

Based on the $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores in the present study, patients who had a high risk of thromboembolic and/or bleeding events were more frequently prescribed apixaban or rivaroxaban compared to dabigatran. However, the baseline characteristics in the present study, such as age, differed considerably from those of previous studies [18,19]. Elderly patients tended to be prescribed apixaban more frequently than rivaroxaban and dabigatran. This is probably due to the results of a subgroup analysis of the ARISTOTLE trial, which demonstrated that, compared to warfarin, apixaban was associated with a lower risk of thromboembolism, caused less bleeding, and had lower mortality, regardless of age [20]. Moreover, patients with CKD were also more frequently prescribed apixaban in the present study, probably because of another subgroup analysis of the ARISTOTLE trial that demonstrated the benefits of apixaban over warfarin in patients with CKD [21].

4.3. Medication persistence

As with warfarin, the prothrombin time/INR should be controlled adequately, and DOACs should be taken correctly once or twice per day for maintenance of the blood concentration. The importance of adherence to anticoagulants for stroke prevention has already been reported in several studies [22–27]. In our hospital, discontinuation events were seen significantly more frequently in patients prescribed dabigatran (mainly because of digestive symptoms) than in patients prescribed rivaroxaban or apixaban. All of these patients were switched to rivaroxaban, apixaban, or warfarin as soon as possible, and none experienced any thromboembolic event. Some patients requested to be switched from dabigatran or apixaban, which needs to be taken twice per day, to rivaroxaban, edoxaban, or warfarin, where the dosage is only once per day; other patients requested to be switched after complaints regarding ambiguous symptoms such as palpitations or dizziness. In terms of medication adherence, whether other drugs, such as antiplatelet therapy, were also discontinued may have important relevance, especially with regard to the onset of the lacunar infarction; however, as a limitation of a retrospective study, no detailed information was available concerning the discontinuation of other drugs.

4.4. Efficacy and safety outcomes

Although some patients in the rivaroxaban and apixaban groups experienced stroke events, no patients in the dabigatran group experienced a thromboembolic event. Although we could not statistically analyze group differences in thromboembolism, given our small sample size, we speculate that the observed differences were not due to dabigatran being superior to the other two DOACs in terms of stroke prevention; rather, patients who had been prescribed dabigatran had a comparatively lower risk of stroke ($CHADS_2$ score 1.2 ± 1.0, CHA_2DS_2-VASc score 2.1 ± 1.5).

In considering factors that influence the prevention of thromboembolism, strict adherence to anticoagulants is one of the important matters. Fifteen patients had a thromboembolic event; of these, 7 (almost half) had discontinued anticoagulants when they had the stroke or systemic embolism. Ischemic stroke can be divided into 3 types: thrombotic, embolic, and hemodynamic; anticoagulants have a great preventive effect mainly against embolic strokes. Ten patients were diagnosed with or highly suspected of cardiogenic cerebral embolisms (Nos. 1, 5, 6, 7, 9, 10, 11, 12, 13, and 14 in Table 5), and all had a high risk of stroke in terms of their CHA_2DS_2-VASc scores. Surprisingly, 5 of these patients discontinued anticoagulants on their own initiative. Patients Nos. 8 and 15 developed systemic embolism and had discontinued their anticoagulants because of bleeding, even though their CHA_2DS_2-VASc scores were very high. Only 4 patients had an ischemic stroke despite continuing anticoagulants. Given that 440 out of 444 patients with a CHA_2DS_2-VASc score greater than or equal to 3 points did not develop an ischemic stroke as long as the DOAC was taken regularly, it is not too much to say that adherence to anticoagulants is likely to be the most significant factor for stroke prevention.

However, the longer patients continue taking anticoagulants for stroke prevention, the higher the rate of bleeding events. Minor bleedings, such as subcutaneous hemorrhage, were also collected from the medical records because even slight bleeding can lead to a low adherence to medication. Only 6 out of 670 patients had major bleeding events, which is more or less similar to the proportion reported in other large clinical trials [10–12]. Interestingly, the neurological prognosis following intracranial bleeding was comparatively good; 2 patients had only slight symptoms, including higher brain dysfunction, 1 patient had a trivial ataxic gait, and 1 had a reduced level of consciousness (Japan coma scale, 100).

4.5. Suboptimal low-dose DOACs for stroke prevention

A clinical trial of patients prescribed low-dose DOACs has already been reported [28]; however, there are few studies of patients who were treated with suboptimal low-dose DOACs [29]. An analysis of the relation between DOAC dose and clinical outcomes reported in 2016 showed that low-dose DOACs for stroke prevention in AF are associated with worse clinical outcomes in US practice [30]. However, medication adherence was not discussed in the article, while one of the results showed that low-dose patients somehow experienced more major bleeding than did normal-dose patients. In the present study, 129 patients were treated with suboptimal low-dose DOACs; however, only 2 patients (Nos. 8 and 15) had an ischemic stroke, and both of these patients actually discontinued the medication on their own initiative. Although the incidence of bleeding events in patients taking suboptimal low-dose DOACs was not significantly lower than that in those taking the recommended high dose in the rivaroxaban group, the incidence was significantly lower in the apixaban group ($P=0.031$). This difference between the rivaroxaban and apixaban groups could be related to the difference between the proportion of suboptimal low-dose in relation to higher-dose regimens (rivaroxaban 0.67, apixaban 0.50). The importance of adherence to anticoagulants for stroke prevention is already well established; however, patients often desire to stop anticoagulants after even minor bleedings. It is not unusual to discontinue anticoagulants after bleeding, even among patients with a very high risk of stroke. As the present study did not include many patients with a very high risk of bleeding averagely (HAS-BLED score of patients was about 2), we could not apply our findings to every high-risk patient. However, our findings suggest that suboptimal low-dose DOACs may be a better alternative for some patients with a high risk of stroke and bleeding.

4.6. Limitations

The limitations of the present study include the retrospective nature of the design and the small size of the sample, which consisted of patients from a single center. As we could only collect information regarding events from our medical records, we may have missed several patients who complained of minor bleeding, or patients with major bleeding/thromboembolism who were

managed in other hospitals. In addition, we could not statistically analyze group differences in some outcomes, such as major bleeding and stroke, because of the small number of these events. In view of these limitations, we could not strongly support the suggestion of suboptimal low-dose DOACs in the present study. Further studies with a greater number of patients to establish clear standards for suboptimal low-dose DOACs in patients with NVAF will be required.

5. Conclusions

DOACs have shown considerable efficacy in the prevention of stroke, as long as patients adhere to the medications prescribed; the present study shows that this applies equally to patients treated with suboptimal low-dose DOACs. Our findings suggest that continuation of a suboptimal low-dose DOAC may be a better choice for some patients with a high risk of stroke and bleeding, as opposed to complete cessation of DOAC therapy following bleeding events.

Funding

This research received no grant from any funding agency.

Conflict of interest

None of the authors has any conflict of interest related to this study.

Acknowledgements

We are grateful to Drs. R. Kameda and S. Katsushika for their insightful comments and suggestions. We are grateful to Drs. H. Hayashida, T. Tozuka, and S. Yoshimoto for data collection and critical reading of the manuscript. We thank all the doctors in the Department of Neurosurgery and the Stroke Unit at NTT Medical Center Tokyo for their accurate and precise diagnosis of stroke and their good cooperation in medical practice. We also thank Editage (www.editage.jp) for English language editing.

References

[1] Miyasaka Y, Barnes ME, Bailey KR, et al. Mortality trends in patients diagnosed with first atrial fibrillation: a 21-year community-based study. J Am Coll Cardiol 2007;49:986–92.
[2] Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007;146:857–67.
[3] Go AS, Hylek EM, Borowsky LH, et al. Warfarin use among ambulatory patients with nonvalvular atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. Ann Intern Med 1999;131:927–34.
[4] Birman-Deych E, Radford MJ, Nilasena DS, et al. Use and effectiveness of warfarin in Medicare beneficiaries with atrial fibrillation. Stroke 2006;37:1070–4.
[5] Yeh CH, Fredenburgh JC, Weitz JI. Oral direct factor Xa inhibitors. Circ Res 2012;111:1069–78.
[6] Connolly SJ, Ezekowitz MD, Yusuf S, et al. RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139–51.
[7] Patel MR, Mahaffey KW, Garg J, et al. ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. Engl J Med 2011;365:883–91.
[8] Granger CB, Alexander JH, McMurray JJ, et al. ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. Engl J Med 2011;365:981–92.
[9] Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013;369:2093–104.
[10] Ezekowitz MD, Wallentin L, Connolly SJ, et al. RE-LY Steering Committee and Investigators. Dabigatran and warfarin in vitamin K antagonist-naive and -experienced cohorts with atrial fibrillation. Circulation 2010;122:2246–53.
[11] Hori M, Connolly SJ, Ezekowitz MD, et al. RE-LY Investigators. Efficacy and safety of dabigatran vs. warfarin in patients with atrial fibrillation–sub-analysis in Japanese population in RE-LY trial. Circ J 2011;75:800–5.
[12] Larsen TB, Rasmussen LH, Gorst-Rasmussen A, et al. Dabigatran and warfarin for secondary prevention of stroke in atrial fibrillation patients: a nationwide cohort study. Am J Med 2014;127(1172–8):e5.
[13] Camm AJ, Amarenco P, Haas S, et al. XANTUS Investigators. XANTUS: a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation. Eur Heart J 2016;37:1145–53.
[14] Gage BF, van Walraven C, Pearce L, et al. Selecting patients with atrial fibrillation for anticoagulation: stroke risk stratification in patients taking aspirin. Circulation 2004;110:2287–92.
[15] Lip GY, Nieuwlaat R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest 2010;137:263–72.
[16] Pisters R, Lane DA, Nieuwlaat R, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest 2010;138:1093–100.
[17] Larsen TB, Skjøth F, Nielsen PB, et al. Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. BMJ 2016;353:i3189.
[18] Olesen JB, Sørensen R, Hansen ML, et al. Non-vitamin K antagonist oral anticoagulation agents in anticoagulant naïve atrial fibrillation patients: Danish nationwide descriptive data 2011-2013. Europace 2015;17:187–93.
[19] Shiga T, Naganuma M, Nagao T, et al. Persistence of non-vitamin K antagonist oral anticoagulant use in Japanese patients with atrial fibrillation: A single-center observational study. J Arrhythm 2015;31:339–44.
[20] Halvorsen S, Atar D, Yang H, et al. Efficacy and safety of apixaban compared with warfarin according to age for stroke prevention in atrial fibrillation: observations from the ARISTOTLE trial. Eur Heart J 2014;35:1864–72.
[21] Hohnloser SH, Hijazi Z, Thomas L, et al. Efficacy of apixaban when compared with warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial. Eur Heart J 2012;33:2821–30.
[22] Patel MR, Hellkamp AS, Lokhnygina Y, et al. Outcomes of discontinuing rivaroxaban compared with warfarin in patients with nonvalvular atrial fibrillation: analysis from the ROCKET AF trial (Rivaroxaban Once-Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation). J Am Coll Cardiol 2013;61:651–8.
[23] Shore S, Carey EP, Turakhia MP, et al. Adherence to dabigatran therapy and longitudinal patient outcomes: insights from the veterans health administration. N. Am Heart J 2014;167:810–7.
[24] Coleman CI, Tangirala M, Evers T. Medication adherence to rivaroxaban and dabigatran for stroke prevention in patients with non-valvular atrial fibrillation in the United States. Int J Cardiol 2016;212:171–3.
[25] Yao X, Abraham NS, Alexander GC, et al. Effect of adherence to oral anticoagulants on risk of stroke and major bleeding among patients with atrial fibrillation. J Am Heart Assoc 2016:5 pii: e003074.
[26] Brown JD, Shewale AR, Talbert JC. Adherence to rivaroxaban, dabigatran, and apixaban for stroke prevention in incident, treatment-naïve nonvalvular atrial fibrillation. J Manag Care Spec Pharm 2016;22:1319–29.
[27] Beyer-Westendorf J, Ehlken B, Evers T. Real-world persistence and adherence to oral anticoagulation for stroke risk reduction in patients with atrial fibrillation. Europace 2016;18:1150–7.
[28] Staerk L, Fosbøl EL, Lip GY, et al. Ischaemic and haemorrhagic stroke associated with non-vitamin K antagonist oral anticoagulants and warfarin use in patients with atrial fibrillation: a nationwide cohort study. Eur Heart J 2017;38:907–15.
[29] Başaran, Dogan V, Beton O, Collaborators. Suboptimal use of non-vitamin K antagonist oral anticoagulants: Results from the RAMSES study. Medicine (Baltimore) 2016;95:e4672.
[30] Benjamin A, Steinberg BA, Shrader P, Thomas L, et al. ORBIT-AF Investigators and Patients. Off-Label Dosing of Non-Vitamin K Antagonist Oral Anticoagulants and Adverse Outcomes: The ORBIT-AF II Registry. J Am Coll Cardiol 2016;68:2597–604.