Three-Year Clinical Outcomes Associated With Warfarin vs. Direct Oral Anticoagulant Use Among Japanese Patients With Atrial Fibrillation
— Findings From the SAKURA AF Registry —

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Background: Although direct oral anticoagulants (DOACs) are widely used in Japanese patients with atrial fibrillation (AF), large-scale investigations into their use, with suitable follow-up times and rates, are lacking.

Methods and Results: The SAKURA AF Registry is a prospective multicenter registry created to investigate therapeutic outcomes of oral anticoagulant (OAC) use in Japanese AF patients. We conducted a study involving 3,237 enrollees from 63 institutions in the Tokyo area being treated with any of 4 DOACs (n=1,676) or warfarin (n=1,561) and followed-up for a median of 39.3 months (range 28.5–43.6 months). Analyses of 1- and 2-year follow-up data available for 3,157 (97.5%) and 2,952 (91.2%) patients, respectively, showed no significant differences in rates of stroke or systemic embolism (SE), major bleeding, and all-cause mortality for DOAC vs. warfarin users (1.2 vs. 1.8%/year, 0.5 vs. 1.2%/year, and 2.1 vs. 1.7%/year, respectively). Under propensity score matching, the incidence of stroke or SE (P=0.679) and all-cause death (P=0.864) remained equivalent, but the incidence of major bleeding was significantly lower (P=0.014) among DOAC than warfarin users.

Conclusions: A high follow-up rate allowed us to obtain reliable data on the status of OAC use and therapeutic outcomes among AF patients in Japan. Warfarin and DOACs appear to yield equivalent 3-year stroke and all-cause mortality rates, but DOACs appear to reduce the risk of major bleeding.

Key Words: Atrial fibrillation; Direct oral anticoagulant; Japanese patients; Warfarin
of these DOACs in reducing the risk of stroke and bleeding in patients with AF, but because large-scale studies spanning a suitable follow-up period have not been conducted in Japan, the effectiveness and safety of DOACs in Japanese patients with AF are undetermined. Therefore, we established a multicenter registry, the SAKURA AF Registry (UMIN Clinical Trials Registry: UMIN0000014420), to track the status of anticoagulant use among patients with AF in Japan and to support prospective observational research into the outcomes of warfarin and DOAC treatment in Japan. In all, 3,268 patients, including a large number of DOAC users (n=1,690), are enrolled in the registry; thus, data are accumulating on the clinical use of DOACs nationwide. The aims of the registry-based study described herein were to first compare outcomes in terms of stroke, bleeding events, and death between warfarin and DOAC users, and to then compare outcomes between warfarin users and users of each of the 4 different DOACs.

Methods

Patients were enrolled in the SAKURA AF Registry between 1 September 2013 and 31 December 2015, and were followed-up for at least 2 years after their enrollment (with follow-up ending on 31 December 2017). The study design, data collection, and patient baseline characteristics (i.e., clinical characteristics at the time of enrollment) have been reported previously. Patient eligibility for enrollment in the registry included the following: (1) a diagnosis of non-valvular AF based on a 12-lead electrocardiography (ECG) recording, 24-h Holter ECG recording, or event-activated ECG recording; (2) age ≥20 years; and (3) treatment (either just initiated or already in place) with any anticoagulant drug for stroke prophylaxis. The registry included 1,578 patients treated with warfarin at the time of enrollment and 1,690 treated with any of the 4 available DOACs at the time of enrollment. The 3,268 patients were enrolled by 63 institutions (2 cardiovascular centers, 13 affiliated hospitals or community hospitals, and 48 private clinics) in the Tokyo area (see Appendix S1). Analysis of the registry data was approved by our institutional review board (IRB) of Nihon University Itabashi Hospital, Clinical Research Ethics Committee, as well as the IRBs of individual hospitals participating in the registry. All enrollees provided written informed consent for inclusion in the registry.

A website was created for the SAKURA AF Registry and was used to collect patient information through a web-based registration system. The information obtained comprised patients’ clinical characteristics, including comorbidities, medications, and laboratory data, and patient follow-up information. Follow-up information, including laboratory data such as the prothrombin time-international normalized ratio (PT-INR) in warfarin users, creatinine clearance (CrCl), and hemoglobin concentration, was collected through a central registry office twice a year (in March and September). The time in therapeutic range (TTR) was calculated using the method of Rosendaal et al. Use of an oral anticoagulant (OAC), defined as OAC therapy initiated within 3 months before the patient’s enrollment in the registry, was noted.

For the study described herein, the primary endpoint of interest was stroke (ischemic stroke, hemorrhagic stroke, or transient ischemic attack [TIA]) or systemic embolism (SE). Cardiovascular death or death from any other cause was also recorded. Major bleeding was defined as a reduction in the hemoglobin concentration of at least 2 g/dL, transfusion of at least 2 units of blood, or symptomatic bleeding in a critical area or organ, and was specified as the safety endpoint. The net clinical outcome (composite of stroke or SE, major bleeding, or death from any cause) was also taken as a study endpoint.

Statistical Analysis

Continuous variables are shown as the mean±SD or as the median (interquartile range [IQR]). Categorical variables are shown as the number and percentage of patients. The significance of differences in continuous variables between warfarin and DOAC users was analyzed by 2-sample t-test, whereas the significance of differences in categorical variables was analyzed by the χ² test. The significance of differences in continuous variables between users of the 4 different DOACs was tested by 1-way analysis of variance (ANOVA), and differences in categorical variables between these 4 groups were analyzed by the χ² test. Kaplan-Meier curves were drawn for the cumulative incidence of events, and differences in events between patients who were initially given warfarin and those who were initially given a DOAC were analyzed by log-rank test. In some patients, the originally prescribed OAC was switched to a different OAC during the follow-up period, so the switch was noted, and time-dependent Cox proportional hazards modeling was used to consider the effect of the change in the OAC. The date of the final switch from warfarin to a DOAC or from a DOAC to warfarin was used in this analysis. If at any time a DOAC was switched to a different DOAC, the switch was not included in the analysis. The results of Cox proportional hazards modeling for clinical outcomes are expressed as hazard ratios (HRs) and 95% confidence intervals (CIs) with adjustment for all components of the CHADS-VASc score (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, vascular disease, and a history of stroke or TIA) and other potential covariates that were judged to be of clinical importance. To determine the association between OAC use and clinical outcomes, propensity score matching was performed on key baseline characteristics (age, sex, height and weight, paroxysmal AF, hypertension, diabetes mellitus, heart failure, vascular disease, stroke or TIA, major bleeding, history of ablation, antiplatelet agent use, non-steroidal anti-inflammatory drug use, OAC therapy duration, and CrCl) to balance the treatment groups with regard to possible confounding factors. Matching was achieved by a 1:1 nearest neighbor approach (without replacement) within a caliper of 0.05 of the SD. All statistical analyses were performed using JMP 11.0.2 (SAS Institute Inc., Cary, NC, USA) or SPSS Statistics 24 (IBM Corp., Armonk, NY, USA), and P<0.05 was considered significant.

Results

Of the 3,268 patients enrolled in the SAKURA AF Registry, 31 were lost to follow-up. At the time of this study, 1- and 2-year follow-up information had been entered into the registry database for a respective 3,157 (97.5%) and 2,952 (91.2%) of the remaining 3,237 enrollees. No difference was found in baseline clinical characteristics between patients for whom 2-year follow-up data were available and the 285 patients for whom the 2-year follow-up data were not available. Specifically, no difference was found in age
Table 1. Clinical Characteristics of WF vs. DOAC Users and DA vs. Riv vs. Api vs. Edoxaban Users

<table>
<thead>
<tr>
<th></th>
<th>WF (n=1,561)</th>
<th>DOAC (n=1,676)</th>
<th>P value*</th>
<th>DA (n=456)</th>
<th>Riv (n=761)</th>
<th>Api (n=428)</th>
<th>Edo (n=31)</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>72.2±9.3</td>
<td>71.8±9.5</td>
<td>0.217</td>
<td>70.9±9.5</td>
<td>71.5±9.1</td>
<td>73.2±10.1</td>
<td>73.6±8.1</td>
<td>0.002</td>
</tr>
<tr>
<td>Female sex</td>
<td>367 (23.5)</td>
<td>480 (28.6)</td>
<td>0.001</td>
<td>113 (24.8)</td>
<td>204 (26.8)</td>
<td>153 (35.8)</td>
<td>10 (32.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>162.8±9.4</td>
<td>162.1±9.6</td>
<td>0.025</td>
<td>163.5±8.9</td>
<td>162.2±9.4</td>
<td>160.6±10.2</td>
<td>160.8±10.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>64.0±12.5</td>
<td>63.7±13.4</td>
<td>0.352</td>
<td>65.1±13.3</td>
<td>63.8±13.4</td>
<td>62.5±13.5</td>
<td>50.0±11.5</td>
<td>0.006</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.0±3.6</td>
<td>24.1±3.9</td>
<td>0.665</td>
<td>24.2±3.6</td>
<td>24.1±4.0</td>
<td>24.1±4.0</td>
<td>22.7±2.9</td>
<td>0.204</td>
</tr>
<tr>
<td>Asthma</td>
<td>162 (10.3)</td>
<td>155 (9.2)</td>
<td>0.511</td>
<td>35 (7.6)</td>
<td>37 (4.9)</td>
<td>25 (5.8)</td>
<td>1 (3.2)</td>
<td>0.227</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>78 (5.0)</td>
<td>83 (5.0)</td>
<td>0.511</td>
<td>16 (3.5)</td>
<td>20 (2.6)</td>
<td>12 (2.8)</td>
<td>2 (6.5)</td>
<td>0.227</td>
</tr>
<tr>
<td>Smoking</td>
<td>332 (21.2)</td>
<td>364 (21.5)</td>
<td>0.864</td>
<td>87 (18.8)</td>
<td>103 (13.6)</td>
<td>78 (18.2)</td>
<td>11 (35.5)</td>
<td>0.388</td>
</tr>
<tr>
<td>Hypertension</td>
<td>945 (60.5)</td>
<td>954 (56.6)</td>
<td>0.217</td>
<td>210 (45.7)</td>
<td>228 (29.7)</td>
<td>189 (44.4)</td>
<td>30 (97.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>378 (24.2)</td>
<td>362 (21.6)</td>
<td>0.062</td>
<td>150 (31.5)</td>
<td>141 (18.4)</td>
<td>109 (25.2)</td>
<td>20 (64.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>204 (13.1)</td>
<td>195 (11.6)</td>
<td>0.203</td>
<td>43 (9.1)</td>
<td>96 (12.6)</td>
<td>53 (12.4)</td>
<td>3 (9.7)</td>
<td>0.358</td>
</tr>
<tr>
<td>Stroke or TIA</td>
<td>190 (12.2)</td>
<td>176 (10.5)</td>
<td>0.112</td>
<td>58 (12.7)</td>
<td>78 (10.3)</td>
<td>37 (8.6)</td>
<td>10 (32.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>15 (1.0)</td>
<td>13 (0.8)</td>
<td>0.112</td>
<td>5 (1.1)</td>
<td>8 (1.0)</td>
<td>3 (0.7)</td>
<td>0 (0)</td>
<td>0.001</td>
</tr>
<tr>
<td>HAS-BLED score</td>
<td>1.61±0.88</td>
<td>1.28±0.78</td>
<td>&lt;0.001</td>
<td>1.07±0.71</td>
<td>1.32±0.77</td>
<td>1.42±0.81</td>
<td>1.58±0.99</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CHADS2 score</td>
<td>1.89±1.16</td>
<td>1.72±1.14</td>
<td>&lt;0.001</td>
<td>1.71±1.17</td>
<td>1.68±1.12</td>
<td>1.83±1.13</td>
<td>1.58±1.20</td>
<td>0.12</td>
</tr>
<tr>
<td>CHA2DS2-VASc score</td>
<td>3.08±1.51</td>
<td>2.92±1.46</td>
<td>0.002</td>
<td>2.83±1.46</td>
<td>2.87±1.45</td>
<td>3.12±1.47</td>
<td>2.84±1.53</td>
<td>0.006</td>
</tr>
<tr>
<td>OAC use (months)</td>
<td>46.5</td>
<td>66.6</td>
<td>&lt;0.001</td>
<td>16.2</td>
<td>6.2</td>
<td>2.6</td>
<td>0.5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Unless indicated otherwise, data are presented as mean±SD, median [interquartile range] or n (%). *Comparisons of warfarin (WF) and direct oral anticoagulant (DOAC) users (Student’s t-test or χ² test, as appropriate). †Comparisons among DOAC users (ANOVA or t-test, as appropriate). AF, atrial fibrillation; APTT, activated partial thromboplastin time; BMI, body mass index; CrCl, creatinine clearance; CHA2DS2-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes, stroke, vascular disease, age 65–74 years, and sex category; CHADS2, congestive heart failure, hypertension, age ≥75 years, diabetes, and stroke; DA, dabigatran; HAS-BLED, uncontrolled hypertension (baseline systolic blood pressure >160 mmHg), abnormal renal function (serum creatinine ≥2.6 mg/dL), or liver function (chronic hepatic disease or aspartate aminotransferase and/or alanine aminotransferase >3× normal range), stroke, prior major bleeding, age ≥65 years, drug use (heavy alcohol consumption or anti-platelet drugs or non-steroidal anti-inflammatory drugs [NSAIDs]), labile international normalized ratio (INR; overdosing shown by baseline prothrombin time [PT]; INR in WF users); high alcohol consumption, ≥160 g alcohol/day; LS-AF, long-standing persistent AF (AF lasting >1 year); new OAC use, oral anticoagulant (OAC) therapy duration <3 months; Riv, rivaroxaban; TIA, transient ischemic attack.

(71.9±9.3 vs. 72.3±10.4 years, respectively; P=0.542), female sex (26.3% vs. 25.3%, respectively; P=0.717), CHADS2 score (1.81±1.15 vs. 1.79±1.18, respectively; P=0.864), or CHA2DS2-VASc score (3.00±1.46 vs. 2.94±1.58, respectively; P=0.511). The follow-up rate differed significantly between the high-volume cardiovascular centers, the affiliated or community hospitals, and the private clinics (94.3% vs. 90.3% vs. 87.9%, respectively; P<0.001).

Of the 3,237 study patients, 1,561 (48.2%) were warfarin users at the time of enrollment, and 1,676 (51.8%) were DOAC users (dabigatran, n=456 [14.1%]; rivaroxaban, n=761 [23.5%]; apixaban, n=428 [13.2%]; or edoxaban, n=31[1.0%]).

Clinical Characteristics of Warfarin Users and DOAC Users

The clinical characteristics of the warfarin users and DOAC users are summarized in Table 1. (The medications and laboratory test results of these patients have been reported in detail elsewhere.) For 1,441 (92.3%) of the 1,561 warfarin users, the TTR was available; mean TTR was 65.4±31.1%. Of these 1,441 warfarin users, 815 (56.6%) had good anticoagulation control, defined as TTR ≥65%. There was no difference in the age, body weight, or body mass index between warfarin users and DOAC users, but female sex and paroxysmal AF were more prevalent among DOAC users than among warfarin users. Overall, comorbidities associated with stroke, such as hypertension and heart failure, tended to be less prevalent among DOAC users than among warfarin users. Concomitant use of antiplatelet drugs was less prevalent among DOAC users than among warfarin users. The CHADS2 and CHA2DS2-VASc scores tended to be lower among DOAC users than among warfarin users. The CrCl was significantly higher among DOAC users. Of importance, the pre-enrollment duration of OAC therapy (i.e., the time from the start of anticoagulation therapy to the time of enrollment in the registry) was significantly shorter among DOAC users than among warfarin users.
Clinical Characteristics of Dabigatran, Rivaroxaban, Apixaban, and Edoxaban Users

Characteristics of the DOAC users are shown according to the specific DOAC they were taking in Table 1. Patients taking rivaroxaban were older than those taking dabigatran, and those taking apixaban or edoxaban were older than those taking rivaroxaban. Apixaban and edoxaban users had lower height and weight than those using dabigatran or rivaroxaban, and were more likely to be female and to have paroxysmal AF. New use of each of these anticoagulants varied, with the proportion of patients initially given dabigatran being lowest (11.8%) and the proportion of those initially given edoxaban being highest (77.4%). Apixaban users were at a relatively high risk for stroke. The CrCl was lower among apixaban and edoxaban users than among dabigatran and rivaroxaban users.

Change in the Anticoagulant Used During the 2-Year Follow-up Period

The percentage of patients taking each of the various anticoagulants at the time of enrollment in the registry and then during the first and second 12 months of follow-up are shown in Figure 1. Whereas 48.2% of patients were warfarin users at the time of enrollment, only 39.5% were warfarin users by the time of the 2-year follow-up examination (representing an 8.7% decrease in the number of warfarin users). Users of a DOAC comprised 51.8% of patients at the time of enrollment, and 54.9% by the time of the 2-year follow-up examination (representing a slight increase of 3.1% in the use of DOACs). Regarding the specific DOACs used, use of the 2 newer DOACs (apixaban and edoxaban) increased over the 2-year period. This was especially true for apixaban, the use of which at enrollment was 13.2%, compared with 17.7% at the time of the 2-year follow-up (representing an increase of 4.5%). Use of dabigatran decreased from 14.1% to 11.0% (representing a decrease of 3.1%). Anticoagulant use decreased overall, by the time of the 2-year follow-up examination, 160 patients

![Figure 1. Graphical representation of the oral anticoagulants (OACs) used by study patients at the time of enrollment in the Registry and at the 1- and 2-year follow-up. The percentage of patients using each OACs is shown. Api, apixaban; DA, dabigatran; Edo, edoxaban; Riv, rivaroxaban; WF, warfarin.](image)

| Table 2. Incidence of Major Clinical Events During the 2-Year Follow-up Among WF vs. DOAC Users and Among WF vs. DA, Riv and Api Users |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| WF (n=1,561) | DOAC (n=1,676) | DA (n=456) | Riv (n=761) | Api (n=428) |                  |                  |                  |
| Stroke or SE |                  |                  |                  |                  |                  |                  |                  |
| MCE (%) at 1 year | 1.8 (1.2–2.5) | 2.8 (2.1–3.7) | 1.2 (0.7–1.8) | 2.9 (2.2–3.9) | 1.15 (0.82–1.62) | 1.2 (0.5–2.7) | 2.1 (1.1–3.9) |
| MCE (%) at 2 years | 0.5 (0.3–1.0) | 0.8 (0.5–1.4) | 0.1 (0.03–0.5) | 0.8 (0.5–1.4) | 1.03 (0.57–1.87) | 0.2 (0.03–1.6) | 0.2 (0.03–1.6) |
| Intracranial hemorrhage |                  |                  |                  |                  |                  |                  |                  |
| MCE (%) at 1 year | 1.2 (0.7–1.9) | 2.4 (1.7–3.3) | 0.5 (0.3–1.1) | 2.2 (1.6–3.1) | 0.90 (0.63–1.28) | 0.4 (0.1–1.8) | 1.6 (0.8–3.4) |
| MCE (%) at 2 years | 1.7 (1.1–2.5) | 3.6 (2.7–4.6) | 2.1 (1.5–2.9) | 3.9 (3.0–5.0) | 0.87 (0.66–1.15) | 2.2 (1.2–4.1) | 4.5 (2.9–6.9) |
| Major bleeding |                  |                  |                  |                  |                  |                  |                  |
| MCE (%) at 1 year | 3.5 (2.7–4.5) | 6.7 (5.5–8.1) | 3.5 (2.7–4.5) | 7.6 (6.4–9.0) | 0.95 (0.77–1.16) | 3.1 (1.8–5.1) | 6.7 (4.9–9.7) |
| MCE (%) at 2 years |                  |                  |                  |                  |                  |                  |                  |
| All-cause death |                  |                  |                  |                  |                  |                  |                  |
| MCE (%) at 1 year |                  |                  |                  |                  |                  |                  |                  |
| MCE (%) at 2 years |                  |                  |                  |                  |                  |                  |                  |
| Composite net clinical events |                  |                  |                  |                  |                  |                  |                  |
| MCE (%) at 1 year |                  |                  |                  |                  |                  |                  |                  |
| MCE (%) at 2 years |                  |                  |                  |                  |                  |                  |                  |

The incidence of major clinical events (MCE) at 1 and 2 years and crude hazard ratios (HR) are shown with 95% confidence intervals in parentheses. Composite net clinical events include stroke or systemic embolism (SE), major bleeding, and all-cause mortality. Abbreviations as in Table 1.
clinical outcome was similar between warfarin and DOAC users, as well as between warfarin users and users of the 4 different DOACs. During the follow-up period, fatal stroke or SE occurred in 4 (0.2%) DOAC users vs. 7 (0.4%) warfarin users (P=0.373), fatal intracranial hemorrhage occurred in 5 (0.3%) DOAC users vs. 3 (0.2%) warfarin users (P=0.728), and fatal extracranial bleeding occurred in 1 (0.1%) DOAC user vs. 6 (0.4%) warfarin users (P=0.061). Kaplan-Meier curves for stroke or SE, major bleeding, death from any cause, and net clinical outcome are shown for warfarin and DOAC users in Figure 2. There was no between-group difference in the incidence of stroke or SE (P=0.410), major bleeding (P=0.572), death (P=0.572), and net clinical outcome (P=0.595). Even after adjustment for all components of the CHA2DS2-VASc score and other covariates related to clinical events, with an OAC change during the follow-up taken as a time-dependent covariate, stroke or SE (HR 0.99; 95% CI 0.68–1.44), major bleeding (HR 1.02; 95% CI 0.69–1.49), death (HR 1.04; 95% CI 0.77–1.41), and net clinical outcome (HR 1.00; 95% CI 0.80–1.25) did not differ between DOAC and warfarin users (Table 3). Age ≥75 years, history of stroke or TIA, new use of an OAC, and CrCl ≤50 mL/min (4.9%) were no longer taking an anticoagulant. The anticoagulant therapy was discontinued for the following reasons: no AF recurrence after ablation (43 [26.9%] patients), no new episode of AF (63 [39.4%] patients), side effects including major or minor bleeding (16 [10.0%] patients), patient refusal or preference (15 [9.3%] patients), and other circumstances (11 [6.9%] patients). For the remaining 12 (7.5%) patients, the reason for discontinuation was not recorded.

Clinical Events Among Warfarin vs. DOAC Users and Among Warfarin vs. Dabigatran, Rivaroxaban and Apixaban Users

After the end of the follow-up period since registry enrollment (median 39.3 months [IQR 28.5–43.6 months]), a stroke or SE event had occurred in 134 patients (4.1%), major bleeding had occurred in 124 (3.8%) patients, and 200 (6.2%) patients had died. The estimated incidence and HR of major clinical events first among warfarin vs. DOAC users and then specifically among warfarin vs. dabigatran, rivaroxaban, and apixaban users are summarized in Table 2. The 1- and 2-year incidence of stroke or SE, major bleeding, intracranial hemorrhage, all-cause mortality, and net clinical outcome is shown in Figure 2, Kaplan-Meier curves for stroke or SE, major bleeding, death from any cause, and net clinical outcome are shown for warfarin and DOAC users in Figure 2. There was no between-group difference in the incidence of stroke or SE (P=0.410), major bleeding (P=0.572), death (P=0.340), or net clinical outcome (P=0.595). Even after adjustment for all components of the CHA2DS2-VASc score and other covariates related to clinical events, with an OAC change during the follow-up taken as a time-dependent covariate, stroke or SE (HR 0.99; 95% CI 0.68–1.44), major bleeding (HR 1.02; 95% CI 0.69–1.49), death (HR 1.04; 95% CI 0.77–1.41), and net clinical outcome (HR 1.00; 95% CI 0.80–1.25) did not differ between DOAC and warfarin users (Table 3). Age ≥75 years, history of stroke or TIA, new use of an OAC, and CrCl ≤50 mL/min

Figure 2. Kaplan-Meier curves for stroke or systemic embolism (SE), major bleeding, all-cause mortality, and the net clinical events that occurred among warfarin (WF) and direct oral anticoagulant (DOAC) users. Net clinical events include stroke or SE, major bleeding, and all-cause mortality.
male sex, history of stroke or TIA, new use of an OAC, and CrCl \( \leq 50 \text{ mL/min} \) for net clinical outcome (Table 3).

Propensity score matching resulted in 666 patient pairs, as indicated in Table 4. Analysis of these pairs showed the occurrence of stroke or SE (P=0.679) and the occurrence were independently associated with the occurrence of a stroke or SE. CrCl \( \leq 50 \text{ mL/min} \) was independently associated with major bleeding events. Major determinants were age \( \geq 75 \) years, male sex, body weight \( \leq 50 \text{ kg} \), heart failure, and CrCl \( \leq 50 \text{ mL/min} \) for all-cause death, and age \( \geq 75 \) years,
matched, equivalence in both stroke or SE and all-cause death was observed, but major bleeding and net clinical outcome rates were significantly lower among DOAC than warfarin users.

**Prevalence of the Use of OACs Over Time**
This study revealed notable changes in the anticoagulants used during the 2-year follow-up period. The use of warfarin decreased substantially, whereas the overall use of DOACs increased modestly, and the use of apixaban and edoxaban in particular increased substantially. Previous reports from the J-RHYTHM Registry and Fushimi AF Registry also documented an increase in the use of DOACs, once DOACs were introduced in Japan.8,9 RCTs have revealed the superiority of apixaban or edoxaban over warfarin in terms of major bleeding events, and there was a notable reduction in such events among elderly patients when either of these DOACs was used.4,5 One problem in switching from warfarin to rivaroxaban emerged, namely that there is an increased risk of stroke and major bleeding within the first few months after the switch, a point that was brought to light in the ROCKET AF.3 The published RCT findings may have prompted the switch from warfarin to DOACs, but the risks associated with the initial period of switching should be considered when making treatment decisions.

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**Figure 3.** Kaplan-Meier curves for stroke or systemic embolism (SE), major bleeding, all-cause mortality, and the net clinical events that occurred among warfarin (WF) and direct oral anticoagulant (DOAC) users after propensity score matching (n=666 for each group).

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**Discussion**

The main findings of this study regarding the use of anticoagulants in patients followed-up over a 2-year period after enrollment in the AF SAKURA Registry are as follows. First, the use of warfarin decreased, whereas the use of DOACs increased, especially the use of apixaban. Second, although the risk of stroke was lower among DOAC than warfarin users, there was no difference in the rates of stroke or SE events, major bleeding, or all-cause death between these 2 groups of patients. There was also no difference in the 2-year major clinical event rate between warfarin users and users of dabigatran, rivaroxaban, or apixaban. Third, equivalence in terms of stroke or SE, major bleeding, all-cause death, and net clinical outcome between DOAC and warfarin users persisted even when the change from 1 anticoagulant to another was accounted for as a time-dependent covariate. Upon propensity matching, equivalence in both stroke or SE and all-cause death was observed, but major bleeding and net clinical outcome rates were significantly lower among DOAC than warfarin users.
to apixaban or edoxaban in real-world clinical practice.

Outcomes Among DOAC and Warfarin Users

In our study patients, overall stroke or SE, major bleeding, and all-cause mortality rates were 4.1%, 3.8%, and 6.2%, respectively, and the rates were equivalent between DOAC and warfarin users. Equivalence in terms of these events persisted even after adjustment for potential covariates. Similarly, published RCTs show that the reduction in stroke or SE rates achieved with the use of DOACs was similar or even superior to that achieved with the use of warfarin.\(^8\) In addition, many investigators have provided real-world evidence of improved effectiveness and safety of DOACs compared with warfarin.\(^8\)\(^9\)\(^11\)\(^–\)\(^14\) However, not many reports have addressed these particulars in Japanese patients.\(^8\)\(^8\)\(^15\)\(^–\)\(^16\)

According to a report based on the largest Japanese registry of patients with AF, the J-RHYTHM Registry 2, stroke or SE occurred in 2%/ (18/918) of DOAC users during a 5-year follow-up period, and major bleeding occurred in 2.3% (21/918) of DOAC users.\(^8\)\(^9\)\(^11\)\(^–\)\(^14\) The incidence of stroke or SE was significantly higher among warfarin than DOAC users (5.9% [232/3,959] vs. 5.0% [196/3,959], respectively). The J-RHYTHM Registry 2 was a multicenter observational study that expanded the follow-up period of the J-RHYTHM Registry,\(^8\)\(^9\)\(^11\)\(^–\)\(^14\) and patients were classified as warfarin users, DOAC users, and non-users according to their final status during the follow-up period. However, for these patients, the exact follow-up time after the switch from warfarin to a DOAC is unknown. Excluded from the study population (n=6,616) were 976 (14.8%) patients for whom the specific anticoagulants were not known, and a substantial number of patients dropped out. These are factors that could have influenced the study results. According to a recent report from the Fushimi AF Registry, stroke or SE and major bleeding rates during the 3-year follow-up period (1-year follow up rate: 89.6%) were equivalent between warfarin and DOAC users (P=0.70 [by log-rank test] for stroke; P=0.34 [by log-rank test] for major bleeding), but only 270 of the total 3,731 patients were DOAC users.\(^8\)\(^9\)\(^11\)

Compared with other registry-based studies, the present SAKURA AF Registry study covered a large number of DOAC users (n=1,676) who were followed up for a relatively long period. At ≥900%, the follow-up rate at 2 years was good, and this is the only registry to have included TTR. The clinical characteristics of patients in the SAKURA AF Registry should be considered in the interpretation of our study results. The study patients were at lower risk of stroke and bleeding than those in the Fushimi AF Registry but at higher risk than those in the J-RHYTHM Registry 2,\(^8\)\(^9\)\(^11\)\(^–\)\(^14\) and this led to lower rates of stroke and major bleeding events among our study patients than among those in the Fushimi AF Registry, but higher rates in the present study than among patients in the J-RHYTHM Registry 2. The main difference between warfarin and DOAC users was the median duration of OAC therapy before enrolment (i.e., 46.5 vs. 6.6 months, respectively), but this difference is similar to the differences in the J-RHYTHM Registry 2 and Fushimi Registry.\(^8\)\(^9\)

Vulnerability to ischemic stroke is increased during a short period after the start of warfarin.\(^17\) Fortunately, only a small number of OAC-naïve patients in our registry were given warfarin, but it is possible that some warfarin-treated patients who were highly susceptible to stroke or serious bleeding were excluded from the study. Further, the mean TTR of our registry patients was relatively good (65.4±31.1%) in light of reported values from 4 recent RCT trials (mean TTR: 55–68%).\(^2\)\(^5\)\(^15\)\(^–\)\(^16\) We believe the longer OAC therapy and relatively good TTR in our warfarin users explain the low major clinical event rate (1.8%/year for stroke or SE, 0.5%/year for intracranial hemorrhage, 1.2%/year for major bleeding, and 1.7%/year for all-cause mortality) among the warfarin users. This may explain the lack of difference in the incidence of stroke and major bleeding and in the net clinical outcomes among these patients compared with DOAC users. Despite the propensity score matching, which resulted in a median OAC therapy duration of 15 months in each group, major bleeding and net clinical outcome rates were significantly lower among DOAC than warfarin users. Therefore, we believe that in real-world practice DOACs are beneficial over warfarin in patients who are not naïve to OAC treatment.

Our analysis adds to the previously reported RCTs and real-world studies because it includes a comparison of the effectiveness and safety of DOACs against those of warfarin in a Japanese cohort. As in other cohort-based studies and RCTs,\(^2\)\(^5\)\(^8\)\(^9\)\(^11\)\(^–\)\(^14\) older age, male sex, history of stroke or TIA, and a low CrCl were shown to be independent factors for composite events including stroke or SE, major bleeding, and all-cause death. In addition, new use of an OAC was associated with increased stroke or SE and composite events. In one real-life study, 1-year adherence to DOAC therapy was reported to be poor in new users of an OAC.\(^18\) Previously, we assessed patient satisfaction with OAC therapy using the Anti-Clot Treatment Scale in half the patients enrolled in the SAKURA AF Registry.\(^8\) At that time, we found (per the Benefits scale) a strong association between poor satisfaction and relatively short OAC therapy. Those factors would tend to increase the incidence of stroke or SE. Thus, physicians should exercise caution when they start patients on OACs, especially elderly patients or those with a history of stroke or TIA or renal dysfunction. However, an interesting finding of our study was that age ≥75 years was a significant predictor of stroke or SE, but not of major bleeding. This suggests that anticoagulation may be particularly beneficial in elderly patients.

In this study, despite the small number of patients taking each of the 4 DOACs, stroke or SE, major bleeding, and death occurred equally between DOAC users and warfarin users. No RCT data exist comparing DOACs, but our real-world observational data are consistent with the safety and effectiveness reported from clinical trials.\(^11\)\(^–\)\(^13\) In an analysis of real-world data from the Korean National Health Insurance Service database,\(^12\) the risk of ischemic stroke was shown to be similar between all 3 DOACs used and that of warfarin (rivaroxaban, 1.9%/year; dabigatran, 1.8%/year; apixaban, 1.3%/year; warfarin, 1.5%/year), whereas the risk of intracranial bleeding was lower for DOACs (rivaroxaban, 0.9%/year; dabigatran, 0.6%/year; apixaban, 0.5%/year; warfarin 1.3%/year). All-cause mortality was significantly lower only with dabigatran and apixaban.\(^12\) A study based on the Truven MarketScan Commercial and Medicare Supplemental US Claims database showed that patients who were started on rivaroxaban were significantly more likely to have a major bleeding event than matched patients who were started on apixaban.\(^13\) These findings were reinforced by a large meta-analysis of comparative, matched, or adjusted data pertaining to DOACs and VKAs in patients with AF.
with the data having been obtained from observational nationwide or health insurance databases. Dabigatran, rivaroxaban, and apixaban, compared with VKAs, are associated with a lower risk of intracranial hemorrhage and similar risk of ischemic stroke or SE, but apixaban and dabigatran are associated with a lower risk of mortality. The relatively low annual incidence of stroke and major bleeding, intracranial bleeding, and all-cause death among users of each of the 4 DOACs is well in line with the reported real-world incidence.

Differences Between RCTs and Registry-Based Studies of Real-World Patients

According to 4 global RCTs that compared warfarin and DOACs for stroke prevention, annual stroke or SE rates were approximately 1–3% and notably lower than the annual major bleeding event rates of approximately 2–5%. Conversely, among our SAKURA AF Registry patients, the annual stroke or SE rate was 1.4% (44 patients) and notably higher than the major bleeding rate of 0.8%/26 patients. The trends we observed are in line with those seen in other registries in Japan. The real-world incidence of stroke seems low, but may actually be high when patients’ stroke risk is considered. The average real-world CHADS2 score documented in registries in Japan are in the range 1.8–2.1, whereas those documented in RCTs range from 2.1 to 3.5. The relatively high real-world stroke or SE event rates documented in the registries may be due to poor patient adherence or to inappropriately reduced doses of DOACs (despite the standard dose criteria having been met or of warfarin compared with the appropriate dosing and strict follow-up that would have occurred in the RCTs.

Study Limitations

This study has several limitations. First, because it was a prospective observational study, there could have been a selection bias despite the use of Cox proportional hazards models to minimize the influence of patient background factors. For example, patients for whom anticoagulant therapy was almost contraindicated (because of a high risk of bleeding) would not have been included in the registry. Second, the study was conducted in Tokyo, and the results may not reflect all of Japan. However, we note that patient selection and regional enrollment biases are limitations of all prospective observational studies. Third, the study did not include a large enough number of users of each of the 4 DOACs for outcome analyses with multivariable adjustment. Fourth, the SAKURA AF Registry does not include patients not given anticoagulant drugs. This is because the annual incidence of stroke and bleeding has already been well evaluated in Japanese AF patients not taking an anticoagulant.

Conclusions

The high follow-up rate for patients enrolled in the SAKURA AF Registry allowed us to obtain reliable data on the status of OACs used in patients in Japan and the therapeutic outcomes. The rates of stroke or SE, bleeding, and all-cause mortality appeared to be equivalent between warfarin users and DOAC users. The rates also appeared to be equivalent regardless of whether the DOAC used was dabigatran, rivaroxaban, or apixaban. However, upon propensity score matching, the stroke or SE and all-cause mortality rates were shown to be equivalent, whereas the rates of major bleeding were significantly lower in DOAC than warfarin users.

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Conflict of Interest

Y. Okumura has accepted remuneration from Daiichi-Sankyo. A.H. has received research funding from Bayer Healthcare, Daiichi-Sankyo, Otsuka Pharmaceutical, Astellas Pharma, Eisai, Sumitomo Dainippon Pharma, MSD, Nihon Medi-Physics, Bristol-Meyers Squibb, Boehringer Ingelheim, Pfizer, Boston Scientific Corporation, Hokushin Medical, and has accepted remuneration from Bayer Healthcare, Daiichi-Sankyo, Eisai, Bristol-Meyers Squibb, Astellas Pharma, Sanofi, and Takeda Pharmaceutical. N.M. has received research funding from Daiichi-Sankyo, Otsuka Pharmaceutical, and Sumitomo Dainippon Pharma, and has accepted remuneration from Nihon Medi-Physics, FUJIFILM RI Pharma, and Biosensors Interventional Technologies Japan.

References


**Supplementary Files**

**Appendix S1**

Please find supplementary file(s);