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Original Article

Current use of direct oral anticoagulants for atrial fibrillation in Japan: Findings from the SAKURA AF Registry

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ABSTRACT

Background: Large-scale investigations on the use of oral anticoagulants including direct oral anticoagulants (DOACs) in patients with atrial fibrillation (AF) have not included Japanese patients.
Methods: We established the multicenter SAKURA AF Registry to support prospective observational research on the status of anticoagulation treatment, especially with DOAC, for AF in Japan. We enrolled 3266 AF patients treated with warfarin ($n=1577$) or any of 4 DOACs ($n=1689$) from 63 institutions (2 cardiovascular centers, 13 affiliated hospitals or community hospitals, and 48 private clinics) in the Tokyo area.
Results: We conducted our first analysis of the registry data, and although we found equivalent mean age between the DOAC and warfarin users (71.8 ± 9.5 vs. 72.3 ± 9.4 years, $p=0.2117$), we found a slightly lower risk of stroke ($CHADS_2$ score of 0 or 1 [46.9% vs. 39.4%, $p < 0.0001$]) and significantly better creatinine clearance in DOAC users (70.4 ± 27 vs. 65.6 ± 25.7 mL/min, $p < 0.0001$). Importantly, we documented under-dosing in 32% of warfarin users and inappropriate-low-dosing in 19.7–27.6% of DOAC users.
Conclusions: Our initial analysis of the SAKURA AF Registry data clarified the real-world use of anticoagulants, which includes DOACs and warfarin in Japan. The DOAC users were at a lower risk for stroke than the warfarin users. In 20–30% of DOAC users, the dose was inappropriately reduced.

1. Introduction

Atrial fibrillation (AF), the most common arrhythmia in the elderly, affects approximately 0.6% of the Japanese population, with its prevalence expected to increase to over 1 million persons

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by 2050 [1]. AF is an independent risk factor for stroke and death. Although anticoagulation with warfarin provides effective stroke prophylaxis in patients with AF, its use can be troublesome because of issues such as food-drug interactions, a narrow therapeutic window, and the need for frequent monitoring of the prothrombin-international normalized ratio (PT-INR). To overcome the limitations of warfarin, direct oral anticoagulants (DOACs) have been developed.

The benefits of DOACs over warfarin in reducing the risk of vascular events and bleeding complications in patients with AF have been substantiated in randomized clinical trials (RCTs) [2–5]. Although there have been several "real-world" larger-scale registries in Japan such as the J-RHYTHM Registry [6,7], Fushimi AF Registry [8,9], and SHINKEN database [10], these registries included very few DOAC users. As such, no large-scale studies on the use of DOACs in Japan have been conducted to clarify the clinical characteristics of the AF patients for whom they are prescribed or to confirm the efficacy and safety of these drugs. We therefore established the multicenter SAKURA AF Registry to support prospective observational research on the status of anticoagulation treatment, i.e., treatment with DOACs and warfarin and to clarify the associated long-term outcomes in terms of strokes and bleeding complications in Japanese patients with AF (SAKURA AF Registry: UMIN Clinical Trials Registry: UMIN000014420). The study described herein stands as the first analysis of the SAKURA AF Registry data and was designed specifically to characterize DOAC and warfarin users separately.

2. Methods

2.1. The SAKURA AF Registry

The SAKURA AF Registry was set up to track the results of the follow-up examinations and clinical events of AF patients for at least 1 year and up to 3 years after their enrollment. Recruitment began in September 2013 and ceased in December 2015. The participating institutions consisted of 2 cardiovascular centers (Nihon University Itabashi Hospital and Nihon University Hospital), 13 affiliated or community hospitals, and 48 private clinics, all located mainly in the capital city of Tokyo or a Tokyo suburb. The analysis of the registry data was approved by our institutional review board (IRB) and individual hospital IRBs. All enrollees provided written informed consent for participation in the registry.

2.2. SAKURA AF Registry population

Patients enrolled in the registry were those aged ≥ 20 years in whom AF was diagnosed by 12-lead electrocardiograms (ECGs), 24-hour Holter ECGs, or event-activated ECGs, and who had been given warfarin or DOACs as stroke prophylaxis. Patients with rheumatic mitral valve disease, history of prosthetic valve replacements, active infective endocarditis, or who failed to provide written informed consent were not enrolled.

2.3. Data collection

Baseline data collected for the registry included the following: patient clinical characteristics, including the age, sex, body weight, and height; type of AF (paroxysmal AF [AF lasting ≤ 7 days], persistent AF [AF lasting > 7 days and ≤ 1 year], or long-standing persistent AF [AF lasting > 1 year]); current medications used, including antiarrhythmic, anticoagulant, and antiplatelet agents; co-morbidities and/or risk factors including hypertension, diabetes, strokes or transient ischemic attacks, coronary heart disease, and congestive heart failure, and whether the patients smoked or consumed alcohol at the time of enrollment. Any prior major bleeding events were also recorded. The $CHADS_2$[11] and CHA_2DS_2-VASc [12] scores (for stroke risk) and HAS-BLED [13] score (for bleeding risk) were calculated and recorded. If available in the patient clinical records, the N-terminal pro-natriuretic peptide (NT-proBNP) levels were obtained. If available, the BNP was converted to NT-proBNP (NT-proBNP$=$BNP$^{1.341}$ $-$ 15). The PT-INR was recorded for warfarin users. Hypertension, diabetes, dyslipidemia, and heart failure were diagnosed as previously reported. [9] Creatinine clearance (CrCl) was calculated according to the Cockcroft-Gault formula [14].

2.4. Data management

A website created for the SAKURA AF Registry was used to collect all patient data through a web-based registration system. Each participating investigator was trained on how to use the study website, and received a personal ID and password for access. The patients' baseline clinical data were entered into online forms and saved to the website. The data entry was checked by clinical research coordinators at the general registry office.

2.5. Study goals and factors analyzed

In addition to ascertaining the characteristics of the total patient population enrolled in the SAKURA AF Registry and then characterizing the warfarin and DOAC users, we explored whether warfarin and DOACs were being appropriately prescribed. In analyzing the warfarin administration, we looked at the PT-INR and accepted 1.6–2.6 as the optimal therapeutic range for those aged ≥ 70 years and 2.0–3.0 for those aged ≤ 69 years [7]. "Overdosing" was defined as a warfarin-related PT-INR above the therapeutic range, and "under-dosing" as that below the therapeutic range. In analyzing the DOAC administration, "appropriate-standard-dosing" and "appropriate-low-dosing" were defined as an administration according to a standard or low-dose regimen, respectively. The definition of a low-dose regimen for each DOAC is shown in Table 1. Inappropriate-low-dosing was defined as administering low-dose DOACs despite the standard dosage criteria being met. Inappropriate-standard-dosing was defined as administering standard-dose DOACs despite the low-dose regimen criteria being met. Dabigatran was considered to be contraindicated if the patient's CrCl was < 30 mL/min; the other DOACs were considered to be contraindicated if the patient's CrCl was < 15 mL/min.

Table 1
Low-dose regimen for each of the direct oral anticoagulants.

Dabigatran 110 mg bid (vs. a standard dosage of 150 mg bid)	Rivaroxaban 10 mg od (vs. a standard dosage of 15 mg od)	Apixaban 2.5 mg bid (vs. a standard dosage of 5 mg bid)	Edoxan 30 mg od (vs. a standard dosage of 60 mg od)
If CrCl is 30–50 mL/min, age is ≥ 70 years, or the patient has a prior bleeding history.	If CrCl is 15–50 mL/min.	Two of the following characteristics: ≥ 80 years, body weight < 60 kg, or serum Cr level ≥ 1.5 mg/dL.	If CrCl is 15–50 mL/min or body weight is ≤ 60 kg.[a]

CrCl, creatinine clearance.

[a] The use of P-plycoprotein inhibitors (verapamil and quinidine or short-term azithromycin, clarithromycin, cyclosporine, or ketoconazole) was not available in this study.

Table 2
Patient clinical characteristics upon enrollment in the SAKURA AF Registry.

	Total patients ($n=3266$)	DOAC users ($n=1689$)	Warfarin users ($n=1577$)	P value*
Age (years)	72.0 ± 9.4	71.8 ± 9.5	72.2 ± 9.3	0.2117
Female sex	840 (25.7)	477 (28.2)	363 (23.0)	0.0006
Height (cm)	162.5 ± 9.5	162.1 ± 9.6	162.7 ± 9.4	0.0202
Weight (kg)	63.8 ± 13.0	63.7 ± 13.4	64.0 ± 12.5	0.4487
BMI (kg/m^2)	24.1 ± 3.7	24.1 ± 3.9	24.0 ± 3.6	0.6238
AF type				
Paroxysmal AF	1210 (37.0)	716 (42.4)	494 (31.3)	< 0.0001
Persistent AF	723 (22.1)	355 (21.0)	368 (23.3)	
LS-AF	1301 (39.8)	602 (35.6)	699 (44.3)	
Not reported	32 (1.0)	16 (1.0)	16 (1.0)	
Systolic BP (mmHg)	127.5 ± 16.1	128.3 ± 16.1	126.8 ± 16.0	0.0089
Diastolic BP (mmHg)	74.6 ± 11.3	74.9 ± 11.6	74.2 ± 11.0	0.0601
Heart rate (bpm)	73.7 ± 15.4	73.5 ± 15.9	73.9 ± 14.8	0.4911
Current smoking status	398 (12.2)	210 (12.4)	188 (11.9)	0.4744
Current alcohol use	1877 (57.5)	981 (58.1)	896 (56.8)	0.1147
Institution type				
High-volume center	1200 (36.7)	591 (35.0)	609 (38.6)	< 0.0001
Hospital	1310 (40.1)	650 (38.5)	660 (41.9)	
Clinic	756 (23.1)	448 (26.5)	308 (19.5)	
Clinical history				
Hypertension	2330 (71.3)	1169 (69.1)	1161 (73.6)	0.0053
Diabetes mellitus	744 (22.8)	362 (21.4)	382 (24.2)	0.0574
Dyslipidemia	1263 (38.7)	618 (36.6)	654 (40.9)	0.0115
Hyperuricemia	657 (20.1)	314 (18.6)	343 (21.8)	0.0244
Heart failure	722 (22.1)	320 (19.0)	402 (25.5)	< 0.0001
Stroke/TIA	368 (11.2)	176 (10.4)	192 (12.2)	0.1130
CAD	313 (9.6)	149 (8.8)	164 (10.4)	0.1316
Major bleeding	30 (0.9)	15 (0.9)	15 (1.0)	0.8502
AF ablation	287 (8.8)	159 (9.4)	128 (8.1)	0.1907
CHAD$_{S2}$ score	1.80 ± 1.15	1.72 ± 1.14	1.90 ± 1.16	< 0.0001
0	364 (11.1)	211 (12.5)	153 (9.7)	0.0007
1	1050 (32.2)	581 (34.4)	469 (29.7)	
2	1056 (32.3)	533 (31.6)	523 (33.2)	
3	529 (16.2)	240 (14.2)	289 (18.3)	
4	202 (6.2)	93 (5.5)	109 (6.9)	
5	59 (1.8)	28 (1.7)	31 (2.0)	
6	6 (0.2)	3 (0.2)	3 (0.2)	
CHA2DS2-VASc score	2.74 ± 1.38	2.63 ± 1.36	2.85 ± 1.40	< 0.0001
0	129 (4.0)	72 (4.3)	57 (3.6)	0.0023
1	470 (14.4)	272 (16.1)	198 (12.6)	
2	862 (26.4)	470 (27.8)	392 (24.9)	
3	929 (28.4)	465 (27.5)	464 (29.4)	
4	547 (16.7)	265 (15.7)	282 (17.9)	
5	223 (6.8)	100 (5.9)	123 (7.8)	
6	83 (2.5)	34 (2.0)	49 (3.1)	
7	23 (0.7)	11 (0.7)	12 (0.8)	
≥ 8	0 (0)	0 (0)	0 (0)	
HAS-BLED score	1.44 ± 0.85	1.28 ± 0.78	1.62 ± 0.88	< 0.0001
0	309 (9.5)	212 (12.6)	97 (6.2)	
1	1602 (49.1)	914 (54.1)	688 (43.7)	
2	1015 (31.1)	452 (26.7)	563 (35.7)	
3	286 (8.7)	100 (5.9)	186 (11.8)	< 0.0001
4	51 (1.6)	11 (0.7)	40 (2.5)	
5	3 (0.1)	0 (0.0)	3 (0.2)	
6	0 (0)	0 (0)	0 (0)	

Values are shown as the mean ± SD or n (%). AF atrial fibrillation; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CHADS$_2$, congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus and stroke; CHA$_2$DS$_2$-VASc, congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke, vascular disease, age 65–74 years and sex category; Center, cardiovascular center; DOAC, direct oral anticoagulant; HAS-BLED, uncontrolled hypertension (baseline systolic blood pressure ≥ 160 mmHg), abnormal renal function (serum creatinine clearance ≥ 2.26 mg/dL)/liver function (chronic hepatic disease [e.g., cirrhosis] or aspartate aminotransferase and/or alanine aminotransferase > 3x normal range), stroke, prior major bleeding, elderly (age ≥ 65 years), drugs (anti-platelet drugs or non-steroidal anti-inflammatory drugs)/alcohol (160 g/day or more), Labile INR (overdosing shown by baseline PT-INR in warfarin users); LS-AF, long-standing persistent AF, Hospital, affiliated hospital or community hospital; TIA, transient ischemic attack.

* Per the Student t-test or chi-square test, as appropriate.

2.6. Statistical analysis

Continuous variables are expressed as the mean ± SD or median value and interquartile range for the warfarin user group and each DOAC user group. Differences in the clinical characteristics between warfarin and DOAC users were analyzed by unpaired Student t-test, Mann–Whitney test, or chi-square test, as appropriate. The results of the 4 types of DOAC users were compared using an analysis of variance (ANOVA) or chi-square test, followed by the Tukey'sHSD (honest significant difference) multiple comparison test or a residual analysis. Multiple logistic regression analyses were performed to identify the clinical characteristics associated with DOAC inappropriate-low-dosing, and odds ratios were calculated for the relationship between the identified characteristics and inappropriate-low-dosing. The appropriate standard DOAC doses were used for reference. Between-group differences in the categorical variables were analyzed by chi-square tests. All statistical analyses were performed with JMP software version 11.0.2 (SAS Institute Inc., Cary, NC, USA), with a $p < 0.05$ considered as statistically significant.

3. Results

3.1. Total enrollment

A total of 3266 patients with AF were enrolled in the registry between September 1, 2013 and December 31, 2015: 1200 (36.7%) from cardiovascular centers, 1310 (40.1%) from affiliated or community hospitals, and 756 (23.1%) from private clinics (see the Appendix). Regionally, 2094 (64.1%) patients were from Tokyo city, 763 (23.4%) from Saitama prefecture, 281 (8.6%) from Kanagawa prefecture, and 47 (1.4%) from other prefectures of Tokyo suburbs. The majority of the patients (1277 [39.1%] patients) were from the northern (referred to as "Johoku") region of Tokyo city, and in particular, one-third of the registered patients (1051 [32.2%] patients) came from Itabashi-Ku, Tokyo.

3.2. Characteristics of the SAKURA AF patients

The characteristics of the registry patients are summarized in Table 2. Of the total of 3266 patients, 1577 (48.3%) were on warfarin while 1689 (51.7%) were on a DOAC (dabigatran, $n=456$ [14.0%], rivaroxaban, $n=766$ [23.5%], apixaban, $n=437$ [13.4%], or edoxaban, $n=30$ [0.9%]). The total patients' mean age was 72.0 years, and 840 (25.7%) were women. The mean body weight was 63.8 kg. AF was paroxysmal in 1210 (37.0%) patients, persistent in 723 (22.1%), and long-standing persistent in 1301 (39.8%); the type of AF was not recorded in the remaining 32 patients. Although there was no difference between the warfarin and DOAC groups in the age, body mass index, smoking status, or drinking status, DOAC users were more likely than warfarin users to be female and have paroxysmal AF. Overall, the co-morbidities associated with strokes, such as hypertension and heart failure, tended to be less prevalent among DOAC users than among warfarin users. The average CHADS$_2$ and CHA$_2$DS$_2$-VASc scores were 1.80 and 2.74, respectively. The CHADS$_2$, CHA$_2$DS$_2$-VASc, and HAS-BLED scores were significantly lower among DOAC users than among warfarin users.

3.3. Medications used, laboratory test results, and dosing in the warfarin and DOAC groups

The medications used by the patients at the time of enrollment are summarized in Table 3. Importantly, only 5.1% of warfarin group patients were new users (oral anticoagulant administered within 3 months before the enrollment date), compared to 33.4%

Table 3

Patient use of medications and laboratory test results upon enrollment in the SAKURA AF Registry.

	Total patients (n=3266)	DOAC users (n=1689)	Warfarin users (n=1577)	P value*
New use	645 (19.7)	564 (33.4)	81 (5.1)	< 0.0001
Antiplatelet drugs	513 (15.7)	207 (12.3)	306 (19.4)	< 0.0001
Aspirin	385 (11.8)	151 (8.9)	234 (14.8)	< 0.0001
Ticlopidine	8 (0.2)	0 (0.0)	8 (0.5)	0.0034
Clopidogrel	88 (2.7)	40 (2.4)	48 (3.0)	0.2335
Prasugrel	19 (0.6)	7 (0.4)	12 (0.8)	0.0001
Cilostazol	31 (0.9)	10 (0.6)	21 (1.3)	0.0294
Other	25 (0.8)	16 (1.0)	9 (0.6)	0.2172
NSAID	56 (1.7)	34 (2.0)	22 (1.4)	0.1740
Rate control drugs	1979 (60.6)	958 (56.7)	1021 (64.7)	< 0.0001
Digitalis	436 (13.4)	172 (10.2)	264 (16.7)	< 0.0001
Ca channel blocker	436 (13.4)	214 (12.7)	222 (14.1)	0.2374
Beta blocker	1450 (44.4)	719 (42.6)	731 (46.4)	0.0296
Rhythm control drugs	740 (22.7)	407 (24.2)	333 (21.1)	0.0382
Class I	422 (12.9)	238 (14.1)	184 (11.7)	0.0391
Bepridil	322 (9.9)	173 (10.3)	149 (9.4)	0.4466
Amiodarone	30 (0.9)	11 (0.7)	19 (1.2)	0.0975
Laboratory test results				
CrCl (mL/min)	68.1 ± 26.7	70.5 ± 27.4	65.6 ± 25.6	
> 80	901 (27.6)	495 (29.3)	406 (25.7)	< 0.0001
> 50 to 80	1535 (47.0)	810 (47.8)	725 (46.0)	
> 30 to 50	640 (19.6)	320 (18.9)	320 (20.3)	
≤ 30	152 (4.7)	43 (2.5)	109 (6.9)	< 0.0001
Not reported	38 (1.2)	21 (1.2)	17 (1.1)	
NT-proBNP (pg/mL)	503 (195–1082)	474 (153–1111)	524 (238–1063)	0.0121
Not reported	834 (25.5)	462 (27.3)	372 (23.6)	

Values are shown as the mean ± SD, median and interquartile range, or n (%). AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; NT-proBNP, N-terminal pro brain natriuretic peptide; CrCl, creatinine clearance; new use, warfarin or DOAC starting within 3 months after the registration date; Hb, hemoglobin; HDL, high-density lipoprotein; LDH, lactate dehydrogenase; LDL, low-density lipoprotein; NSAID: non-steroidal anti-inflammatory drug; TC, total cholesterol.

* Per the Student *t*-test, Mann–Whitney test, or chi-square test, as appropriate.

Fig. 1. The percentages of warfarin users with a PT-INR in the therapeutic range upon enrollment, shown per age categories (< 70 years and ≥ 70 years). Refer to the text for the definition of each category.

of the DOAC group. The use of antiplatelet drugs was relatively low (15.7% of patients) and less common among DOAC users than among warfarin users. The DOAC users were preferentially given rhythm control rather than rate control drugs, whereas warfarin users were preferentially given rate control rather than rhythm control drugs.

The CrCl rate was significantly higher and NT-proBNP level significantly lower in the DOAC group than in the warfarin group. The mean PT-INR in the warfarin group was 1.99 ± 0.56 and did not differ significantly between warfarin users aged < 70 years and those aged ≥ 70 years (2.00 ± 0.55 vs. 1.99 ± 0.57, p=0.7942). Only 55.1% of warfarin users had a PT-INR within the optimal therapeutic range; 32% had a PT-INR below the therapeutic range and 8.6% above the therapeutic range. Under-dosing of warfarin was more prevalent among patients aged < 70 years than those aged ≥ 70 years (Fig. 1).

3.4. Clinical characteristics of the dabigatran, rivaroxaban, apixaban, and edoxaban users

The characteristics of the DOAC users are shown per subgroup (i.e., according to the specific DOAC they were taking) in Table 4. Patients taking apixaban were significantly older than those taking dabigatran and rivaroxaban. Apixaban users were significantly
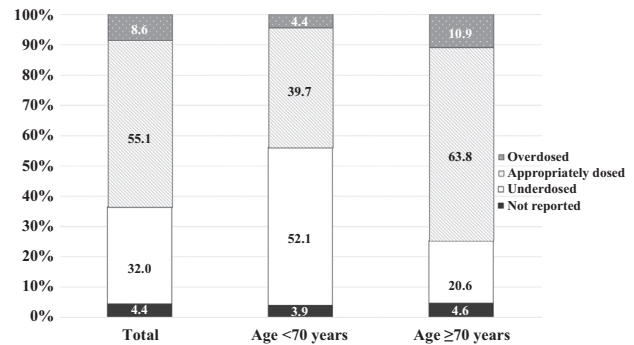
more likely to be female and have a significantly lower height and weight than dabigatran users. The prevalence of persistent AF and long-lasting AF was significantly lower and higher among rivaroxaban users than among apixaban users, respectively. Patients on dabigatran had a significantly higher CrCl than rivaroxaban and apixaban users. The percentage of patients who were new dabigatran users was significantly lower than the percentage of rivaroxaban users. Although not statistically significant, apixaban users were at relatively higher risk for a stroke.

Low drug doses were prescribed for 72.6% of dabigatran users and 72.4% of the edoxaban users, in contrast to only 42.9% of rivaroxaban users and 40.4% of apixaban users. Notably, an inappropriate dose reduction was observed in 19.7–27.6% of DOAC users. Inappropriate-standard-dosing of DOACs occurred in only 0.7–7.7% (Fig. 2). The characteristics of DOAC patients who were prescribed an appropriate standard dose and those who were prescribed an inappropriate low dose are shown in Table 5. Patients on inappropriately low doses of DOACs were significantly older than those taking appropriately-standard-doses and were also more likely to be female. Inappropriately low-dosed DOAC users also had significantly lower body weight, CHADS$_2$ score, hemoglobin level, and CrCl. Fewer inappropriately low-dosed DOAC users consumed alcohol than appropriately-standard-dosed DOAC users. New use of DOACs was less common among inappropriately low-dosed DOAC users than among appropriately-standard-dosed DOAC users. After multivariate adjustment, age ≥ 75 years, non-drinking status, CrCl ≤ 50 mL/min, and use of dabigatran or edoxaban were strongly associated with inappropriately low-dosed DOAC use (Table 5).

4. Discussion

The SAKURA AF Registry is a large-scale registry designed to gather data that can be used for prospective evaluation of AF patients in Japan who are treated with a DOAC or warfarin. The main findings were as follows: (1) although there was no difference between the warfarin and DOAC groups regarding the age and body mass index, the DOAC users were at significantly lower risk for a stroke than warfarin users; (2) we documented under-dosing in 32% of warfarin users and inappropriately low dosing in 19.7–27.6% of DOAC users; (3) inappropriately low dosing of DOACs was strongly associated with age ≥ 75 years, non-drinking status, CrCl ≤ 50 mL/min, and use of dabigatran or edoxaban.

AF patients enrolled in the SAKURA AF Registry were being treated at cardiovascular centers (36.7%), affiliated or community hospitals (40.1%), and general practice clinics (23.2%) in Tokyo or a Tokyo suburb. One-third (1051 patients) of the registry patients were in Itabashi-Ku, which is located in the northern region of

Table 4
Clinical characteristics of the dabigatran, rivaroxaban, apixaban, and edoxaban users.

	Dabigatran users (n=456)	Rivaroxaban users (n=766)	Apixaban users (n=437)	Edoxaban users (n=30)	P value
Age (years)	70.9 ± 9.5*	71.5 ± 9.1*	73.1 ± 10.0	74.0 ± 7.8	0.0014
Female	111 (24.3)*	201 (26.2)	155 (35.5)	10 (33.3)	0.0009
Height (cm)	163.5 ± 9.0*	162.1 ± 9.5	160.7 ± 10.2	160.6 ± 10.6	0.0002
Weight (kg)	65.1 ± 13.3*	63.7 ± 13.5	62.6 ± 13.5	58.7 ± 11.6	0.0077
BMI (kg/m^2)	24.2 ± 3.6	24.1 ± 4.0	24.1 ± 4.0	22.6 ± 3.0	0.1843
AF type					
Paroxysmal AF	193 (42.3)	311 (40.6)	199 (45.5)	13 (43.3)	0.0029
Persistent AF	99 (21.7)	137 (17.9)*	109 (24.9)	10 (33.3)	
LS-AF	162 (35.5)	308 (40.2)*	125 (28.6)	7 (23.3)	
Institution type					
High-volume center	136 (29.8)§	282 (36.8)	156 (35.7)	17 (56.7)	< 0.0001
Hospital	217 (47.6)†	267 (34.9)	156 (35.7)	10 (33.3)	
Clinic	103 (22.6)	217 (28.3)	125 (28.6)	3 (10.0)	
CHADS$_2$ score	1.70 ± 1.17	1.67 ± 1.12	1.81 ± 1.14	1.60 ± 1.22	0.2060
CHA$_2$DS$_2$-VASc score	2.57 ± 1.37	2.61 ± 1.35	2.76 ± 1.37	2.57 ± 1.36	0.1763
New use	57 (12.5)*,§	252 (32.9)	231 (52.9)	24 (80.0)	< 0.0001
PT-INR	NA	1.41 ± 0.42*	1.26 ± 0.38	1.36 ± 0.39	0.0063
APTT (sec)	44.0 ± 9.9	NA	NA	NA	
CrCl (mL/min)	74.6 ± 30.2*,†	70.5 ± 26.1	66.5 ± 26.1	65.8 ± 24.3	0.0001

Values are shown as the mean ± SD or n (%). APTT, activated partial thromboplastin time; NA, not applicable; PT-INR, prothrombin time-international normalized ratio. Other abbreviations are as in Tables 2 and 3. P value by an ANOVA or chi-square test, as appropriate.

  * P < 0.05 vs. apixaban users.
  † P < 0.05 vs. rivaroxaban users.
  § P < 0.05 vs. edoxaban in the HSD Tukey post-hoc analysis or residual analysis.
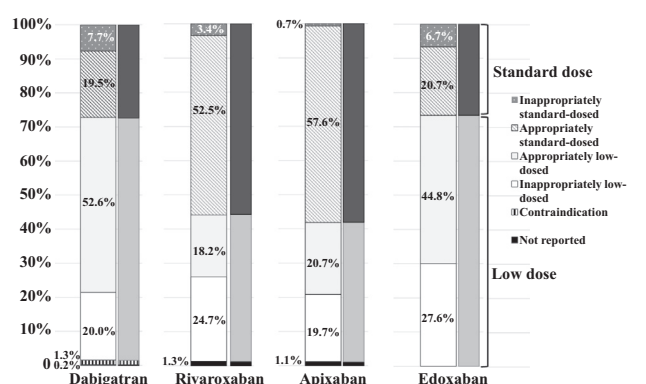

Fig. 2. The percentages of DOAC users appropriately dosed, inappropriately-standard-dosed, inappropriately low-dosed, and for whom the drug was contraindicated. Percentages are shown for the 4 different DOACs prescribed. Refer to the text for the definition of each category.

Tokyo city. The population of Itabashi-Ku is approximately 540,000 people. Based on an epidemiological prevalence of AF in the Japanese population of 0.6% [1], the number of AF patients in Itabashi-Ku is estimated to be approximately 3240. This number is larger than the number enrolled from Itabashi-Ku in this registry; however, the AF patients in this registry were assumed to partially reflect a typical ward in Tokyo city.

In contrast, patients enrolled in the J-RHYTHM Registry, a previously established, well-known registry in Japan [6,7], were from cardiovascular centers throughout Japan. This large registry was further expanded to the J-RHYTHM 2 Registry [16]. The FUSHIMI AF Registry [8,9], and most of the patients enrolled in that Registry, were from general practice clinics in Fushimi-ku, Kyoto. The SAKURA AF Registry clarified the differences in the patient characteristics of these registries. For example, the mean age of the SAKURA AF Registry patients was 72.0 years; this was older than that of the J-RHYTHM Registry (69 years) [6,7] and J-RHYTHM 2 Registry (70 years) [16], but younger than that of the FUSHIMI AF Registry patients (74 years) [8,9]. The CHADS$_2$ score of

1.8 for the SAKURA AF Registry patients was higher than that of both the J-RHYTHM and J-RHYTHM 2 Registry patients (1.7 each) and lower than that of the FUSHIMI AF Registry patients (2.1). Based on the data from the Statistics Bureau, Ministry of Internal Affairs and Communications in Japan, the mean age and its distribution in Fushimi-Ku, Kyoto were similar to those in Itabashi-ku, Tokyo (mean age, 44.2 years vs. 44.5 years; age ≥ 65 years in 22.1% vs. 21.3%, respectively). Therefore, the differences in patient characteristics may be due to the number of patients enrolled from general practice clinics between these registries, rather than the different regions in Japan.

Patients in the SAKURA AF Registry were enrolled very recently (in 2015); therefore, the SAKURA AF Registry is a better reflection of the current status of AF treatment in Japan. Recent studies from the J-RHYTHM and SHINKEN database reported increases in DOAC administration, from 6.1% of patients in 2012 to 20.4% in 2014 [16], and from none in 2007–2009 to 25.5% in 2010–2012 [17]. In fact, the data from our SAKURA AF Registry included the largest cohort of DOAC users in Japan, totaling at 1689 (51.7%) users, compared to none in the J-RHYTHM Registry, 66 (2.1%) in the FUSHIMI AF Registry, and 923 (14.0%) in the J-RHYTHM 2 Registry.

We were able to characterize Japanese DOAC and warfarin users in terms of the clinical characteristics, use of particular medications, and initial laboratory test results. DOAC users did not differ from warfarin users in age, but they were at a lower risk for stroke and major bleeding. DOAC users were preferentially given rhythm control drugs rather than rate control drugs, probably because paroxysmal AF was more prevalent in this group than in the warfarin group. The relatively good health of the DOAC users was reflected by the laboratory test results, i.e., slightly higher CrCl and lower NT-proBNP levels. Physicians tended to be less familiar with DOACs than with warfarin, but DOACs are superior to warfarin in terms of patient management, as they do not require PT-INR monitoring and have are fewer drug-drug interactions. One limitation is that impaired renal function may alter the metabolism of DOACs [2–5,14,15]. These features may have motivated physicians (especially those practicing in small clinics) to prescribe DOACs to patients at low risk for strokes and bleeding and with

Table 5
Results of the univariate and multivariate analyses for factors predictive of DOAC inappropriate-low-dosing.

	Appropriate-standard-dose users (n=746)	Inappropriate-low-dose users (n=374)	P value*	Factors predictive of inappropriate-low-dosing	
				Odds ratio(95% CI)	P value
Age (years)	66.8 ± 9.0	71.2 ± 8.1	< 0.0001		
< 65	256 (34.3)	73 (19.5)		1	
65 to < 75	345 (46.3)	161 (43.1)	< 0.0001	1.48 (1.00–2.20)	0.0489
≥ 75	145 (19.4)	140 (37.4)		3.57 (2.21–5.81)	< 0.0001
Female sex	157 (21.1)	109 (29.1)	0.0027	1.19 (0.82–1.71)	0.3504
Weight (kg)	68.6 ± 13.3	64.6 ± 12.5	< 0.0001		
≤ 60 kg	198 (26.5)	141 (37.7)	0.0001	1.16 (0.84–1.59)	0.6257
Paroxysmal AF	334 (44.8)	166 (44.4)	0.9022		
Current smoking status	113 (15.2)	53 (14.1)	0.5797		
Current alcohol use	515 (69.0)	204 (54.4)	< 0.0001	0.58 (0.43–0.77)	0.0010
Institution type					
Center	321 (43.0)	123 (32.9)		0.76 (0.53–1.09)	0.1364
Hospital	236 (31.6)	152 (40.6)	0.0020	1.02 (0.71–1.45)	0.9320
Clinic	189 (25.3)	99 (26.5)			
Clinical history					
Hypertension	509 (68.2)	262 (70.1)	0.5345		
Diabetes	166 (22.3)	79 (21.1)	0.6664		
Dyslipidemia	304 (40.8)	143 (38.2)	0.4175		
Hyperuricemia	144 (19.3)	55 (14.7)	0.0577		
Heart failure	121 (16.2)	68 (18.2)	0.4083		
Stroke/TIA	70 (9.4)	28 (7.5)	0.2894		
CAD	59 (7.9)	41 (11.0)	0.0910		
Major bleeding	4 (0.5)	5 (1.3)	0.1569		
AF ablation	93 (12.5)	42 (11.2)	0.5489		
CHADS$_2$ score	1.45 ± 1.06	1.62 ± 1.09	0.0129		
CHADS$_2$ ≥ 2	303 (40.7)	181 (48.4)	0.0146	0.91 (0.67–1.25)	0.5708
DOAC agent					
Dabigatran	89 (11.9)	91 (24.3)	< 0.0001	9.88 (6.05–16.37)	< 0.0001
Rivaroxaban	400 (53.6)	188 (50.3)		2.21 (1.54–3.21)	< 0.0001
Apixaban	251 (33.7)	86 (23.0)		1	
Edoxaban	6 (0.8)	9 (2.4)		7.31 (2.31–24.62)	0.0008
New use	296 (39.7)	122 (32.6)	0.0213	0.93 (0.69–1.27)	0.6486
Antiplatelet drugs	85 (11.4)	49 (13.1)	0.4063		
CrCl (mL/min)	84.3 ± 27.4	70.1 ± 21.3	< 0.0001		
> 80	353 (47.3)	99 (26.5)		1	
> 50 to 80	375 (50.3)	243 (65.0)	< 0.0001	1.95 (1.38–2.78)	0.0001
≤ 50	19 (2.6)	34 (9.1)		7.84 (3.79–16.6)	< 0.0001

Values are shown as the mean ± SD or n (%).
CrCl, creatinine clearance.
AF atrial fibrillation; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CHADS$_2$, congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus and stroke; CHA$_2$DS$_2$-VASc, congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke, vascular disease, age 65–74 years and sex category; Center, cardiovascular center; DOAC, direct oral anticoagulant; HAS-BLED, uncontrolled hypertension (baseline systolic blood pressure ≥ 160 mmHg), abnormal renal function (serum creatinine clearance ≥ 2.26 mg/dL)/liver function (chronic hepatic disease [e.g., cirrhosis] or aspartate aminotransferase and/or alanine aminotransferase > 3x normal range), stroke, prior major bleeding, elderly (age ≥ 65 years), drugs (anti-platelet drugs or non-steroidal anti-inflammatory drugs)/alcohol (160 g/day or more), Labile INR (overdosing shown by baseline PT-INR in warfarin users); LS-AF, long-standing persistent AF, Hospital, affiliated hospital or community hospital; TIA, transient ischemic attack.

* Per the Student t-test or chi-square test, as appropriate.

relatively normal kidney function. Apixaban and edoxaban are thought to be safer than the other DOACs for the elderly and patients with moderate renal impairment [2–5], and, as was expected, our registry data showed a tendency for these DOACs to be prescribed to older patients with moderate renal impairment.

We found that 32% of warfarin users were under-dosed. The suboptimal PT-INR was pronounced in patients < 70 years of age; the Japanese guidelines strongly recommend a PT-INR between 2.0 and 3.0 for patients in this age group. The relatively low PT-INR therapeutic ranges aimed at preventing future bleeding episodes are well in line with the J-RHYTHM Registry [6] and FUSHIMI AF Registry [8] data. Most importantly, our registry-based study identified inappropriate-low-dosing in 19.7–27.6% of DOAC users. Inappropriately low-dosed DOAC users were older than appropriately standard-dosed DOAC users; furthermore, they had no history of alcohol abuse and only moderate renal impairment. Age > 75 years and impaired renal function are known risk factors for stroke and bleeding [2–5,14]. Physicians may have reduced the dosages as a precaution against future bleeding events. The low doses were preferentially prescribed to dabigatran and edoxaban users, and inappropriate-low-dosing of these drugs was proportionally greater than appropriate-low-dosing. This trend toward inappropriate-low-dosing may be due to the reported evidence of the effectiveness of these 2 drugs at low doses [2,5]; however, the ROCKET AF and ARISTOTLE trials had too few patients in the low-dose DOAC groups to establish superiority, equivalence, or non-inferiority [3,4].

4.1. Study limitations

Our study has several limitations. First, although this was a large-scale prospective observational study, the registry incorporated only selected institutions in a limited geographical area. Therefore, we cannot conclude that the data reflected all of Japan.

Second, the registry did not include patients without anticoagulant drugs. This was because the annual incidence of strokes and bleeding had already been well evaluated in Japanese AF patients without anticoagulants [10]. Third, because edoxaban was approved last in Japan, the enrollment of edoxaban users was small, which may potentially distort the statistical analysis. Nonetheless, this effect was probably negligible, given the small number of edoxaban users in this study. Fourth, we defined "inappropriate-low-dosing" of DOACs according to the low-dose regimen shown in Table 1 to characterize the use of DOACs. However, inappropriate-low-dosing of dabigatran and edoxaban may not have exactly reflected the same meaning as that of rivaroxaban or apixaban, as the effectiveness and safety of low doses of dabigatran and edoxaban are well-established, even in patients that fulfilled those low-dose regimens in the clinical trials [2,5]. Finally, the follow-up data to explore the incidences of strokes and bleeding and the time in therapeutic range (TTR) for warfarin were not available. Analysis of the full registry follow-up data will resolve any remaining questions regarding the clinical efficacy and safety of DOACs and warfarin, as well as its impact on the TTR in Japanese AF patients.

5. Conclusions

The SAKURA AF Registry data characterized Japanese AF patients recently treated with DOACs and warfarin. The DOAC users were at lower risk for strokes than the warfarin users. Twenty to thirty percent of DOACs were inappropriately low-dosed, while 30% of warfarin users were under-dosed.

Appendix

The key personnel and institutions participating in the registry are as follows:

Chief investigator: Hirayama A (Division of Cardiology, Department of Medicine, Nihon University School of Medicine)
Vice-chief investigator: Okumura Y (Division of Cardiology, Department of Medicine, Nihon University School of Medicine)
Steering Committee: Kunimoto S, Okumura Y, Kato M (Division of Cardiology, Department of Medicine, Nihon University School of Medicine)
Statistical analysis: Udagawa S (Department of Mathematics, Nihon University School of Medicine)
Participating institutions: Division of Cardiology, Department of Medicine, Nihon University School of Medicine (Hirayama A, Okumura Y, Watanabe I, Hiro T, Takayama T, Kunimoto S, Nakai T, Kato M); Department of Cardiology, Nihon University Hospital (Yokoyama K, Matsumoto N); Kawaguchi Municipal Medical Center (Tachibana E, Kuronuma K); Yokohama Chuo Hospital (Oiwa k); Sekishindo Hospital (Kojima T); Asakadai Central General Hospital (Hanada S); Tokyo Rinkai Hospital (Nomoto K); Kasukabe Municipal Hospital (Arima K); Yasuda Hospital (Takahashi F) Itou Cardiovascular Clinic (Itoh T); Makita General Hospital (Kotani T); Itabashi Medical Association Hospital (Ikeya Y); Kondo Clinic (Kondo K); Ukima Central Hospital (Fukushima S); Keiai Clinic (Chiku M); Ohno Medical Clinic (Ohno Y); Onikura Clinic (Onikura M); Kobari General Clinic (Kobari C); Chikuma Central Hospital (Tokai K); Kondo Clinic (Kondo K); Yamada Clinic (Osamura Y); Higashi Saitama General Hospital (Fukuda Y, Nakahara S); Zengyodanchi Ishikawa Clinic (Ishikawa N); Tokutake Clinic (Tokutake E); Sugino Clinic (Sugino K); Yokohama Sotetsu Bldg. Clinic (Mori H); Suzuki Clinic (Suzuki Y); Fujita Clinic (Fujita M); Yumikura Clinic (Yumikura S); Keiai Hospital (Ando H); Sekimachi Clinic (Shin I); Tokiwadai Surgical Hospital (Mochizuki R); Hikarigaoka Clinic (Tokuyasu Y); Osuga Clinic (Osuga E); Nakai Clinic (Nakai K); Kurumatani Clinic (Kurumatani H); Horinaka Hospital (Sato C); Nasu Red Cross Hospital (Akabane M); Sato Clinic (Sato K); Kofune Clinic (Kofune T); Ikebukuro Okubo Clinic (Yamane A); Minami Machida Hospital (Horie T); Ishii Clinic (Ishii N); Akabane Central Hospital (Ominato M); Hirose Clinic (Hirose S); Sekimoto Memorial Hospital (Sekimoto M); Matsumura Clinic (Matsumura K); Tanaka Clinic (Tanaka M); Nakadai Clinic (Ogawa T); Naruse Clinic (Naruse K); Narimune Clinic (Kato A); Miyata Clinic (Miyata H); Aoyama Clinic (Aoyama H); Hara Clinic (Hara K); Yano Clinic (Yano F); Sekino Hospital (Sekino H); Kurokawa Clinic (Kurokawa H); Ishii Clinic (Ishii T); Abe Clinic (Abe Y); Kikuchi Clinic (Kikuchi T); Imamoto Clinic (Imamoto S); Nirenoki Clinic (Nagai C); Kachidoki View Tower Clinic (Sugino K).

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