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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.

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