OPEN

Atrial Fibrillation-Associated Ischemic Stroke Patients With Prior Anticoagulation Have Higher Risk for Recurrent Stroke

Kanta Tanaka, MD; Masatoshi Koga, MD, PhD;
Keon-Joo Lee, MD; Beom Joon Kim, MD, PhD; Eun Lyeong Park, MSc; Juneyoung Lee, PhD;
Tadataka Mizoguchi, MD; Sohei Yoshimura, MD, PhD; Jae-Kwan Cha, MD, PhD;
Byung-Chul Lee, MD, PhD; Jin Nakahara, MD, PhD; Norihiro Suzuki, MD, PhD;
Hee-Joon Bae, MD, PhD; Kazunori Toyoda, MD, PhD;
for the CRCS-K Investigators and the SAMURAI Study Investigators

Background and Purpose—Ischemic stroke associated with nonvalvular atrial fibrillation (NVAF) despite prior anticoagulation may indicate underlying problems that nullify the stroke-preventing effects of oral anticoagulants. We aimed to evaluate the risk for recurrent stroke in patients with NVAF with prior anticoagulation, compared with that in patients without prior anticoagulation.

Methods—This study comprised pooled individual patient data on NVAF-associated acute ischemic stroke or transient ischemic attack from 2011 to 2014 arising from the Clinical Research Collaboration for Stroke in Korea (15 South Korean stroke centers) and the Stroke Acute Management With Urgent Risk-Factor Assessment and Improvement-NVAF registry (18 Japanese stroke centers). Data on 4841 eligible patients from the Clinical Research Collaboration for Stroke in Korea registry were pooled with data on all patients (n=1192) in the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement-NVAF registry. The primary outcome was recurrent ischemic stroke. The secondary outcomes were hemorrhagic stroke and all-cause death. Outcome events were captured up to 1 year after the index event.

Results—Among the 6033 patients in the full cohort, 5645 patients were analyzed, of whom 1129 patients (20.0%) had received prior anticoagulation. Median age was 75 years (interquartile range, 69–81 years), and 2649 patients (46.9%) were women. Follow-up data of 4617 patient-years (median follow-up 365 days, interquartile range 335–365 days) were available. The cumulative incidence of recurrent ischemic stroke in patients with prior anticoagulation was 5.3% (60/1129), compared with the 2.9% (130/4516) incidence in patients without prior anticoagulation. The risk for recurrent ischemic stroke was higher in patients with prior anticoagulation than in those without (multivariable Cox shared-frailty model, hazard ratio 1.50 [95% CI, 1.02–2.21]). No significant differences in the risks for hemorrhagic stroke and mortality were seen between the 2 groups.

Conclusions—The risk for recurrent ischemic stroke may be higher in NVAF-associated stroke patients with prior anticoagulation than in those without prior anticoagulation.

Registration—URL: https://www.clinicaltrials.gov; Unique identifier: NCT01581502.

(*Stroke*. 2020;51:1150-1157. DOI: 10.1161/STROKEAHA.119.027275.)

Key Words: anticoagulants ■ atrial fibrillation ■ death ■ incidence ■ risk

Owing to the dissemination of evidence-based medicine from clinical trials into routine practice, the underuse of anticoagulants for nonvalvular atrial fibrillation (NVAF) is gradually decreasing.[1,2] However, a substantial number of patients with NVAF experience ischemic stroke even under anticoagulation.[2–4] NVAF-associated ischemic stroke despite prior anticoagulation indicates the potential presence of underlying problems that nullify the thromboembolism-preventing

Received August 6, 2019; final revision received January 17, 2020; accepted January 27, 2020.

From the Division of Stroke Care Unit (K. Tanaka) and Department of Cerebrovascular Medicine (M.K., T.M., S.Y., K. Toyoda), National Cerebral and Cardiovascular Center, Suita, Japan; Department of Neurology, Keio University School of Medicine, Tokyo, Japan (K. Tanaka, J.N., N.S., K. Toyoda); Department of Neurology, Cerebrovascular Center, Seoul National University Bundang Hospital, Seongnam-si, South Korea (K.-J.L., B.J.K.); Department of Biostatistics, College of Medicine, Korea University, Seoul, South Korea (E.L.P., J.L., H.-J.B.); Department of Neurology, Dong-A University Hospital, Busan, Korea (J.-K.C.); and Department of Neurology, Hallym University Sacred Heart Hospital, Anyang, Korea (B.-C.L.).

The Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/ 10.1161/STROKEAHA.119.027275.

Correspondence to Masatoshi Koga, MD, PhD, Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, 6-1 Kishibe Shimmachi, Suita 564-8565, Japan. Email koga@ncvc.go.jp

effects of oral anticoagulants, which may include drug noncompliance or other biological factors, including a higher-risk profile of NVAF. This important issue, however, has been escaping attention in the field of stroke care. Here, we hypothesized that patients with NVAF-associated stroke with prior anticoagulation are at a higher risk for recurrent ischemic stroke, compared with anticoagulation-naïve patients. The objective of the present study was to investigate the risk for recurrent stroke in patients with NVAF with prior anticoagulation, compared with that in patients without prior anticoagulation.

Methods

Study Population

We built the East-Asian Ischemic Stroke Patients With Atrial Fibrillation (EAST-AF) registry, which comprised pooled individual patient data from 2 prospective cohort studies, including (1) the Clinical Research Collaboration for Stroke in Korea (CRCS-K, 15 centers in South Korea) and (2) the Stroke Acute Management With Urgent Risk-Factor Assessment and Improvement (SAMURAI)-NVAF registry (18 centers in Japan). The CRCS-K registry is a prospective, ongoing, nationwide, multicenter acute stroke registry in South Korea that has recruited patients with acute stroke or transient ischemic attack (TIA) admitted within 7 days from onset.[5,6] The SAMURAI-NVAF registry was a prospective, multicenter, observational study in Japan designed to determine the choice of anticoagulant therapy during the acute and chronic stages of ischemic stroke/TIA and the short- and long-term outcomes in patients with NVAF. In the SAMURAI-NVAF registry, patients who were hospitalized within 7 days after the onset of ischemic stroke/TIA and who were diagnosed as having NVAF between September 2011 and March 2014 were enrolled.[7–9] The study was registered with the ClinicalTrials.gov and the Japanese University Hospital Medical Information Network Clinical Trials Registry (UMIN000006930). Details of the 2 registries can be obtained from the published reports.[5–9]

At the Korea University, patient information in the CRCS-K registry from January 2011 to December 2014 was pooled with that of the SAMURAI-NVAF registry. From the CRCS-K registry, we included patients aged ≥18 years old and had (1) ischemic stroke or TIA and (2) a diagnosis of NVAF. NVAF was diagnosed from 12-lead electrocardiograms or monitoring for ≥24 hours during acute hospitalization or from previous medical documents. We excluded patients with (1) history of prosthetic valve replacement or hemodynamically relevant mitral valve stenosis or (2) follow-up data unavailable. Consequently, we made a full cohort of the EAST-AF registry (n=6033) using the data of all patients registered to the SAMURAI-NVAF registry (n=1192) and of 4841 eligible patients from the CRCS-K registry.

For the SAMURAI-NVAF registry, secondary use of the data set for this study was approved by the ethics committees of the National Cerebral and Cardiovascular Center. For the CRCS-K registry, data collection and analysis for this study were approved by the ethics committees of the participating centers. The corresponding author had full access to all the data of the EAST-AF registry. Anonymized data that support the findings of this study are available from the corresponding author, upon reasonable request and after permission from the ethics committees.

Clinical Data Collection

The following clinical data were collected: country, registering center, age, sex, prestroke modified Rankin Scale score, body weight, smoking, timing of NVAF detection relative to the index event (known prior or detected after),[10] vascular risk factors (hypertension, diabetes mellitus, and hyperlipidemia), past medical history (stroke, congestive heart failure, and coronary heart disease), prestroke anticoagulation, prestroke antiplatelets, type of index event (ischemic stroke or TIA), baseline National Institutes of Health Stroke Scale score,[11] laboratory data (white blood cell count, hemoglobin, platelet count, glucose, creatinine, and prothrombin time/international normalized ratio [PT-INR]), renal dysfunction, active malignancy (only in the data from the SAMURAI-NVAF registry), and medications at discharge (antiplatelets, warfarin, direct oral anticoagulants, and statins). Creatinine clearance was calculated using the Cockcroft-Gault Equation.[12] Renal dysfunction was defined as creatinine clearance <30 mL/min. Antiplatelets included aspirin, clopidogrel, dipyridamole, ticlopidine, and cilostazol. Direct oral anticoagulants included dabigatran, apixaban, and rivaroxaban; during the study period, edoxaban had not yet been approved in Japan and South Korea.

Outcome Events and Follow-Up Period

The primary outcome was recurrent ischemic stroke. The secondary outcomes were hemorrhagic stroke and all-cause death, including fatal stroke. In the SAMURAI-NVAF registry, follow-up to assess the outcome events was performed at 3 months, 1 year, and 2 years after the index event, personally in the clinic or by telephone interview of the patients or caregivers by the study physicians or trained study coordinators at the participating hospitals. In the CRCS-K registry, the outcome events were collected at 3 months and 1 year after the index event by identification of the events in usual clinical practice or by structured telephone interview by trained study coordinators at the participating hospitals. In this study, the outcome events were captured up to 1 year after the index event. Information about PT-INR at the time of recurrent ischemic stroke was collected whenever possible.

Statistical Analysis

The demographics and clinical characteristics according to the presence or absence of anticoagulant therapy before the index events were summarized as median (interquartile range [IQR]) for continuous variables and as frequencies and percentages for categorical variables. Statistical differences between the 2 groups were assessed using the Mann-Whitney *U* test or Pearson χ^2 test, as appropriate.

The cumulative incidences of the primary and secondary outcomes at 1 year were calculated. Univariate Kaplan-Meier survival probabilities were estimated for those with and without prior anticoagulation, and we used the log-rank test to compare groups. We constructed univariate and multivariable Cox proportional hazard models with adjustments for age, sex, timing of NVAF detection, history of stroke, congestive heart failure, coronary heart disease, hypertension, diabetes mellitus, baseline National Institutes of Health Stroke Scale score, PT-INR, renal dysfunction, oral anticoagulant therapy at discharge, and statins at discharge. To account for the heterogeneity caused by unmeasured covariates among the centers, a shared gamma distributed frailty clustered by registering centers was included into the multivariable Cox models.[13] In addition, to reduce biases between the 2 groups besides the prespecified adjusting covariates, we applied inverse probability of treatment weighting (IPTW) with the multivariable Cox models. The propensity score for each group was estimated using a logistic regression model, which included all of the 27 clinical variables other than active malignancy. A third-order polynomial term of PT-INR was also included (C statistics 0.91). After calculating weight values by the IPTW estimators (1/propensity score for patients with prior anticoagulation; 1/[1−propensity score] for those without prior anticoagulation), weight was trimmed at the 5th and 95th percentiles to avoid extreme weight.[14] Thereafter, data balancing was assessed using absolute standardized differences, most of which were within the margin of 0.10 after IPTW.[15,16] The absolute standardized differences in timing of NVAF detection, history of stroke, and PT-INR, which were prespecified as the adjusting covariates for multivariable models, insistently remained >0.25.[17] We assessed the proportional hazards assumption through visual inspection of log-log plots of the log cumulative hazard against log time. Hazard ratios (HR) with 95% CIs were calculated, and $P<0.05$ was considered statistically significant. Because hemorrhagic stroke and death could compete with ischemic stroke events, we constructed the Fine and Gray competing-risks models, where the above-mentioned prespecified adjusting covariates were included with IPTW.[13] Missing values were accounted for by multiple imputations with chained equations. Inferential statistics were obtained from 40 imputed data sets.

Exploratory subgroup analyses were performed on the basis of patient characteristics, including country, age (<65 and ≥65 years), sex, prestroke modified Rankin Scale score (0–1 and ≥2), timing of NVAF detection, vascular risk factors (hypertension and diabetes mellitus), past medical history (stroke, congestive heart failure, and coronary heart disease), baseline National Institutes of Health Stroke Scale score (0–10 and >10), PT-INR (<2.0 and ≥2.0), renal dysfunction, oral anticoagulant therapy at discharge (warfarin and direct oral anticoagulants), and statins at discharge. We undertook sensitivity analyses to confirm the robustness of our results by excluding patients without oral anticoagulation at hospital discharge. The purpose of this sensitivity analysis was to remove the selection bias for administering

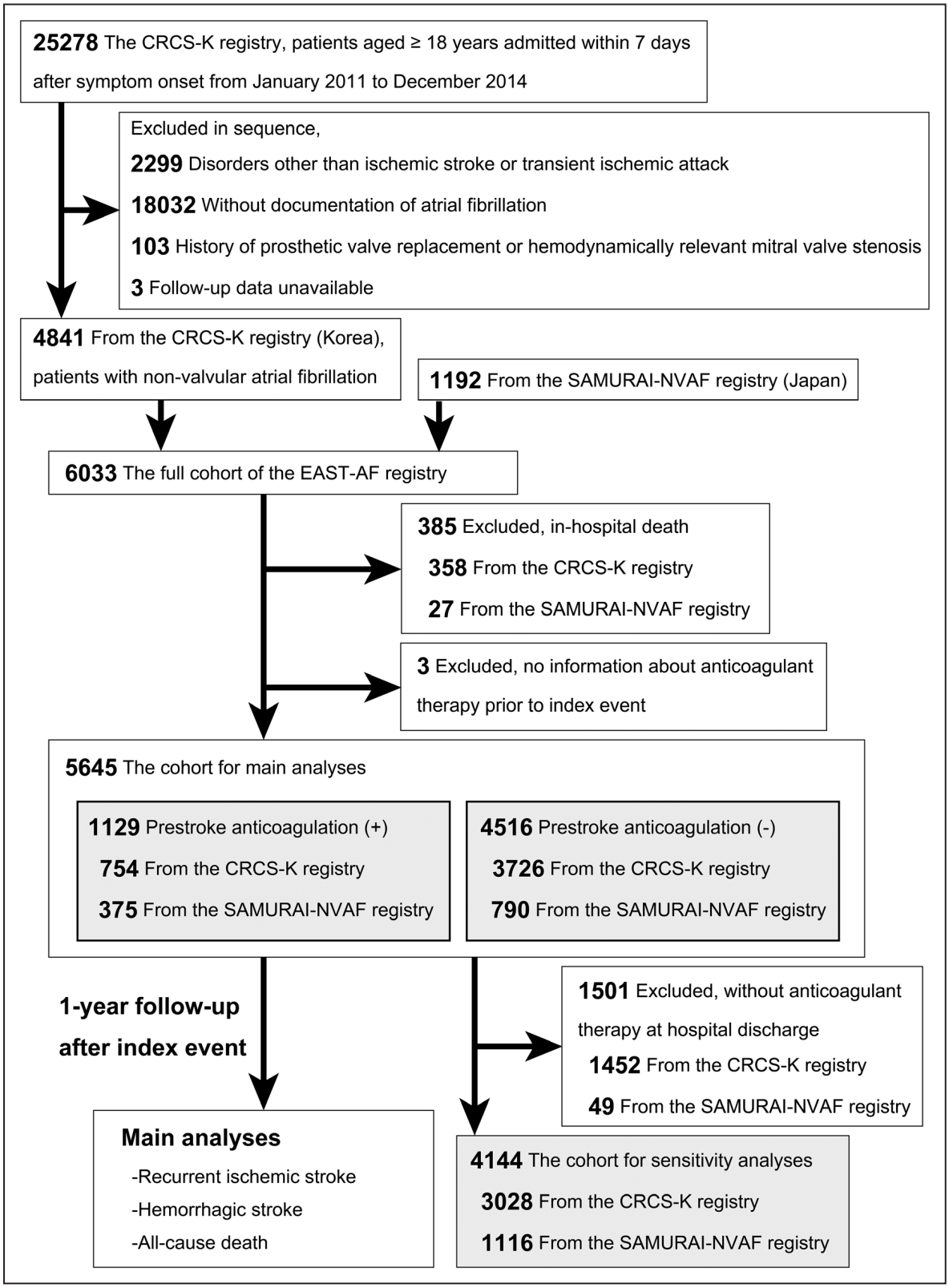

Figure 1. Study flow chart. CRCS-K indicates Clinical Research Collaboration for Stroke in Korea; EAST-AF, East-Asian Ischemic Stroke Patients With Atrial Fibrillation; and SAMURAI-NVAF, Stroke Acute Management With Urgent Risk-Factor Assessment and Improvement-NonValvular Atrial Fibrillation.

oral anticoagulants at hospital discharge between patients with and without prior anticoagulation. In the subgroup and sensitivity analyses, missing values were handled using a pairwise deletion method.

All statistical analyses were performed using the Stata/IC statistical package (version 15.1; Stata Corp LP, College Station, TX).

Results

The study flow chart is shown in Figure 1. From the full cohort of 6033 patients, we excluded cases of in-hospital death, because its rates differed substantially between the

Table 1. Baseline Clinical Data According to Presence or Absence of Prior Anticoagulation

	Prior Anticoagulation (+) (n = 1129)	Prior Anticoagulation (–) (n = 4516)	*P* Value
South Korea, N (%)	757 (66.8)	3726 (82.5)	<0.01
Age, median (IQR), y	75 (70–80)	75 (68–82)	0.68
Female sex, N (%)	516 (45.7)	2133 (47.2)	0.35
Prestroke mRS score, median (IQR)	0 (0–2)	0 (0–1)	<0.01
Body weight, median (IQR), kg	60 (50–66.8)	60 (51.8–68)	<0.01
Smoking, N (%)	337 (29.9)	1403 (31.1)	0.42
NVAF known before index event, N (%)	1071 (94.9)	2151 (47.6)	<0.01
Vascular risk factor, N (%)			
Hypertension	869 (76.9)	3259 (72.2)	<0.01
Diabetes mellitus	317 (28.1)	1191 (26.4)	0.24
Hyperlipidemia	399 (35.3)	1256 (27.8)	<0.01
Past clinical history, N (%)			
Stroke before index event	542 (48.0)	837 (18.5)	<0.01
Congestive heart failure	167 (14.8)	298 (6.6)	<0.01
Coronary heart disease	158 (13.9)	530 (11.7)	0.03
Prestroke antiplatelets, N (%)	235 (20.8)	1821 (40.3)	<0.01
Ischemic stroke as index event, N (%)	1081 (95.8)	4398 (97.4)	<0.01
Baseline NIHSS score, median (IQR)	7 (2–15)	8 (3–16)	<0.01
Laboratory data, median (IQR)			
White blood cell count, /μL	7200 (5800–8900)	7600 (6100–9640)	<0.01
Hemoglobin, g/dL	13.4 (12–14.7)	13.5 (12.2–14.7)	0.01
Platelet count, $\times 10^3/\mu L$	187 (153–228)	196 (161–237)	<0.01
Glucose, mg/dL	124 (105–151)	124 (106–153)	0.40
PT-INR	1.28 (1.1–1.66)	1.04 (0.99–1.1)	<0.01
Renal dysfunction, N (%)*	124 (10.9)	491 (10.9)	0.91
Active malignancy, N (%)†	15 (4.0), n=375	15 (1.9), n=790	0.03
Medication at discharge, N (%)			
Antiplatelets	326 (28.9)	1482 (32.8)	0.01
Warfarin	771 (68.3)	2796 (61.9)	<0.01
Direct oral anticoagulants	152 (13.5)	428 (9.5)	<0.01
Dabigatran	68 (6.0)	197 (4.4)	
Apixaban	7 (0.6)	23 (0.5)	
Rivaroxaban	77 (6.8)	208 (4.6)	
Statins	672 (59.5)	3068 (67.9)	<0.01
mRS score at discharge, median (IQR)	3 (1–4)	3 (1–4)	0.14

IQR indicates interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NVAF, nonvalvular atrial fibrillation; PT-INR, prothrombin time/international normalized ratio; and SAMURAI, Stroke Acute Management With Urgent Risk-Factor Assessment.

*Renal dysfunction was defined as creatinine clearance <30 mL/min.

†Only in the data from the SAMURAI-NVAF registry.

SAMURAI-NVAF registry (2.3%) and the CRCS-K registry (7.4%). The cause of this difference remains unclear, but it might be due to differences in the timing of obtaining informed consent. Three patients were excluded because of the absence of information about anticoagulant therapy before the index event. The cohort consisting of the remaining 5645 patients was used for main analyses. The median age was 75 years (IQR, 69–81 years), and 2649 patients (46.9%) were women. The median baseline National Institutes of Health Stroke Scale score was 8 (IQR, 3–15). At hospital discharge, 4144 patients (73.4%) received anticoagulants.

Of the 5645 patients, 1129 patients (20.0%) had received anticoagulation before the index event. The demographic and clinical characteristics according to the presence or absence of prior anticoagulation are shown in Table 1. Compared with patients without prior anticoagulation, those with prior anticoagulation were less frequently from South Korea (P<0.01); had slightly higher prestroke modified Rankin Scale score (P<0.01); and more frequently had hypertension (P<0.01), hyperlipidemia (P<0.01), and history of stroke before the index event (P<0.01), congestive heart failure (P<0.01), and coronary heart disease (P=0.03). NVAF was known before the index event in most patients with prior anticoagulation and in half of those without prior anticoagulation (P<0.01). Anticoagulation at discharge was more prevalent in patients with prior anticoagulation than in those without prior anticoagulation (warfarin: P<0.01; direct oral anticoagulants: P<0.01). The coexistence of active malignancy was seen in 2.6% (30/1165, only in the data from the SAMURAI-NVAF registry). Patients with prior anticoagulation more frequently had active malignancy compared with those without (P=0.03).

The 5645 patients included in the main analyses provided 4617 patient-years of follow-up data (median follow-up 365 days, IQR, 335–365 days). In this population, there were 190 recurrent ischemic and 42 hemorrhagic stroke events encountered. During the follow-up period, 905 patients died. The cumulative incidence of recurrent ischemic stroke was 5.3% (60/1129) in patients with prior anticoagulation and 2.9% (130/4516) in those without prior anticoagulation. The unadjusted Kaplan-Meier curves for recurrent ischemic stroke are shown in Figure 2A. On the log-rank test, recurrent ischemic strokes were more frequent in patients with prior anticoagulation than in those without prior anticoagulation (P<0.01). In the univariate Cox proportional hazard model, the risk for recurrent ischemic stroke was significantly higher in patients with prior anticoagulation than in those without prior anticoagulation (crude HR, 1.82 [95% CI, 1.34–2.48]); this statistical significance was maintained in the multivariable Cox shared-frailty model (adjusted HR, 1.50 [95% CI, 1.02–2.21], model 1 in Table 2). The multivariable Cox model with IPTW showed a similar effect size (adjusted HR, 1.54 [95% CI, 1.01–2.37], model 2 in Table 2). Likewise, the competing-risks models showed significantly higher risk for ischemic stroke in patients with prior anticoagulation than in those without prior anticoagulation (hemorrhagic stroke as competing event: adjusted sub-HR 1.61 [95% CI, 1.02–2.53], P=0.04; death as competing event: adjusted sub-HR 1.58 [95% CI, 1.03–2.42], P=0.03). The cumulative incidence of hemorrhagic stroke was 0.6% (7/1129) in patients with prior anticoagulation and 0.8% (35/4516) in those without prior anticoagulation. The cumulative mortality was 14.4% (163/1129) in patients with prior anticoagulation and 16.4% (742/4516) in those without prior anticoagulation. No significant differences in the risks for hemorrhagic stroke and death were evident between the 2 groups (Figure 2; Table 2). For each model, visual inspection of the log-log plots suggested that the proportional hazard assumption was satisfactory.

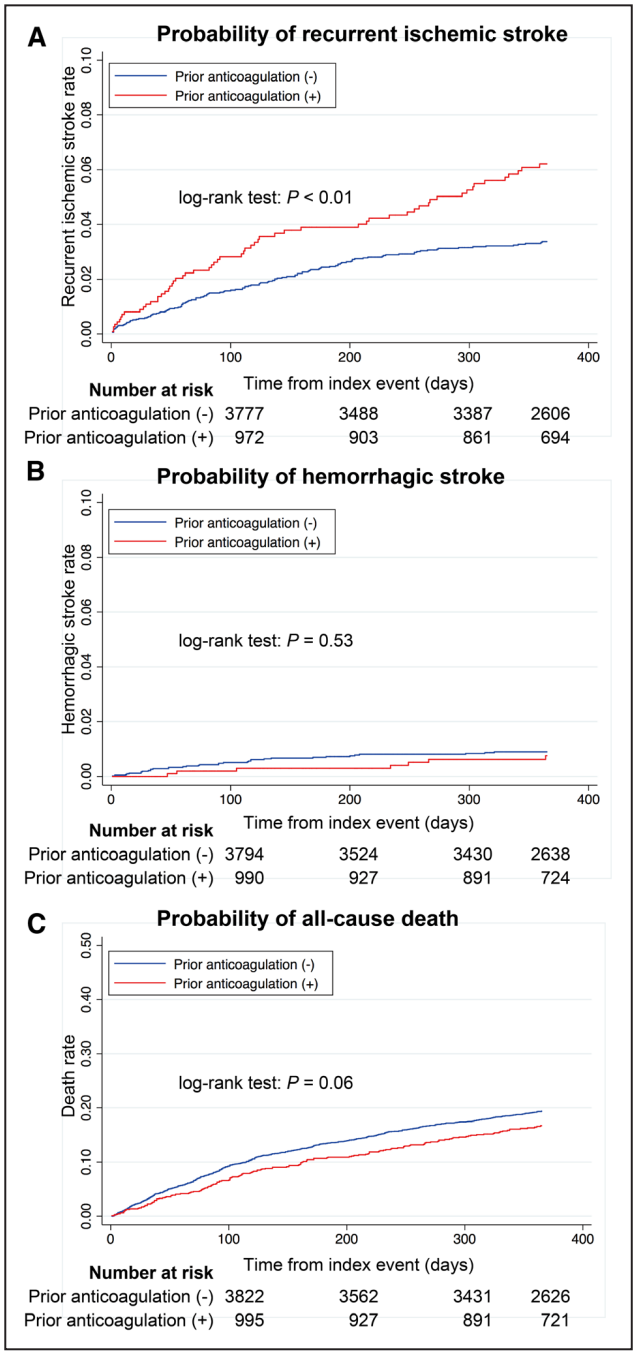

Figure 2. Recurrent ischemic strokes are more frequent in patients with prior anticoagulation than in those without prior anticoagulation. Unadjusted Kaplan-Meier curves for recurrent ischemic stroke (**A**), hemorrhagic stroke (**B**), and all-cause death (**C**).

In the subgroup analysis, no significant interactions were seen between prior anticoagulation and any patient characteristics (Figure 3). In the sensitivity analyses, the adjusted

Table 2. Hazard Ratios for the Outcomes During Follow-Up

	Crude Hazard Ratio (95% CI)	Adjusted Hazard Ratio With Shared Frailty (95% CI): Model 1*	Adjusted Hazard Ratio With IPTW (95% CI): Model 2*
Recurrent ischemic stroke			
Prior anticoagulation (–)	1 (Reference)	1 (Reference)	1 (Reference)
Prior anticoagulation (+)	1.82 (1.34–2.48); *P*<0.01	1.50 (1.02–2.21); *P*=0.03	1.54 (1.01–2.37); *P*=0.04
Hemorrhagic stroke			
Prior anticoagulation (–)	1 (Reference)	1 (Reference)	1 (Reference)
Prior anticoagulation (+)	0.77 (0.34–1.74); *P* =0.53	0.64 (0.24–1.69); *P* =0.37	0.60 (0.24–1.49); *P*=0.27
All-cause death†			
Prior anticoagulation (–)	1 (Reference)	1 (Reference)	1 (Reference)
Prior anticoagulation (+)	0.85 (0.72–1.01); *P*=0.06	0.96 (0.79–1.18); *P*=0.71	0.87 (0.69–1.10); *P*=0.25

IPTW indicates inverse probability of treatment weighting; NIHSS, National Institutes of Health Stroke Scale; NVAF, nonvalvular atrial fibrillation; and PT-INR, prothrombin time/international normalized ratio.

*Adjusted for age, sex, timing of NVAF detection, history of stroke, congestive heart failure, coronary heart disease, hypertension, diabetes mellitus, baseline NIHSS score, PT-INR, renal dysfunction, anticoagulant therapy at discharge, and statins at discharge.

†The causes of 905 deaths during the follow-up period were stroke (6.1%), cardiovascular events (3.1%), infection (19.6%), and unclear (71.2%).

HR for recurrent ischemic strokes in patients with prior anticoagulation was estimated to be 1.78 (95% CI, 1.13–2.79, *P*=0.01) in the multivariable Cox shared-frailty model. The 2 groups had similar risks for hemorrhagic stroke (adjusted HR, 0.83 [95% CI, 0.28–2.45], *P*=0.74) and all-cause death (adjusted HR 0.99 [95% CI, 0.75–1.29], *P*=0.93). The proportional hazard assumption was satisfactory for each model in the sensitivity analyses.

The PT-INR at the time of the recurrent ischemic stroke was available only in patients from the SAMURAI-NVAF registry. The median PT-INR with warfarin at the time of the recurrent ischemic stroke was 1.57 (IQR, 1.21–1.74, n=26). The PT-INR with warfarin at the time of the recurrent ischemic stroke was higher in patients who were anticoagulated before the index event (1.67 [IQR, 1.57–2.19], n=12) than in those without prior anticoagulation (1.36 [IQR, 1.15–1.68], n=14; *P*=0.03). The prevalence of active malignancy was not significantly different between patients with recurrent ischemic stroke (1.6%, 1/61) and those without it (2.6%, 29/1104; *P*=0.63).

Discussion

In this multinational East-Asian cohort that comprised pooled individual patient data from 2 prospective, observational multicenter registries of patients after NVAF-associated ischemic stroke or TIA indicates that the risk for future recurrent ischemic stroke is higher in stroke patients with prior anticoagulation than in those without prior anticoagulation. This increased risk for recurrent ischemic stroke was reproducible even in the sensitivity analysis cohort, which included only patients who were on oral anticoagulation at hospital discharge. Our data indicate that developing stroke under anticoagulation is itself a risk factor for recurrent stroke, regardless of the standard anticoagulant therapy. This finding has profound clinical implications, because clarification of the underlying mechanisms would lead to further optimization of preventive measures for NVAF-associated stroke, which remains a devastating disorder.

Drug adherence should first be considered as an underlying link in our findings. In the EAST-AF registry, most patients with prior anticoagulation were warfarin users, and the PT-INR at the time of the index event in the prior anticoagulation group was 1.28, which was fairly below the therapeutic range.[2] This may have been related with insufficient warfarin dosage, but it also indicated poor drug adherence. Based on the data from the SAMURAI-NVAF registry, the PT-INR at the time of the recurrent ischemic stroke in patients anticoagulated with warfarin was 1.57, which was also lower than the therapeutic range. However, patients who were anticoagulated before the index event had higher PT-INR at the time of the recurrent ischemic stroke, compared with that in patients without prior anticoagulation. Therefore, mechanisms other than drug adherence should be considered; these may include atrial cardiomyopathy, which is histopathologically characterized by variable degrees of interstitial fibrosis.[18,19] King et al[20] recently showed that severe atrial fibrosis, as quantified by cardiac magnetic resonance imaging, was associated with increased risk for future stroke or TIA. Stroke history and heart failure were reported to be independent predictors of thromboembolic events even in anticoagulated patients with NVAF.[21] The higher prevalence of stroke history or congestive heart failure in stroke patients with prior anticoagulation may reflect the higher-risk profile of NVAF in this patient group.

Failed anticoagulation in NVAF may indicate the importance of searching for mechanisms other than AF, including a prothrombotic state, such as in patients with malignancy. In the data from the SAMURAI-NVAF registry, active malignancy was more frequently encountered in patients with prior anticoagulation than in those without prior anticoagulation. However, the presence of malignancy was not significantly associated with recurrent ischemic stroke. In addition, the higher proportion of patients with hypertension, hyperlipidemia, or coronary heart disease suggests a greater prevalence of atherosclerotic pathology in the prior anticoagulation group.

Some limitations need to be considered when interpreting the results of the present study. First, the biases in the groups

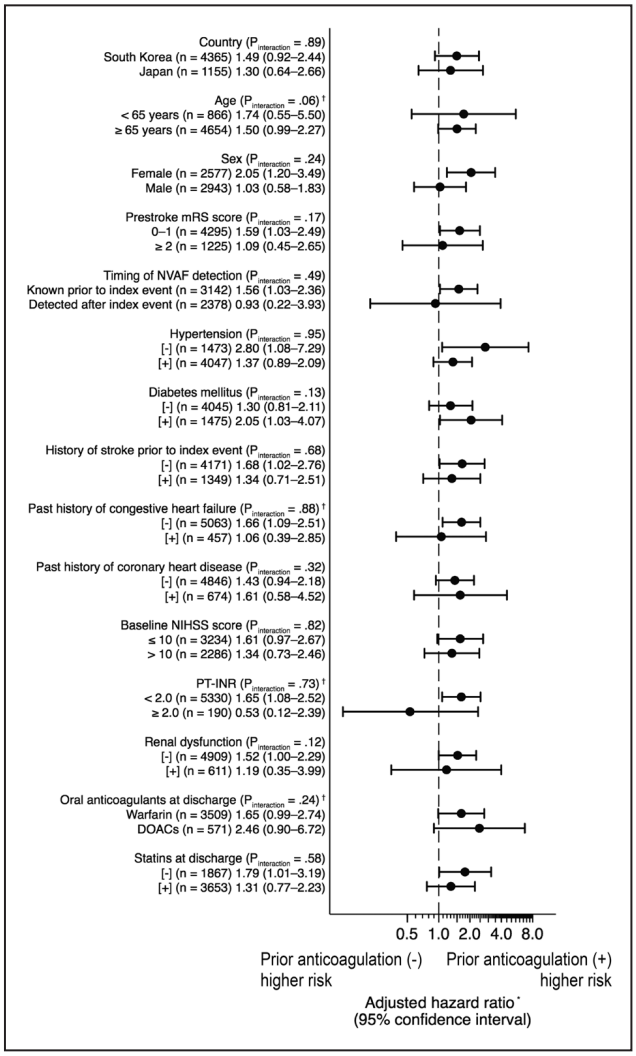

Figure 3. Adjusted hazard ratios of recurrent ischemic stroke by subgroups. DOACs indicates direct oral anticoagulants; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NVAF, nonvalvular atrial fibrillation; and PT-INR, prothrombin time/international normalized ratio. *Multivariable Cox shared-frailty models. Missing values were handled with a pairwise deletion approach. †Multivariable Cox models without shared-frailty were applied for these 4 variables, because the shared-frailty models did not converge to a solution through the maximization process.

could not be perfectly controlled, even after using multivariable adjustment with shared frailty and with IPTW. In particular, history of stroke before the index event and congestive heart failure were clearly more frequent in the patients with prior anticoagulation than in those without prior anticoagulation; this suggests caution when interpreting our data. However, because these biases simultaneously indicate the high-risk nature of the prior anticoagulation group, the clinical relevance of our study still remains significant. Second, the presence of unmeasured confounders, including the parameters associated with ischemic stroke risk in NVAF (eg, sustained or paroxysmal AF, duration of AF, untreated obstructive sleep apnea, natriuretic peptides, or troponins) should be considered.[8,19,22] Third, this study used pooled individual patient data from South Korea and Japan. Between the 2 countries, there are differences in drug indications and approved dosage of rivaroxaban, as well as stroke care process and health care environments.[23] These circumstances for patients with stroke or NVAF possibly affected the results in this study. Fourth, the duration of follow-up was relatively short. Last, the applicability of our findings to ethnicities other than East-Asian is unknown.

Conclusions

The risk for recurrent ischemic stroke may be higher in NVAF-associated stroke patients with prior anticoagulation than in those without prior anticoagulation.

Acknowledgments

K. Tanaka, Dr Koga, Dr Kim, K.-J. Lee, and Dr Bae had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The study concept and design were done by Dr Koga, K. Tanaka, Dr Kim, K.-J. Lee, Dr Yoshimura, Dr Bae, and K. Toyoda. All authors participated in the acquisition, analysis, or interpretation of data. K. Tanaka drafted the article. Critical revision of the article for important intellectual content was done by Dr Koga, Dr Kim, J.-K. Cha, B.-C. Lee, Dr Nakahara, Dr Suzuki, K. Toyoda, and Dr Bae. Statistical analysis was done by K. Tanaka, E. L. Park, and J. Lee. The participating investigators and institutions are listed in Table I in the Data Supplement.

Sources of Funding

This study was supported by a Grant-in-Aid (H23-JunkankiIppan-010) from the Ministry of Health, Labour and Welfare, Japan; the Japan Agency for Medical Research and Development (AMED) (19lk0201094h0001); Bristol-Myers Squibb Korea; and the Korea Centers for Disease Control and Prevention (no. 2017ER620101). The funding sources did not participate in any part of the study, from study conception to article preparation.

Disclosures

Dr Koga received honoraria from Mitsubishi Tanabe Pharma Corporation, Bayer, and BMS/Pfizer; consulting fee from Ono; research supports and honoraria from Nippon Boehringer Ingelheim and Daiichi-Sankyo; and research support from Takeda, Astellas, Pfizer, and Shionogi. Dr Cha received lecture honoraria from Sanofi, Otsuka, and Pfizer. B. -C. Lee received research grants from Daiichi-Sankyo, Boehringer Ingelheim, Astra Zeneca, and Eisai and lecture honoraria from Sanofi and Bayer. Dr Nakahara received research support and honoraria from Daiichi-Sankyo, Boehringer Ingelheim, and Eisai and research support from Pfizer. Dr Bae is a principal investigator, a member of the steering committee, and/or a site investigator of multicenter clinical trials or clinical studies that are sponsored by BMS Korea, Otsuka Korea, Bayer, Boehringer Ingelheim, Daewoong Pharmaceutical, Daiichi-Sankyo, Astra Zeneca Korea, and Dong-A Pharmaceutical and received lecture honoraria from Otsuka Korea, Daiichi-Sankyo, and Astra Zeneca Korea. K. Toyoda received lecture honoraria from Nippon Boehringer Ingelheim, Bayer, Daiichi-Sankyo, and Bristol-Myers Squibb. The other authors report no conflicts.

References

1. Shroff GR, Solid CA, Herzog CA. Temporal trends in ischemic stroke and anticoagulation therapy among Medicare patients with atrial fibrillation: a 15-year perspective (1992-2007). *JAMA Intern Med*. 2013;173:159–160. doi: 10.1001/jamainternmed.2013.1579
2. Suzuki S, Otsuka T, Sagara K, Semba H, Kano H, Matsuno S, et al. Nine-year trend of anticoagulation use, thromboembolic events, and major bleeding in patients with non-valvular atrial fibrillation- shinken database analysis. *Circ J*. 2016;80:639–649. doi: 10.1253/circj.CJ-15-1237
3. Paciaroni M, Agnelli G, Falocci N, Caso V, Becattini C, Marcheselli S, et al. Early recurrence and cerebral bleeding in patients

with acute ischemic stroke and atrial fibrillation: effect of anticoagulation and its timing: the RAF study. *Stroke*. 2015;46:2175–2182. doi: 10.1161/STROKEAHA.115.008891
4. Seiffge DJ, Traenka C, Polymeris A, Hert L, Peters N, Lyrer P, et al. Early start of DOAC after ischemic stroke: risk of intracranial hemorrhage and recurrent events. *Neurology*. 2016;87:1856–1862. doi: 10.1212/WNL.0000000000003283
5. Kim BJ, Park JM, Kang K, Lee SJ, Ko Y, Kim JG, et al. Case characteristics, hyperacute treatment, and outcome information from the clinical research center for stroke-fifth division registry in South Korea. *J Stroke*. 2015;17:38–53. doi: 10.5853/jos.2015.17.1.38
6. Kim BJ, Cho YJ, Hong KS, Lee J, Kim JT, Choi KH, et al. Trajectory groups of 24-hour systolic blood pressure after acute ischemic stroke and recurrent vascular events. *Stroke*. 2018;49:1836–1842. doi: 10.1161/STROKEAHA.118.021117
7. Toyoda K, Arihiro S, Todo K, Yamagami H, Kimura K, Furui E, et al. Trends in oral anticoagulant choice for acute stroke patients with nonvalvular atrial fibrillation in Japan: the SAMURAI-NVAF study. *Int J Stroke*. 2015;10:836–842. doi: 10.1111/ijs.12452
8. Koga M, Yoshimura S, Hasegawa Y, Shibuya S, Ito Y, Matsuoka H, et al. Higher risk of ischemic events in secondary prevention for patients with persistent than those with paroxysmal atrial fibrillation. *Stroke*. 2016;47:2582–2588. doi: 10.1161/STROKEAHA.116.013746
9. Yoshimura S, Koga M, Sato S, Todo K, Yamagami H, Kumamoto M, et al; SAMURAI Study Investigators. Two-year outcomes of anticoagulation for Acute Ischemic Stroke With Nonvalvular Atrial Fibrillation-SAMURAI-NVAF Study. *Circ J*. 2018;82:1935–1942. doi: 10.1253/circj.CJ-18-0067
10. Sposat LA, Cerasuolo JO, Cipriano LE, Fang J, Fridman S, Paquet M, et al. Atrial fibrillation detected after stroke is related to a low risk of ischemic stroke recurrence. *Neurology*. 2018;90:e924–e931. doi: 10.1212/WNL.0000000000005126
11. Lyden P, Brott T, Tilley B, Welch KM, Mascha EJ, Levine S, et al. Improved reliability of the NIH Stroke Scale using video training. NINDS TPA Stroke Study Group. *Stroke*. 1994;25:2220–2226. doi: 10.1161/01.str.25.11.2220
12. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16:31–41. doi: 10.1159/000180580
13. Cleves M, Gould WM, Marchenko YV. *An Introduction to Survival Analysis Using Stata, Third Edition*. College Station, TX: Stata Press; 2016.
14. Cole SR, Hernán MA. Constructing inverse probability weights for marginal structural models. *Am J Epidemiol*. 2008;168:656–664. doi: 10.1093/aje/kwn164
15. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med.* 2015;34:3661–3679. doi: 10.1002/sim.6607
16. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med*. 2009;28:3083–3107. doi: 10.1002/sim.3697
17. Rubin DB. Using propensity scores to help design observational studies: application to the tobacco litigation. *Health Services & Outcomes Research Methodology*. 2001;2:169–188.
18. Goette A, Kalman JM, Aguinaga L, Akar J, Cabrera JA, Chen SA, et al. EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: definition, characterization, and clinical implication. *Heart Rhythm*. 2017;14:e3–e40. doi: 10.1016/j.hrthm.2016.05.028
19. Calenda BW, Fuster V, Halperin JL, Granger CB. Stroke risk assessment in atrial fibrillation: risk factors and markers of atrial myopathy. *Nat Rev Cardiol.* 2016;13:549–559. doi: 10.1038/nrcardio.2016.106
20. King JB, Azadani PN, Suksaranjit P, Bress AP, Witt DM, Han FT, et al. Left atrial fibrosis and risk of cerebrovascular and cardiovascular events in patients with atrial fibrillation. *J Am Coll Cardiol*. 2017;70:1311–1321. doi: 10.1016/j.jacc.2017.07.758
21. Rohla M, Weiss TW, Pecen L, Patti G, Siller-Matula JM, Schnabel RB, et al. Risk factors for thromboembolic and bleeding events in anticoagulated patients with atrial fibrillation: the prospective, multicentre observational PREvention oF thromboembolic events–European Registry in Atrial Fibrillation (PREFER in AF). *BMJ Open*. 2019;9:e022478. doi: 10.1136/bmjopen-2018-022478
22. Chen LY, Chung MK, Allen LA, Ezekowitz M, Furie KL, McCabe P, et al. Atrial fibrillation burden: moving beyond atrial fibrillation as a binary entity: a scientific statement from the American Heart Association. *Circulation*. 2018;137:e623–e644. doi: 10.1161/CIR.0000000000000568
23. Song D, Tanaka E, Lee K, Sato S, Koga M, Kim YD, et al. Factors associated with early hospital arrival in patients with acute ischemic stroke. *J Stroke*. 2015;17:159–167. doi: 10.5853/jos.2015.17.2.159