Two-Year Outcomes of Anticoagulation for Acute Ischemic Stroke With Nonvalvular Atrial Fibrillation
— SAMURAI-NVAF Study —

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Background: We determined the 2-year long-term risk-benefit profile in patients with stroke or transient ischemic attack (TIA) receiving warfarin or direct oral anticoagulants (DOACs) for nonvalvular atrial fibrillation (NVAF) using a prospective, multicenter, observational registry in Japan.

Methods and Results: NVAF patients within 7 days after onset of ischemic stroke/TIA were enrolled in 18 stroke centers. Outcome measures included ischemic and bleeding events and death in the 2-year follow-up period. We enrolled 1,116 patients taking either warfarin (650 patients) or DOACs (466 patients) at acute hospital discharge. DOAC users were younger and had lower National Institutes of Health Stroke Scale, CHADS2 and discharge modified Rankin Scale scores than warfarin users (P<0.0001 each). Incidences of stroke/systemic embolism (adjusted hazard ratio, 1.07; 95% CI, 0.66–1.72), all ischemic events (1.13; 0.72–1.75), and ischemic stroke/TIA (1.58; 0.95–2.62) were similar between groups. Risks of intracranial hemorrhage (0.32; 0.09–0.97) and death (0.41; 0.26–0.63) were significantly lower for DOAC users. Infection was the leading cause of death, accounting for 40% of deaths among warfarin users.

Conclusions: Stroke/TIA patients receiving DOACs for secondary prevention were younger and had lower stroke severity and risk indices than those receiving warfarin. Estimated cumulative incidences of stroke and systemic embolism within 2 years were similar between warfarin and DOAC users, but those of death and intracranial hemorrhage were significantly lower among DOAC users.

Key Words: Acute stroke; Atrial fibrillation; Direct oral anticoagulants; Intracranial hemorrhage; Warfarin

Ischemic stroke related to atrial fibrillation (AF) is associated with more severe disability, higher mortality and recurrence rates and greater medical costs than that without AF.1–3 These days, direct oral anticoagulants (DOACs) have been broadly adopted for primary and secondary prevention of stroke caused by nonvalvular AF (NVAF). In a meta-analysis including 4 phase III randomized control trials (RCTs) of DOACs, these agents significantly reduced stroke or systemic embolic events, all-cause death, and intracranial hemorrhage when compared with warfarin.4,5 However, patients with some conditions, such as acute stroke, severe disability, malig-
nancy, dual antiplatelet therapy, and advanced renal failure, were excluded from those RCTs. Real-world data are important for evaluating DOAC effectiveness and safety in such patients. Although some observational studies, including post-marketing surveys, insurance database analysis, nationwide cohort studies, and hospital-based data analyses, have reported DOAC risk-benefit profiles, each of those studies have particular limitations, such as the inclusion of users of specific DOACs, limited subject numbers, and lack of clinical information, such as cause of death. Moreover, real-world data for patients with acute stroke receiving DOACs in Japan are lacking.

The Stroke Acute Management with Urgent Risk-factor Assessment and Improvement—Non-Valvular Atrial Fibrillation (SAMURAI-NVAF) registry is a prospective, multicenter, observational study of acute stroke and transient ischemic attack (TIA) patients with NVAF in Japan. The study was registered with ClinicalTrials.gov (NCT01581502) and the Japanese University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN000006930). We have previously reported on clinical processes and outcomes in acute hospitals, and the short-term risk-benefit profile of anticoagulation within 3 months among patients, using data from the SAMURAI-NVAF. In the present study, we used the data from the same registry to examine the 2-year long-term risk-benefit profile among patients receiving warfarin or DOACs.

Methods

Participants

The SAMURAI-NVAF database included 1,192 NVAF patients hospitalized within 7 days of the onset of ischemic stroke or TIA between September 2011 and March 2014 and enrolled from 18 stroke centers in Japan (Appendix S1). NVAF was diagnosed on 12-lead ECG or by ≥24-h monitoring during the acute hospitalization or detected from past medical documents. The design and main baseline data have been published elsewhere.

Procedures

All study procedures were reviewed and approved by the ethics committees of the participating institutions, and written informed consent was obtained from patients or family if the patient was incapable of providing consent. Baseline clinical information, ischemic and hemorrhagic indices, and stroke features were registered via a web-based system. The eligibility and choice of OACs for patients were determined by each investigator without randomization. Target intensity and dosages of OACs have been described elsewhere. In brief, the target prothrombin time-international normalized ratio in warfarin users was 2.0–3.0 for patients younger than 70 years old and 1.6–2.6 for those aged 70 years or older according to Japanese guidelines. Dosages of DOACs were determined according to each medical package insert. Patients were assigned to the warfarin or DOAC group based on the OAC taken on the day of acute hospital discharge (or as of 30 days after hospital admission, whichever occurred first).

The primary outcome was stroke or systemic embolism, and the primary safety outcome was major bleeding by 2 years after the index stroke/TIA. Secondary outcomes were any ischemic events, ischemic stroke or TIA, intracerebral hemorrhage, subarachnoid hemorrhage, subdural hematoma, and death at 2 years. Events were assessed at the hospital clinic (or by telephone survey for patients with aftereffects too severe to allow a visit to the clinic). Events at 1 year were also assessed. Ischemic events included ischemic stroke, TIA, systemic embolism, acute coronary syndrome, aortic dissection, aortic aneurysm rupture, peripheral artery disease requiring hospitalization, venous thromboembolism, and revascularization including carotid endarterectomy, carotid artery stenting, and coronary intervention. Major bleeding events were defined according to the International Society on Thrombosis and Hemostasis statement. Causes of death were surveyed as precisely as possible and classified as ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, other stroke, other cardiovascular events, infection, malignancy, or other causes. Observation was discontinued when any endpoint occurred, except when assessing deaths. Changes or discontinuation of OACs after discharge were assessed at 3 months, 1 year and 2 years.

Statistical Analysis

Data are presented as mean ± standard deviation, median (interquartile range [IQR]), or number (%). Variables were compared using Student’s t-test, Wilcoxon’s test, or Pearson’s chi-square test, as appropriate. The Kaplan-Meier method was used to estimate cumulative incidences. Cox proportional hazards modeling was used to calculate hazard ratios (HR) for primary and secondary outcomes from the choice of OACs. Crude HRs from the choice of DOAC as compared with warfarin were calculated and adjusted by potential confounding factors, including sex, age, CHADS2 score, and CCI. In Model 1, we also adjusted the HR by propensity scoring calculated using sex, age, body weight, CCI, infarct size, NIHSS score on admission, CHADS2 score, CHA2DS2-VASc score, HAS-BLED score, and the modified Rankin Scale (mRS) score at discharge. Statistical analyses were conducted using JMP version 13.4.6-9843 All rights are reserved to the Japanese Circulation Society. For permissions, please e-mail: cj@j-circ.or.jp

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Results Among the 1,192 patients, 27 who died in hospital and 49 who were not receiving OACs at discharge, mainly because of severe neurological deficits, were excluded. The remaining 1,116 patients (all Japanese, 480 women; mean age, 77±10 years) taking OACs at acute hospital discharge were assessed. Of them, warfarin was administered to 650 patients, dabigatran to 203 (52 with 150 mg bid, 150 with 110 mg bid, and 1 with 75 mg bid), rivaroxaban to 238 (128 with 15 mg qd, 109 with 10 mg qd, and 1 with 7.5 mg qd), and apixaban to 25 (17 with 5 mg bid and 8 with 2.5 mg bid). Median duration of follow-up was 700 days (IQR, 340–728 days) for all 1,116 patients. A total of 970 patients (86.9%) completed the 2 years of follow-up. The major underlying characteristics and features of stroke are listed in Table 1. DOAC users included more male patients who were younger, and heavier in body weight, had better renal function and lower premorbid mRS scores, and less likely to have malignancy than warfarin users. NIHSS score at baseline was lower, large infarcts were less frequent, and the CHADS2, CHA2D2-VASc, and HAS-BLED scores after the index stroke event and the mRS at discharge were lower among DOAC users than among warfarin users. DOAC users were more likely to change or discontinue

<table>
<thead>
<tr>
<th>Table 1. Underlying Characteristics and Stroke Features of Study Patients</th>
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<tr>
<td><strong>Baseline characteristics</strong></td>
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<tr>
<td>Men</td>
</tr>
<tr>
<td>Age, years</td>
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<tr>
<td>Body weight, kg</td>
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<tr>
<td>Premorbid mRS</td>
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<tr>
<td>Ccr, ml/min*</td>
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<tr>
<td>Renal insufficiency†</td>
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<tr>
<td>Not cured malignancy</td>
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<tr>
<td><strong>Features of index stroke/TIA</strong></td>
</tr>
<tr>
<td>TIA</td>
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<tr>
<td>Infarct size‡</td>
</tr>
<tr>
<td>Small</td>
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<tr>
<td>Medium</td>
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<tr>
<td>Large</td>
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<tr>
<td>NIHSS score on admission</td>
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<tr>
<td><strong>Risk indices after index stroke/TIA</strong></td>
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<tr>
<td>CHADS₂ score</td>
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<tr>
<td>CHADS₂ score ≥2</td>
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<tr>
<td>CHA₂DS₂-VASc score</td>
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<tr>
<td>CHA₂DS₂-VASc score ≥3</td>
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<tr>
<td>HAS-BLED score ≥3</td>
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<tr>
<td><strong>Therapy and clinical course during acute hospitalization</strong></td>
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<tr>
<td>Reperfusion therapy§</td>
</tr>
<tr>
<td>Hemorrhagic events</td>
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<tr>
<td>Ischemic events</td>
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<tr>
<td>mRS at discharge</td>
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<tr>
<td>mRS at discharge ≥4</td>
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<tr>
<td>Antiplatelet drugs at discharge</td>
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<tr>
<td>DAPT at discharge</td>
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<tr>
<td><strong>Change in OACs after discharge</strong></td>
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<tr>
<td>Drug change‖ or discontinuation</td>
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<tr>
<td>Discontinuation of OACs</td>
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<tr>
<td>Change to another OAC type¶</td>
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</tbody>
</table>

Data are presented as mean±standard deviation, median [interquartile range], or number (%). *Ccr estimated using the Cockcroft and Gault formula. †Dialysis, transplant, or Cr >200μmol/L. ‡Small infarct, ≤15 mm in largest diameter; Large, infarct, larger than one-third of affected cerebral artery territory; Medium, infarct, all other cases. ¶Unravenous thrombolysis or acute endovascular therapy. ‡Change from warfarin to DOACs or from OACs to warfarin. **Change from one DOAC to another, from warfarin to a DOAC, or from DOACs to warfarin. CCr, creatinine clearance; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulant; mRS, modified Rankin Scale score; NIHSS, National Institutes of Health Stroke Scale; OAC, oral anticoagulant; TIA, transient ischemic attack.
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OACs after discharge and less likely to discontinue OACs than warfarin users. There was no difference in the change to the other OAC type between the 2 groups. Percentage of OACs use in patients with different discharge mRS, age and CCr, and change of warfarin and DOAC use over the period of discharge are shown in Figure S1 and Figure S2.

Table 2 shows the number of ischemic and major bleeding events among users of warfarin and DOACs. Kaplan-Meier curves for primary and secondary endpoints are shown in Figure 1. Estimated annual incidences and HRs of the primary and secondary outcomes are summarized in Table 3.

Ischemic events occurred in 58 warfarin users and 40 DOAC users (Table 2). No significant differences in the risk of ischemic events or ischemic stroke/TIA were identified (Table 3). Major bleeding events occurred in 27 warfarin users and 10 DOAC users (Table 2). Risk of intracranial hemorrhage was significantly lower among DOAC users after Model 1 multivariate adjustment (2.79%/2 years vs. 1.03%/2 years, adjusted HR 0.32; 95% confidence interval (CI) 0.09–0.97). However, this difference did not remain significant after adjustment using propensity scores (Model 2: adjusted HR 0.34, 95% CI 0.09–1.06) (Table 3).

Stroke/systemic embolism risk per 2 years was 10.50% in warfarin users and 8.40% in DOAC users (Table 3). After multivariate adjustment, no significant difference in the risk of the primary outcome was seen between warfarin and DOACs users. Major bleeding risk was lower among

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Table 2. Types of Events During Study Period

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Warfarin (n=650)</th>
<th>Any DOACs (n=466)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ischemic events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>58 (8.9)</td>
<td>40 (8.6)</td>
</tr>
<tr>
<td>TIA</td>
<td>39 (6.0)</td>
<td>31 (6.7)</td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>2 (0.3)</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>ACS or PCI</td>
<td>5 (0.8)</td>
<td>0</td>
</tr>
<tr>
<td>PAD</td>
<td>8 (1.2)</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Carotid endarterectomy</td>
<td>2 (0.3)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Aortic dissection/aortic aneurysm rupture</td>
<td>1 (0.2)</td>
<td>0</td>
</tr>
<tr>
<td>Other ischemic events</td>
<td>1 (0.2)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Major bleeding events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td>24 (4.2)</td>
<td>10 (2.1)</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>6 (0.9)</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Other intracranial hemorrhage</td>
<td>5 (0.8)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>6 (0.9)</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Retroperitoneal</td>
<td>1 (0.2)</td>
<td>0</td>
</tr>
<tr>
<td>Intraarticular</td>
<td>1 (0.2)</td>
<td>0</td>
</tr>
<tr>
<td>Intramuscular</td>
<td>1 (0.2)</td>
<td>0</td>
</tr>
<tr>
<td>Decrease in hemoglobin</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Other major bleeding</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data represent number (%) of patients. ACS, acute coronary syndrome; PAD, peripheral artery disease; PCI, percutaneous coronary intervention. Other abbreviations as in Table 1.

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Figure 1. Event rates for primary and secondary outcomes. *Days after acute hospital discharge or 30 days after hospital admission, whichever occurred first. CI, confidence interval; DOAC, direct oral anticoagulant; HR, hazard ratio (DOACs/warfarin).
Table 3. Primary and Secondary Outcomes of the Study Patients

<table>
<thead>
<tr>
<th>Primary outcome</th>
<th>Warfarin (n=650)</th>
<th>DOACs (n=466)</th>
<th>HR (DOACs/warfarin at 2 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%/1 year (95% CI)</td>
<td>2% years (95% CI)</td>
<td>%/1 year (95% CI)</td>
</tr>
<tr>
<td>Stroke/systemic embolism</td>
<td>5.39 (4.12–7.03)</td>
<td>10.50 (8.07–13.55)</td>
<td>4.29 (3.08–5.95)</td>
</tr>
<tr>
<td>Primary safety outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>2.89 (1.99–4.19)</td>
<td>2.55 (1.38–4.67)</td>
<td>1.28 (0.69–2.37)</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic events</td>
<td>6.01 (4.66–7.71)</td>
<td>11.66 (9.10–14.81)</td>
<td>5.03 (3.71–6.78)</td>
</tr>
<tr>
<td>Ischemic stroke/TIA</td>
<td>4.26 (3.14–5.75)</td>
<td>8.33 (6.17–11.16)</td>
<td>4.29 (3.08–5.95)</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>1.40 (0.82–2.40)</td>
<td>2.79 (1.63–4.74)</td>
<td>0.52 (0.19–1.36)</td>
</tr>
<tr>
<td>Death</td>
<td>15.36 (13.32–17.64)</td>
<td>28.36 (24.85–32.15)</td>
<td>3.25 (2.23–4.69)</td>
</tr>
</tbody>
</table>

*P<0.05, †P<0.0001. Model 1: adjusted by sex, age, CHADS2, National Institutes of Health Stroke Scale score on admission, and creatinine clearance. Model 2: adjusted by propensity score calculated using sex, age, body weight, creatinine clearance, infarct size, National Institutes of Health Stroke Scale score on admission, CHADS2 score, CHA2DS2-VASc score, HAS-BLED score, and modified Rankin Scale score at discharge. CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.

Figure 2. Relative risk of primary outcomes by subgroup. Adjusted by sex, age, CHADS2, National Institutes of Health Stroke Scale (NIHSS) score on admission, and creatinine clearance (CCr). CI, confidence interval; DOAC, direct oral anticoagulant; mRS, modified Rankin Scale score.
DOAC users in the univariate analysis (5.70%/2 years vs. 2.55%/2 years, crude HR 0.46, 95% CI 0.21–0.91), but the risk no longer showed any significant difference after multivariate adjustment. In the subgroup analysis, no significant interactions were seen between OAC choice and any patient characteristics (Figure 2).

Death within 2 years occurred in 164 patients taking warfarin and in 27 taking DOACs. Causes of death are summarized in Table 4. In the warfarin group, infection was the leading cause (40%), with pneumonia accounting for at least 38% of the infectious foci. Ischemic stroke was the leading cause of death among DOAC group (19%), after excluding unclear causes. No significant differences between groups were seen in the proportions of causes of death. The mortality rate was significantly lower among DOAC users after adjustment (28.36%/2 years vs. 6.38%/2 years, adjusted HR 0.41, 95% CI 0.26–0.63). This result remained intact after adjustment using propensity scores (adjusted HR 0.58, 95% CI 0.36–0.89; Table 3).

### Discussion

The major findings of this study included the following: (1) patients receiving DOACs experienced milder symptoms and lower scores on risk indices than those taking warfarin; (2) cumulative incidences of stroke/systemic embolism, all ischemic events, and ischemic stroke/TIA were similar between groups; and (3) DOAC users showed a more favorable clinical course regarding risks of bleeding and death, for the reasons that follow. First, major bleeding tended to be less frequent among DOAC users on univariate analysis. Second, intracranial hemorrhage was less frequent among DOAC users after adjusting for sex, age, CHADS: score, NIHSS score, and Ccr. Third, mortality rates were significantly lower among DOAC users after multivariate adjustment, as well as after propensity score analysis.

Several observational studies of acute ischemic stroke patients with AF have investigated the effectiveness of OACs. The Virtual International Stroke Trials Archive (VISTA) was a collaborative registry of completed acute stroke trial data including 1,644 post-stroke AF patients, but DOACs were not prescribed during the study period. The Early Recurrence and Cerebral Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation (RAF) study was a multicenter prospective observational study of 1,029 patients, 93 (12.1%) of whom received DOACs. Each of these studies reported 90-day risks of ischemic and hemorrhagic events after ischemic stroke. The Novel Oral Anticoagulants in Ischemic Stroke Patients (NOACISP) was a single-center prospective registry that reported events between 3 and 6 months after stroke in 204 AF patients, including 155 (76.0%) DOAC users. Our multicenter registry included more DOAC users (466 patients) and reported longer-term outcomes (2 years).

Among the patients administered OACs in the VISTA and RAF studies, ischemic stroke (8.2%/90 days vs. 14.5%/90 days in VISTA) and ischemic stroke/TIA and systemic embolism (6.4%/90 days vs. 10.6%/90 days in RAF) were less common compared with those without OACs. The NOACISP and our SAMURAI-NVAF included higher proportions of patients using DOACs, and demonstrated similarly lower recurrent risks of ischemic stroke/TIA among patients on OACs (2.9%/3–6 months and 2.6%/90 days, respectively). Although our study enrolled patients with more severe neurological deficits than the NOACISP (median NIHSS 7 vs. 4, respectively). In our study, long-term risks for ischemic stroke/TIA were relatively low (4.3%/1 year and 8.4%/2 years, respectively). Possible reasons include the exclusion of events during acute hospitalization and the possibility that high mortality rates, particularly in the warfarin group, might have concealed the occurrence of other ischemic or hemorrhagic events.

Each of the 4 DOAC RCTs show all-cause mortality rates of 3.5–4.9%/1 year among both DOAC users and warfarin users, and the majority of deaths have a cardiovascular cause (62.6–72.8%). In our study, the mortality rate in the DOAC group was 3.3%/1 year and that in the warfarin group was 15.4%/1 year and noncardiovascular diseases such as infection accounted for the majority of deaths. The North Dublin Population Stroke Study (mean age, 76.5 years; median CHADS: score, 4) also revealed a considerably low long-term survival rate for AF-related stroke (39%/5 years), although causes of death were not determined. Compared with the RCTs, the advanced age and risk scores of our registry patients may have adversely influenced the mortality rate. Similarly, the present patients were more dependent, more frail, more dysphagic, and more cognitively impaired. In addition, maintenance of a prolonged time in the therapeutic range for warfarin over an extended period of years is much more difficult in real-world observational studies than in RCTs, which might contribute to more fatal events. Patients with dysphagia who needed powder formulations might often be treated using warfarin, because administration of capsule-release dabigatran granules is not recommended for fear of blood level elevation, and crushed factor Xa inhibitor tablets were underused during our study period. This might be why infections, particularly pneumonia, were the leading cause of death among warfarin users in our study.

The cumulative incidence of intracranial hemorrhage was higher among the warfarin users (1.40%/1 year vs. 0.70–0.85%/1 year), but similar among the DOAC users (0.52%/1 year vs. 0.23–0.50%/1 year) in our study as compared with the DOAC RCTs. The RAF study sug-

<table>
<thead>
<tr>
<th>Table 4. Causes of Death</th>
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<tbody>
<tr>
<td><strong>Warfarin</strong> (n=164)</td>
</tr>
<tr>
<td><strong>Ischemic stroke</strong></td>
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<tr>
<td><strong>Intracerebral hemorrhage</strong></td>
</tr>
<tr>
<td><strong>Subarachnoid hemorrhage</strong></td>
</tr>
<tr>
<td><strong>Heart failure</strong></td>
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<tr>
<td><strong>Other cardiovascular events</strong></td>
</tr>
<tr>
<td><strong>Gastrointestinal bleeding</strong></td>
</tr>
<tr>
<td><strong>Infection</strong></td>
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<tr>
<td><strong>Malignancy</strong></td>
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<tr>
<td><strong>Respiratory failure</strong></td>
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<tr>
<td><strong>Other diseases</strong></td>
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<tr>
<td><strong>Old age</strong></td>
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<tr>
<td><strong>Unclear</strong></td>
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</tbody>
</table>

Data are presented as numbers (%). *Other cardiovascular events include myocardial infarction, systemic embolism, peripheral vascular disease, venous thromboembolism, and aortic dissection. DOAC, direct oral anticoagulant.
gested an optimal timing of 4–14 days from stroke onset. In the NOACISP registry, patients who started DOACs within 7 days appeared to have a reduced risk of intracranial hemorrhage. DOACs were initiated very early (median, 4 days) after stroke in the SAMURAI-NVAF, and the rate of intracranial hemorrhage tended to be lower among DOAC users than among warfarin users within the initial 3 months, including the acute hospitalization days. These results suggested favorable effects of early DOAC use for reducing the risk of intracranial hemorrhage throughout the acute to chronic periods.

### Study Strengths and Limitations

The strengths of our study include its prospective cohort design, real-world data from a relatively large number of acute stroke patients in the era of DOACs, high follow-up rate (86.9% for 2 years), and detailed clinical information, such as ischemic and hemorrhagic indices, stroke lesions, and causes of deaths, as defined by well-trained stroke neurologists. Key limitations included, first, that the observational design might have led to the inclusion of study biases even with the use of Cox proportional hazards models and propensity scoring to minimize the influence of background for anticoagulant choice. Second, this study was conducted in specialist stroke centers in Japan and the results might not be representative of the clinical course of inpatients in general hospitals or in populations outside of Japan. Specific situational factors such as low body weight and low clinical events and the unique healthcare system in Japan might have influenced our results. Third, physicians in charge might have been nervous about selecting DOACs and dabigatran had not yet been approved and edoxaban had not yet been approved during the study period.

In conclusion, Japanese stroke/TIA patients receiving DOACs for secondary prevention were younger and exhibited lower stroke severity and risk indices than those receiving warfarin. Estimated cumulative incidences of stroke/systemic embolism within 2 years were similar between groups, but those of death and intracranial hemorrhage were significantly lower among DOAC users.

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### Conflict of Interests

None.

### References


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**Supplementary Files**

Supplementary File 1

Appendix S1. Sites and Investigators Participating in the SAMURAI-NVAF Study

**Figure S1.** Choice of oral anticoagulant at discharge in all patients and in patients with different discharge mRS.

**Figure S2.** Choice of oral anticoagulants at discharge in patients with different ages and creatinine clearance (CCr) data.

Please find supplementary file(s):