Higher Risk of Ischemic Events in Secondary Prevention for Patients With Persistent Than Those With Paroxysmal Atrial Fibrillation

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Background and Purpose—The discrimination between paroxysmal and sustained (persistent or permanent) atrial fibrillation (AF) has not been considered in the approach to secondary stroke prevention. We aimed to assess the differences in clinical outcomes between mostly anticoagulated patients with sustained and paroxysmal AF who had previous ischemic stroke or transient ischemic attack.

Methods—Using data from 1192 nonvalvular AF patients with acute ischemic stroke or transient ischemic attack who were registered in the SAMURAI-NV AF study (Stroke Management With Urgent Risk-Factor Assessment and Improvement—Nonvalvular AF; a prospective, multicenter, observational study), we divided patients into those with paroxysmal AF and those with sustained AF. We compared clinical outcomes between the 2 groups.

Results—The median follow-up period was 1.8 (interquartile range, 0.93–2.0) years. Of the 1192 patients, 758 (336 women; 77.9±9.9 years old) and 434 (191 women; 77.3±10.0 years old) were assigned to the sustained AF group and paroxysmal AF groups, respectively. After adjusting for sex, age, previous anticoagulation, and initial National Institutes of Health Stroke Scale score, sustained AF was negatively associated with 3-month independence (multivariable-adjusted odds ratio, 0.61; 95% confidence interval, 0.43–0.87; P=0.006). The annual rate of stroke or systemic embolism was 8.3 and 4.6 per 100 person-years, respectively (multivariable-adjusted hazard ratio, 1.95; 95% confidence interval, 1.26–3.14) and that of major bleeding events was 3.4 and 3.1, respectively (hazard ratio, 1.13; 95% confidence interval, 0.63–2.08).

Conclusions—Among patients with previous ischemic stroke or transient ischemic attack, those with sustained AF had a higher risk of stroke or systemic embolism compared with those with paroxysmal AF.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01581502.

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Key Words: atrial fibrillation ■ hemorrhage ■ secondary prevention ■ stroke ■ thromboembolism
Trial fibrillation (AF) is the most common cardiac arrhythmia and becomes more prevalent with age. AF is one of the major risk factors in patients with ischemic stroke or transient ischemic attack (TIA). Cardioembolic stroke accounts for 14% to 30% of ischemic strokes. Generally, cardioembolic stroke causes more severe neurological symptoms and disability than other subtypes. As shown in the risk stratification scheme using the CHADS$_2$ (an acronym for congestive heart failure, hypertension, age ≥75 y, diabetes mellitus, and prior stroke or TIA) and CHA$_2$DS$_2$-VASc (an acronym for congestive heart failure/left ventricular systolic dysfunction; hypertension; age 65–74 or ≥75 y; diabetes mellitus; prior stroke, TIA or thrombembolism; vascular disease; and sex category) scores, the AF population has a heterogeneous risk for ischemic stroke. Patients with cardioembolic stroke can have either paroxysmal or persistent or permanent AF. Paroxysmal AF spontaneously terminates within 7 days, and persistent or permanent AF persists beyond 7 days. It is disputed whether the risk of thromboembolism varies with AF type. Since early 2000, there have been several reports that showed a similar risk of thromboembolism for patients with paroxysmal AF and those with persistent or permanent AF. Recently, data showing a higher risk for stroke or systemic embolism in patients with persistent or permanent AF than for those with paroxysmal AF has been accumulating, mainly from post hoc analyses of large randomized controlled trials (RCTs) of oral anticoagulants (OACs) or antiplatelets for AF patients and an AF registry. Large randomized controlled trials (RCTs) of oral anticoagulants (OACs) or antiplatelets for AF patients and an AF registry. Since early 2000, there have been several reports that showed a similar risk of thromboembolism for patients with paroxysmal AF and those with persistent or permanent AF. Recently, data showing a higher risk for stroke or systemic embolism in patients with persistent or permanent AF than for those with paroxysmal AF has been accumulating, mainly from post hoc analyses of large randomized controlled trials (RCTs) of oral anticoagulants (OACs) or antiplatelets for AF patients and an AF registry. Because previous reports mainly included primary prevention cohorts; the role of AF type in the risk stratification is still unclear in secondary prevention cohorts. Furthermore, there have been little data showing the effect of AF type on initial stroke severity and clinical independence after stroke/TIA. Therefore, we conducted a subanalysis to assess differences in initial stroke severity, functional independence after stroke/TIA, and ischemic and hemorrhagic events between patients with paroxysmal AF and those with persistent or permanent AF using the SAMURAI-NVAF registry (Stroke Management With Urgent Risk-Factor Assessment and Improvement-Nonvalvular AF: ClinicalTrials. gov identifier: NCT01581502; the Japanese University Hospital Medical Information Network Clinical Trials Registry: UMIN000006930), a large secondary prevention cohort.

Methods
The SAMURAI-NVAF study is an ongoing prospective, multicenter, observational study designed to determine choices of anticoagulant therapy during the acute and chronic stages of ischemic stroke/TIA and short- and long-term outcomes, including stroke recurrence and bleeding complications, in patients with NVAF. The main baseline data were published elsewhere. In brief, we enrolled 1192 acute ischemic stroke/TIA patients with NVAF who were hospitalized within 7 days after onset between April 2011 and March 2014 from 18 Japanese stroke centers. Ischemic stroke and TIA were diagnosed based on rapidly developing clinical signs of focal (or global) disturbance of cerebral function with no apparent cause other than a vascular origin that was confirmed by computed tomography or magnetic resonance imaging. NVAF was diagnosed on 12-lead ECG or 24-hour or longer monitoring for AF detection during acute hospitalization or from previous medical documents. Baseline clinical information such as sex, age, vascular risk factors, congestive heart failure, CHADS$_2$ score, HAS-BLED score, stroke features (infarct size, neurological severity assessed by the National Institutes of Health Stroke Scale [NIHSS] score on admission, 3-month functional outcome assessed by modified Rankin Scale score), creatinine clearance (Cockcroft–Gault Equation), and choice of OACs (warfarin or non–vitamin K antagonist oral anticoagulants [NOACs]) at 30 days after onset or at discharge, and others were registered via a web-based registration system. The CHADS$_2$ score is a scoring system for the prediction of stroke risk in patients with AF. One point is given for each of congestive heart failure, hypertension, age 275 years, and diabetes mellitus. Two points are given for any previous stroke or embolic episode. The HAS-BLED (an acronym for hypertension, abnormal renal and liver function, prior stroke, bleeding history or predisposition, labile international normalized ratios, elderly, and drug or alcohol) score is a scoring system for bleeding risk in patients with AF. One point each is given for hypertension (systolic blood pressure >160 mm Hg), renal abnormal liver function, previous stroke, age >65 years, previous major bleeding or predisposition, labile international normalized ratios (<60% of time in therapeutic range) on warfarin, drug use of antiplatelet or nonsteroidal anti-inflammatory drugs, and alcohol use. Two-year observation for short- and long-term outcomes will be ending in 2016.

AF type was defined as follows: paroxysmal AF is defined as recurrent AF that terminates spontaneously; persistent AF can be terminated by either pharmacological therapy or electric cardioversion; and permanent AF has been present for a long time and pharmacological or electric cardioversion has not been performed, or one or several attempts have failed to restore sinus rhythm. In this study, we combined persistent AF and permanent AF into 1 category (sustained AF) because discrimination between persistent and permanent AF is sometimes difficult at the time of enrollment. Patients were assigned to the paroxysmal AF or sustained AF group at the time of enrollment based on the attending physician’s judgment with baseline ECG recordings, long-term ECG monitoring, and previous clinical history, irrespective of later changes during follow-up. We compared baseline clinical characteristics, initial neurological severity, 3-month functional independence defined by modified Rankin Scale score of 0 to 2 after the index event, and ischemic and hemorrhagic outcomes. The primary efficacy end point in this analysis was stroke or systemic embolism, and the primary safety end point was a major bleeding event. Secondary end points included ischemic stroke or TIA, intracranial hemorrhage, and all-cause death during the follow-up period. Follow-up to assess end points was performed at 3 months and 1 year after the index event, and 2-year follow-up is ongoing at a hospital clinic (or by telephone survey for patients with too severe aftereffects to visit the clinic).

Statistical Analysis
Continuous variables were compared using the Student t test or Mann–Whitney U test on the basis of the distribution and are presented as mean±SD or median and interquartile range. Categorical variables are expressed as numbers and percentages. Categorical variables were compared using the χ$^2$ test or Fisher exact test as appropriate. About analyses for functional independence (modified Rankin Scale score of 0–2) at 3 months, patients with previous modified Rankin Scale score of 3 to 5 were excluded. The Kaplan–Meier method was used to estimate the cumulative rates of clinical events. We also calculated each incidence per person-year. We performed multivariable analysis using a logistic regression model for 3-month independence. Sex, age, previous anticoagulation, and initial NIHSS were used as confounding factors of 3-month independence. We performed multivariable analysis using a Cox proportional hazards model for primary and secondary end points. Sex, age, initial NIHSS score, presence of congestive heart failure, hypertension, diabetes mellitus, previous stroke/TIA, previous intracerebral hemorrhage, vascular disease, ischemic heart disease, renal insufficiency, liver insufficiency, history of hemorrhage, antiplatelet or nonsteroidal anti-inflammatory drug, habitual drinking, dyslipidemia, current smoking, large infarct size, and creatinine clearance (Cockcroft–Gault Equation), and use of NOAC (versus warfarin) were used as potential confounding factors of primary and secondary end points.

Data analysis was performed with JMP version 12.0 (SAS Institute, Cary, NC). P<0.05 in the 2-sided test was considered statistically significant.
Results
A total of 1192 patients (527 women; 77.7±9.9 years old) were enrolled by the end of March 2014. Among these patients, 758 (63.6%) had sustained AF and 434 patients (36.4%) had paroxysmal AF. The number of patients who completed follow-up and those lost was 1135 and 57, respectively, at 3 months, 1056 and 136, respectively, at 1 year and 828 and 95, respectively, at 2 years after the index ischemic stroke or TIA, and 269 patients were still scheduled to have 2-year follow-up. The median follow-up period was 1.8 (interquartile range, 0.93–2.0) years.

The baseline characteristics and index stroke features are summarized in Table 1. Patients with sustained AF more commonly had congestive heart failure, previous stroke/TIA, history of hemorrhage, and previous warfarin intake and were

<table>
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<tr>
<th>Table 1. Baseline Characteristics, Baseline Neurological Severity, Functional Status, and CHADS2/HAS-BLED Scores After Stroke/TIA</th>
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<tbody>
<tr>
<td><strong>Total (n=1192)</strong></td>
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<tr>
<td><strong>Women</strong></td>
</tr>
<tr>
<td><strong>Age, y</strong></td>
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<tr>
<td><strong>Body weight, kg</strong></td>
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<tr>
<td><strong>Congestive heart failure</strong></td>
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<td><strong>Hypertension</strong></td>
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<td><strong>Diabetes mellitus</strong></td>
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<td><strong>Previous stroke/TIA</strong></td>
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<tr>
<td><strong>Previous intracerebral hemorrhage</strong></td>
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<td><strong>Vascular disease</strong></td>
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<td><strong>Ischemic heart disease</strong></td>
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<td><strong>Labile PT-INRs on previous warfarin</strong></td>
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<tr>
<td><strong>Renal insufficiency</strong></td>
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<td><strong>Liver insufficiency</strong></td>
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<td><strong>History of hemorrhage</strong></td>
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<td><strong>Previous drug (antiplatelet or NSAIDs)</strong></td>
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<td><strong>Habitual drinking</strong></td>
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<td><strong>Dyslipidemia</strong></td>
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<td><strong>Current smoking</strong></td>
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<tr>
<td><strong>Previous warfarin</strong></td>
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<tr>
<td><strong>Previous dabigatran/rivaroxaban/apixaban</strong></td>
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<tr>
<td><strong>Previous antplatelet</strong></td>
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<td><strong>Previous antihypertensive drug</strong></td>
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<td><strong>Previous oral hypoglycemic agent</strong></td>
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<td><strong>Previous insulin</strong></td>
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<td><strong>Previous statin</strong></td>
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<tr>
<td><strong>Large size infarct</strong></td>
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<tr>
<td><strong>Creatinine clearance, mL/min</strong></td>
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<td><strong>Baseline NIHSS score</strong></td>
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<td><strong>mRS score at 3 mo after stroke/TIA†</strong></td>
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<tr>
<td><strong>Functional independence (mRS, 0–2)†</strong></td>
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<tr>
<td><strong>CHADS2 after stroke/TIA</strong></td>
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<td><strong>HAS-BLED after stroke/TIA</strong></td>
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Data are presented as mean±SD, median (interquartile range), or number (percent). AF indicates atrial fibrillation; CHADS2, an acronym for congestive heart failure, hypertension, age ≥75, diabetes mellitus, and prior stroke or TIA; HAS-BLED, an acronym for hypertension, abnormal renal and liver function, prior stroke, bleeding history or predisposition, labile international normalized ratios, elderly, and drug or alcohol; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NSAID, nonsteroidal anti-inflammatory drug; PT-INR, international normalized ratios of prothrombin time; and TIA, transient ischemic attack.

*Infarct of more than one third of the affected cerebral artery territory.
†Excluding patients with previous mRS scores of 3–5.
more likely to have liver insufficiency and alcohol intake than those with paroxysmal AF. Baseline NIHSS scores tended to be higher in patients with sustained AF than in those with paroxysmal AF. Three-month independence was more commonly observed in the paroxysmal AF group than in the persistent AF group. After adjusting for sex, age, previous warfarin use, and initial NIHSS, paroxysmal AF (versus sustained AF) was independently associated with 3-month independence (adjusted odd ratio, 1.67; 95% confidence interval, 1.18–2.37; 
P =0.004). The CHADS, and HAS-BLED scores were significantly higher in patients with sustained AF than in patients with paroxysmal AF. Of patients with sustained AF and those with paroxysmal AF, 718 (94.7%) and 419 (96.5%), respectively, received OACs during acute hospitalization (Table 2). Patients with sustained AF were more frequently taking warfarin than those with paroxysmal AF.

The numbers of all ischemic events, major bleeding events, stroke or systemic embolism, and any cause of death during the follow-up period are shown in Table 3. Stroke or systemic embolism occurred in 81 patients with sustained AF and in 29 with paroxysmal AF. Major bleeding events occurred in 34 and 20, respectively, and 153 and 63 patients died, respectively. The annual incidence of stroke or systemic embolism was 8.3 and 4.6 per 100 person-years, respectively, and that of major bleeding events was 3.4 and 3.1, respectively (Table 4). About secondary outcomes, the incidence of ischemic stroke or TIA was 7.8 and 3.6, that of intracranial hemorrhage was 1.5 and 1.2, and that of mortality was 14.7 and 9.7. After adjustment for potential confounding factors, sustained AF was an independent risk factor for stroke or systemic embolism (adjusted hazard ratio, 1.95; 95% confidence interval, 1.26–3.14; 
P =0.003) and that of ischemic stroke or TIA (adjusted hazard ratio, 2.15; 95% confidence interval, 1.34–3.59; 
P =0.001). There were no significant differences on the rate of major bleeding, intracranial hemorrhage, or mortality between patients with sustained AF and those with paroxysmal AF after multivariate adjustments. Kaplan–Meier curves for the rate of stroke/systemic embolism, major bleeding, ischemic stroke/TIA, intracranial hemorrhage, and mortality are shown in Figures 1 and 2. A higher risk of stroke/systemic embolism and ischemic stroke/TIA during the follow-up period was consistently more frequently observed in patients with sustained AF versus in those with paroxysmal AF.

### Discussion

Using the SAMURAI-NVAF study database, which was created from a secondary prevention cohort, we observed that patients with sustained AF had a higher rate of stroke or systemic embolism and a higher rate of ischemic stroke or TIA than those with paroxysmal AF. We also observed that 3-month functional independence was less attainable for patients with sustained AF than for those with paroxysmal AF. Our data showed the difference in thromboembolism risk between patients with sustained AF and those with paroxysmal AF in a large secondary prevention cohort.

There is a well-known controversy about the type of AF and the risk of thromboembolism. Several major studies, including the substudy of the ACTIVE-W (Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events), the SPAF study (Stroke Prevention in Atrial Fibrillation), and the report from the Stockholm cohort showed similar risk for thromboembolic events between patients with sustained AF and those with paroxysmal AF.6–8 The Loire Valley Atrial Fibrillation Project with a large real-world cohort did not show a difference between patients with paroxysmal AF and those with permanent AF after multivariate adjustments.9 In contrast, recent post hoc analyses or a combined analysis of RCTs on NOACs have shown a higher risk of thromboembolism in patients with sustained AF than in those with paroxysmal AF.11–13 Such inconsistent results on the AF type and risk of thromboembolism might be attributable to the difference in the frequency of oral anticoagulant use among reports. In the former studies, the
rate of anticoagulation therapy was generally low in patients with paroxysmal AF than in those with sustained AF: 64.8% versus 79.5% in the ACTIVE-W substudy, 28% versus 49% in the Stockholm cohort, and none for either group in the SPAF study. The tendency for underuse of anticoagulants for patients with paroxysmal AF might close the gap of the incidence for thromboembolism. In contrast, all participants received a NOAC or warfarin in the ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) and the ARISTOTLE trials (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation),11,12 or all had aspirin in 1 pooled analysis.13 Another possible reason for the inconsistent results might be because of the difference in thromboembolic risk indices scores among reports. The mean CHADS2 score was ≈2 in the ACTIVE-W substudy and the Stockholm cohort, whereas it was >3 in recent reports11,12 and ≈4 in the present study. Thus, the difference in ischemic risk between 2 AF types can be clearer as the scores of ischemic risk indices among the study subjects are higher, in particular the subjects have high frequency of previous stroke like the present cohort.

There are few prospective studies from Asian countries about the association between types of AF and thromboembolic risk. There could be ethnic differences in the prognosis of NV AF patients.18 In the J-RHYTHM Registry (a large, contemporary, prospective observational investigation, with a 2-year follow-up, of patients with AF) from Japan, crude rate of thromboembolic events was higher in permanent NV AF than in paroxysmal NV AF, but the difference was no more significant after adjusting for CHADS2 or CHA2DS2-VASc components.19 Recently, the Fushimi Atrial Fibrillation Registry (a large prospective community-based cohort of Japanese patients with AF) showed a higher risk of stroke/systemic embolism in patients with sustained AF than in those with paroxysmal AF, regardless of whether they were on oral anticoagulants, and even after multivariate adjustments.14 Both the J-RHYTHM Registry and Fushimi Registry mainly included

Table 4. Event Incidences and Hazard Ratios of Outcomes

<table>
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<tr>
<th></th>
<th>Incidences (per 100 Person-Years)</th>
<th>Hazard Ratio (95% CI) for Sustained vs Paroxysmal AF</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Sustained AF</td>
<td>Paroxysmal AF</td>
</tr>
<tr>
<td>Primary outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke or systemic embolism</td>
<td>8.3</td>
<td>4.6</td>
</tr>
<tr>
<td>Major bleeding events</td>
<td>3.4</td>
<td>3.1</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke or TIA</td>
<td>7.8</td>
<td>3.6</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>1.5</td>
<td>1.2</td>
</tr>
<tr>
<td>Mortality</td>
<td>14.7</td>
<td>9.7</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; CI, confidence interval; and TIA, transient ischemic attack.

*Adjusted for sex, age, initial National Institutes of Health Stroke Scale score, the presence of congestive heart failure, hypertension, diabetes mellitus, previous stroke/TIA, previous intracerebral hemorrhage, vascular disease, ischemic heart disease, renal insufficiency, liver insufficiency, history of hemorrhage, antiplatelet or nonsteroidal anti-inflammatory drug, habitual drinking, dyslipidemia, current smoking, large infarct size, and creatinine clearance (Cockcroft–Gault Equation), and use of non–vitamin K antagonist oral anticoagulant (versus warfarin).
patients free from stroke or TIA. Because our results were similar to those of RCTs on NOACs from Western countries and the Fushimi Registry, the risk difference of thromboembolism among types of AF is likely to be similar among Western countries and Asian countries.

Long-term thromboembolic risk could be attributable to thrombus formation tendency in the left atrial appendage (LAA). Because patients with sustained AF have larger LAA size and severer LAA blood stasis (lower LAA ejection fraction) than those with paroxysmal AF,20,21 cardiac clots in LAA are likely to grow in size and become organized in those with sustained AF when compared with those with paroxysmal AF. Therefore, patients with sustained AF seem to have a long-term higher risk of thromboembolism than those with paroxysmal AF.

About stroke severity and short-term independence after ischemic stroke or TIA, Naess et al22 reported that patients with sustained AF had more severe neurological deficits and poorer short-term outcome at 7 days after ischemic stroke in a single-center registry. Deguchi et al23,24 also reported similar findings using a single-center retrospective study and a large registry in the Japanese Stroke data bank. Our findings are in line with these previous reports in this regard although the difference in initial stroke severity was not significant. In our cohort, patients with sustained AF were more dependent at 3 months than those with paroxysmal AF although the former more frequently took warfarin before initial stroke/TIA than the latter. Stroke severity and short-term functional outcomes could be also attributable to the thrombus formation tendency in the LAA. Because the morphological and functional differences in the LAA between the 2 groups may affect cardiac embolus size and hardness or resistance to thrombolysis, these may affect stroke severity and short-term functional outcome.

From the post hoc analyses of recent RCTs, the Fushimi registry and this study, the type of AF seems to affect the incidence of thromboembolism. Therefore, the prevention strategy for ischemic event may improve with the involvement of the AF type into the risk stratification scheme. Because the progression from paroxysmal to sustained AF is likely to cause a higher risk of thromboembolism, prevention with catheter ablation or drugs could be beneficial in patients with paroxysmal AF.

There were several limitations to this study. First, baseline characteristics were considerably different between the patients with different AF types because this was an observational study. Although potential confounding factors were adjusted, this might have caused a selection bias. Second, permanent AF was not distinguished from persistent AF. These 2 types of AF may have different risks of thromboembolism. Third, we did not evaluate the details of LAA in this cohort although we suggested the difference of morphological and functional change in the LAA between the 2 groups. Fourth, our follow-up method either in the outpatient clinic or by telephone survey may have caused a bias to detect clinical end points. Of patients who had follow-up and were alive, at least 71.6% with sustained AF and 79.5% with paroxysmal AF at 3 months, 71.7% and 78.8%, respectively, at 1 year and 75.5% and 82.6%, respectively, at 2 years had a clinic follow-up based on blood pressure measurement records at the clinic in our case report forms. Finally, we adjusted the models using potential confounding diseases (eg, the presence of hypertension), but could not adequately control for disease severity (eg, duration and severity of hypertension). Because patients with persistent AF were generally older and sicker than those with paroxysmal AF, severity of each confounding disease might be different among groups.

In conclusion, our study shows that patients with persistent or permanent AF who recently had ischemic stroke or TIA had a lower rate of short-term independence, a higher rate of stroke or systemic embolism, and a higher rate of ischemic stroke or TIA during ≈2-year follow-up period than those with paroxysmal AF. These findings are consistent with those from recent post hoc analyses of RCTs of OACs and a subanalysis of a prospective population-based cohort, which both mainly included patients who did not have ischemic stroke or TIA. The prevention of progress to persistent AF from paroxysmal AF may be beneficial for secondary prevention in patients with NVAF.

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Disclosures
None.

References
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SUPPLEMENTAL MATERIAL

APPENDIX

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