ORIGINAL RESEARCH

Prior Anticoagulation and Short- or Long-Term Clinical Outcomes in Ischemic Stroke or Transient Ischemic Attack Patients With Nonvalvular Atrial Fibrillation

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***Background*—**We aimed to clarify associations between prior anticoagulation and short- or long-term clinical outcomes in ischemic stroke or transient ischemic attack patients with nonvalvular atrial fibrillation.

***Methods and Results*—**A total of 1189 ischemic stroke or transient ischemic attack patients with nonvalvular atrial fibrillation who were hospitalized within 7 days after onset were analyzed. Of these, 813 patients (68.4%) received no prior anticoagulation, 310 (26.1%) received prior warfarin treatment with an international normalized ratio (INR) <2 on admission, 28 (2.4%) received prior warfarin treatment with an INR ≥2 on admission, and the remaining 38 (3.2%) received prior direct oral anticoagulant treatment. Prior warfarin treatment was associated with a lower risk of death or disability at 3 months compared with no prior anticoagulation (INR <2: adjusted odds ratio: 0.58; 95% CI, 0.42–0.81; *P*=0.001; INR ≥2: adjusted odds ratio: 0.40; 95% CI, 0.16–0.97; *P*=0.043) but was not associated with a lower risk of death or disability at 2 years. Prior warfarin treatment with an INR ≥2 on admission was associated with a higher risk of ischemic events within 2 years compared with no prior anticoagulation (adjusted hazard ratio: 2.94; 95% CI, 1.20–6.15; *P*=0.021).

***Conclusions*—**Prior warfarin treatment was associated with a lower risk of death or disability at 3 months but was not associated with a lower risk of death or disability at 2 years in ischemic stroke or transient ischemic attack patients with nonvalvular atrial fibrillation. Prior warfarin treatment with an INR ≥2 on admission was associated with a higher risk of ischemic events within 2 years.

***Clinical Trial Registration*—**URL: http://www.clinicaltrials.gov. Unique identifier: NCT01581502. **(*J Am Heart Assoc*. 2019;8: e010593. DOI: 10.1161/JAHA.118.010593.)**

Key Words: anticoagulation • atrial fibrillation • ischemic stroke • outcome • transient ischemic attack

Atrial fibrillation is one of the most important risk factors for ischemic stroke. Warfarin, a vitamin K antagonist, is in wide clinical use to prevent ischemic stroke in patients with atrial fibrillation. Several multicenter studies have proven that prior therapeutic warfarin treatment reduces stroke severity.[1–5] Recently developed direct oral anticoagulants (DOACs) are at least as effective and safe as warfarin and have wider therapeutic ranges and fewer drug and food reactions than warfarin. Several studies have shown that prior DOAC treatment also reduced stroke severity.[5–8] In these studies, relatively short-term clinical outcomes were generally assessed. Few studies have shown associations between prior

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Accompanying Data S1 and Tables S1, S2 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.010593

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Clinical Perspective

What Is New?

- Prior warfarin treatment was associated with a lower risk of short-term death or disability but was not associated with a lower risk of long-term death or disability in ischemic stroke or transient ischemic attack patients with nonvalvular atrial fibrillation.
- Prior therapeutic warfarin treatment was associated with a higher risk of subsequent ischemic events in these patients.

What Are the Clinical Implications?

- Patients developing ischemic stroke or transient ischemic attack during therapeutic warfarin treatment should receive close follow-up in case ischemic events recur.

anticoagulation and long-term clinical outcomes in patients with ischemic stroke.

Recently, we completed 2-year follow-up of a prospective multicenter observational study in ischemic stroke or transient ischemic attack (TIA) patients with nonvalvular atrial fibrillation (NVAF; SAMURAI-NVAF [Stroke Acute Management with Urgent Risk-Factor Assessment and Improvement Study on Anticoagulant Therapy in Nonvalvular Atrial Fibrillation], ClinicalTrials.gov identifier NCT01581502; Japanese University Hospital Medical Information Network Clinical Trials Registry identifier UMIN000006930).[9–13] In this study, we aimed to clarify associations between prior anticoagulation and short- or long-term clinical outcomes, as well as subsequent ischemic events, in ischemic stroke or TIA patients with NVAF, using the SAMURAI-NVAF registry.

Methods

The data supporting the present findings are available from the corresponding author on reasonable request. From 18 Japanese stroke centers, ischemic stroke or TIA patients with NVAF who were hospitalized within 7 days after onset between September 2011 and March 2014 were enrolled in the SAMURAI-NVAF study. The study design and main baseline data, as well as clinical outcomes of all participants at 3 months and 2 years, have been described elsewhere.[9,11,13] All study procedures were reviewed and approved by local ethics committees. Written informed consent was obtained from all patients. In the present study, patients with prior warfarin treatment but without the international normalized ratio (INR) value on admission were excluded.

Ischemic stroke was diagnosed based on rapidly developing neurological deficits lasting >24 hours or leading to death without an apparent nonischemic origin, confirmed using magnetic resonance imaging (or computed tomography if magnetic resonance imaging was contraindicated or unavailable). TIA was diagnosed based on these deficits resolving in ≤24 hours. NVAF was diagnosed on 12-lead ECG or 24-hour monitoring during acute hospitalization or from previous medical documents. *Vascular disease* was defined as myocardial infarction, peripheral artery disease, or aortic plaque.[14] Creatinine clearance was calculated using the Cockcroft-Gault equation. Severe neurological deficit was defined as a National Institutes of Health Stroke Scale (NIHSS) score ≥10.[15–18] *Large infarct size* was defined as ≥33% of the territory of the middle cerebral artery, the anterior cerebral artery, or the posterior cerebral artery or the cerebellar hemisphere. *Major artery occlusion* was defined as occlusion at the internal carotid artery, the horizontal segment of the middle cerebral artery, or the basilar artery, leading to the index event. *Acute reperfusion therapy* was defined as intravenous recombinant tissue-type plasminogen activator or acute endovascular treatment.

Outcome measures were defined as death or disability (modified Rankin Scale [mRS] score ≥3) at 3 months and 2 years and ischemic events within 2 years. *Ischemic events* were defined as ischemic stroke, TIA, acute coronary syndrome or percutaneous coronary intervention, systemic embolism, aortic aneurysm rupture or dissection, peripheral artery disease requiring hospitalization, venous thromboembolism, carotid endarterectomy, and carotid artery stenting. Follow-up to assess outcome measures was performed by outpatient visits (or telephone surveys for patients with too severe after effects to attend the outpatient clinic) at 3 months, 1 year, and 2 years after onset.

Statistical Analysis

Patients were classified into the following 4 subgroups according to prior anticoagulation: (1) no prior anticoagulation, (2) prior warfarin treatment with INR <2 on admission, (3) prior warfarin treatment with INR ≥2 on admission, and (4) prior DOAC treatment. Clinical characteristics according to prior anticoagulation were compared using logistic regression analysis or ANOVA, as appropriate. Associations between prior anticoagulation and severe neurological deficit, large infarct size, or major artery occlusion on admission were assessed using crude and the following multivariable models: the minimally adjusted model adjusted for age; sex; congestive heart failure; hypertension; diabetes mellitus; prior stroke, TIA, or thromboembolism; and prior mRS score, and the fully adjusted model adjusted for age; sex; congestive heart failure; hypertension; diabetes mellitus; prior stroke, TIA, or thromboembolism; vascular disease; dyslipidemia; current smoking; creatinine clearance on admission; prior antiplatelet therapy; and prior mRS score. Cumulative ischemic event-free rates according to prior anticoagulation were assessed using the

Kaplan–Meier method. Associations between prior anticoagulation and outcome measures were assessed using crude and the following multivariable models: the minimally adjusted model adjusted for age; sex; congestive heart failure; hypertension; diabetes mellitus; prior stroke, TIA, or thromboembolism; prior mRS score; and acute reperfusion therapy, and the fully adjusted model adjusted for age; sex; congestive heart failure; hypertension; diabetes mellitus; prior stroke, TIA, or thromboembolism; vascular disease; dyslipidemia; current smoking; creatinine clearance on admission; prior antiplatelet therapy; prior mRS score; and acute reperfusion therapy. In these multivariable models, logistic regression analysis or Cox regression analysis was used, as appropriate. Patients lost to follow-up were excluded from logistic regression analysis for death or disability. Values of $P<0.05$ were considered statistically significant. Statistical analyses were performed using JMP v12.2.0 statistical software (SAS Institute).

Results

Of 1192 patients enrolled in the SAMURAI-NVAF study, 3 with prior warfarin treatment but without the INR value on admission were excluded, and the remaining 1189 (527 women; mean age: 78±10 years), including 1138 with ischemic stroke and 51 with TIA, were analyzed. Of these participants, 813 (68.4%) received no prior anticoagulation, 310 (26.1%) received prior warfarin treatment with an INR <2 on admission, 28 (2.4%) received prior warfarin treatment with an INR ≥2 on admission, and the remaining 38 (3.2%) received prior DOAC treatment with dabigatran (23, comprising 5 with 150 mg twice daily, 17 with 110 mg twice daily, and 1 with 75 mg once daily) or rivaroxaban (15, comprising 6 with 15 mg once daily, 8 with 10 mg once daily, and 1 with 7.5 mg once daily). Clinical characteristics according to prior anticoagulation are shown in Table 1.

Of the participants, 57 (4.8%) were lost to follow-up at 3 months, and 155 (13.0%) were lost to follow-up at 2 years. Of these 155 patients, 112 received no prior anticoagulation, 35 received prior warfarin treatment with an INR <2 on admission, 2 received prior warfarin treatment with an INR ≥2 on admission, and the remaining 6 received prior DOAC treatment. Clinical characteristics according to completion of 2-year follow-up are shown in Table S1 (see Data S1 for statistical analysis). There were significant differences in sex ($P<0.001$), diabetes mellitus ($P=0.037$), and NIHSS score on admission ($P=0.043$) between these 155 patients and those who completed 2-year follow-up. The median follow-up period was 2.0 years (interquartile range: 1.0–2.1 years).

On admission, 549 patients (46.2%) developed severe neurological deficit, 312 (26.2%) developed large infarct size, and 405 (34.1%) developed major artery occlusion. Associations between prior anticoagulation and severe neurological deficit, large infarct size, or major artery occlusion on admission in logistic regression models are shown in Table 2. Prior warfarin treatment was associated with a lower risk of severe neurological deficit (INR <2: adjusted odds ratio [OR]: 0.64; 95% CI, 0.47–0.87; $P=0.004$; INR ≥2: adjusted OR: 0.24; 95% CI, 0.08–0.62; $P=0.002$) and large infarct size (INR <2:

Table 1. Clinical Characteristics According to Prior Anticoagulation

Clinical Characteristic	Prior Anticoagulation				*P* Value
	None (n=813)	Warfarin, INR <2 (n=310)	Warfarin, INR ≥2 (n=28)	DOAC (n=38)	
Age, y, mean±SD	78±10	77±9	75±9	77±11	0.478
Women, n (%)	372 (46)	135 (44)	6 (21)	14 (37)	0.056
Congestive heart failure, n (%)	144 (18)	85 (27)	9 (32)	11 (29)	<0.001
Hypertension, n (%)	564 (69)	251 (81)	22 (79)	32 (84)	<0.001
Diabetes mellitus, n (%)	164 (20)	61 (20)	9 (32)	10 (26)	0.348
Prior stroke, TIA, or thromboembolism, n (%)	146 (18)	132 (43)	14 (50)	19 (50)	<0.001
Vascular disease, n (%)	98 (12)	55 (18)	8 (29)	6 (16)	0.011
Dyslipidemia, n (%)	257 (32)	112 (36)	9 (32)	13 (34)	0.549
Current smoking, n (%)	133 (16)	40 (13)	5 (18)	9 (24)	0.259
Creatinine clearance on admission, mL/min, mean±SD	58±27	53±25	61±33	60±25	0.037
Prior antiplatelet therapy, n (%)	223 (27)	57 (18)	6 (21)	3 (8)	0.001
Prior modified Rankin Scale score, median (IQR)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–2)	0.023
NIHSS score on admission, median (IQR)	9 (3–18)	6 (2–18)	4 (1–8)	9 (4–19)	<0.001
Acute reperfusion therapy, n (%)	190 (23)	68 (22)	1 (4)	6 (16)	0.067

DOAC indicates direct oral anticoagulant; INR, international normalized ratio; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack.

Table 2. Associations Between Prior Anticoagulation and Severe Neurological Deficit, Large Infarct Size, or Major Artery Occlusion on Admission in Logistic Regression Models

	Crude			Minimally Adjusted*			Fully Adjusted†		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Severe neurological deficit									
None (n=813)	1.00	…	…	1.00	…	…	1.00	…	…
Warfarin, INR <2 (n=310)	0.67	0.51–0.87	0.003	0.67	0.50–0.89	0.007	0.64	0.47–0.87	0.004
Warfarin, INR ≥2 (n=28)	0.22	0.07–0.54	<0.001	0.26	0.09–0.66	0.004	0.24	0.08–0.62	0.002
DOAC (n=38)	0.92	0.47–1.76	0.791	1.02	0.51–2.05	0.952	0.97	0.48–1.96	0.934
Large infarct size									
None (n=813)	1.00	…	…	1.00	…	…	1.00	…	…
Warfarin, INR <2 (n=310)	0.66	0.48–0.90	0.008	0.71	0.51–0.99	0.040	0.68	0.48–0.95	0.024
Warfarin, INR ≥2 (n=28)	0.19	0.03–0.65	0.005	0.23	0.04–0.81	0.018	0.21	0.03–0.74	0.012
DOAC (n=38)	1.15	0.55–2.27	0.700	1.35	0.63–2.74	0.423	1.32	0.62–2.70	0.460
Major artery occlusion									
None (n=813)	1.00	…	…	1.00	…	…	1.00	…	…
Warfarin, INR <2 (n=310)	0.85	0.64–1.12	0.242	0.89	0.66–1.20	0.454	0.88	0.65–1.19	0.407
Warfarin, INR ≥2 (n=28)	0.22	0.05–0.63	0.003	0.27	0.06–0.78	0.014	0.26	0.06–0.76	0.011
DOAC (n=38)	1.48	0.76–2.85	0.242	1.74	0.87–3.44	0.115	1.80	0.89–3.58	0.099

DOAC indicates direct oral anticoagulant; INR, international normalized ratio; OR, odds ratio; TIA, transient ischemic attack.
*Adjusted for age; sex; congestive heart failure; hypertension; diabetes mellitus; prior stroke, TIA, or thromboembolism; and prior modified Rankin Scale score.
†Adjusted for age; sex; congestive heart failure; hypertension; diabetes mellitus; prior stroke, TIA, or thromboembolism; vascular disease; dyslipidemia; current smoking; creatinine clearance on admission; prior antiplatelet therapy; and prior modified Rankin Scale score.

adjusted OR:, 0.68; 95% CI, 0.48–0.95; *P*=0.024; INR ≥2: adjusted OR: 0.21; 95% CI, 0.03–0.74; *P*=0.012) on admission compared with no prior anticoagulation. Prior warfarin treatment with an INR ≥2 on admission was also associated with a lower risk of major artery occlusion on admission compared with no prior anticoagulation (adjusted OR: 0.26; 95% CI, 0.06–0.76; *P*=0.011). There were no significant associations between prior DOAC treatment and severe neurological deficit, large infarct size, or major artery occlusion on admission.

Of 1132 patients completing 3-month follow-up, 71 (6.3%) were deceased, and 560 (49.5%) had a disability at 3 months. Of 1034 patients completing 2-year follow-up, 251 (24.3%) were deceased, and 550 (53.2%) had a disability at 2 years. Associations between prior anticoagulation and death or disability at 3 months or 2 years in logistic regression models are shown in Table 3. Prior warfarin treatment was associated with a lower risk of death or disability at 3 months compared with no prior anticoagulation (INR <2: adjusted OR: 0.58; 95% CI, 0.42–0.81; *P*=0.001; INR ≥2: adjusted OR: 0.40; 95% CI, 0.16–0.97; *P*=0.043) but not associated with a lower risk of death or disability at 2 years. There were no significant associations between prior DOAC treatment and death or disability at 3 months or 2 years.

Numbers of ischemic events within 2 years according to prior anticoagulation are shown in Table 4. Cumulative ischemic event–free rates according to prior anticoagulation are shown in Figure. The association between prior anticoagulation and ischemic events within 2 years in Cox proportional hazards models is shown in Table 5. Prior warfarin treatment with INR ≥2 on admission was associated with a higher risk of ischemic events within 2 years compared with no prior anticoagulation (adjusted hazard ratio: 2.94; 95% CI, 1.20–6.15; *P*=0.021). In addition, the association between prior anticoagulation and hemorrhagic events within 2 years in Cox proportional hazards models is shown in Table S2 (see Data S1 for statistical analysis). There was no significant association between prior anticoagulation and hemorrhagic events within 2 years.

Discussion

In this study, associations between prior anticoagulation and short- or long-term clinical outcomes, as well as subsequent ischemic events, in ischemic stroke or TIA patients with NVAF were assessed. Major findings of this study were that prior warfarin treatment was associated with a lower risk of death or disability (mRS score ≥3) at 3 months but was not associated with a lower risk of death or disability at 2 years

Table 3. Associations Between Prior Anticoagulation and Death or Disability at 3 Months or 2 Years in Logistic Regression Models

	Crude			Minimally Adjusted*			Fully Adjusted†		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Death or disability at 3 mo									
None (n=775)	1.00	…	…	1.00	…	…	1.00	…	…
Warfarin, INR <2 (n=292)	0.77	0.58–1.004	0.054	0.59	0.42–0.82	0.001	0.58	0.42–0.81	0.001
Warfarin, INR ≥2 (n=28)	0.45	0.19–0.97	0.042	0.42	0.17–0.997	0.049	0.40	0.16–0.97	0.043
DOAC (n=37)	1.24	0.64–2.44	0.530	1.18	0.54–2.59	0.677	1.21	0.55–2.68	0.638
Death or disability at 2 y									
None (n=701)	1.00	…	…	1.00	…	…	1.00	…	…
Warfarin, INR <2 (n=275)	0.93	0.70–1.23	0.603	0.77	0.54–1.10	0.147	0.75	0.52–1.07	0.117
Warfarin, INR ≥2 (n=26)	0.62	0.27–1.36	0.233	0.59	0.23–1.48	0.265	0.56	0.21–1.46	0.238
DOAC (n=32)	0.75	0.36–1.52	0.417	0.71	0.29–1.71	0.445	0.68	0.27–1.68	0.406

DOAC indicates direct oral anticoagulant; INR, international normalized ratio; OR, odds ratio; TIA, transient ischemic attack.
*Adjusted for age; sex; congestive heart failure; hypertension; diabetes mellitus; prior stroke, TIA, or thromboembolism; prior modified Rankin Scale score; and acute reperfusion therapy.
†Adjusted for age; sex; congestive heart failure; hypertension; diabetes mellitus; prior stroke, TIA, or thromboembolism; vascular disease; dyslipidemia; current smoking; creatinine clearance on admission; prior antiplatelet therapy; prior modified Rankin Scale score; and acute reperfusion therapy.

and that prior therapeutic warfarin treatment was associated with a higher risk of ischemic events within 2 years.

Several multicenter studies have proven that prior therapeutic warfarin treatment reduces stroke severity.[1–5] In the present study, similarly, prior warfarin treatment was associated with lower initial severity and a lower risk of death or disability at 3 months. The resolution of intracardiac thrombi by warfarin treatment[19] leading to decreased frequencies of large infarct size and major artery occlusion may contribute to these results. Indeed, a previous study showed that prior warfarin treatment reduced infarct volume.[20] The present study clearly showed that prior therapeutic warfarin treatment was associated with a lower risk not only of large infarct size but also of major artery occlusion on admission.

Table 4. Numbers of Each Ischemic Event Within 2 Years According to Prior Anticoagulation

Ischemic Event	Total (n=1189)	Prior Anticoagulation			
		None (n=813)	Warfarin, INR <2 (n=310)	Warfarin, INR ≥2 (n=28)	DOAC (n=38)
Ischemic stroke	104	62	32	6	4
TIA	11	4	4	1	2
Acute coronary syndrome or percutaneous coronary intervention	22	15	6	0	1
Systemic embolism	5	3	1	1	0
Aortic aneurysm rupture or dissection	1	0	1	0	0
Peripheral artery disease requiring hospitalization	7	3	1	3	0
Carotid endarterectomy	2	2	0	0	0
Total	152	89	45	11	7

DOAC indicates direct oral anticoagulant; INR, international normalized ratio.

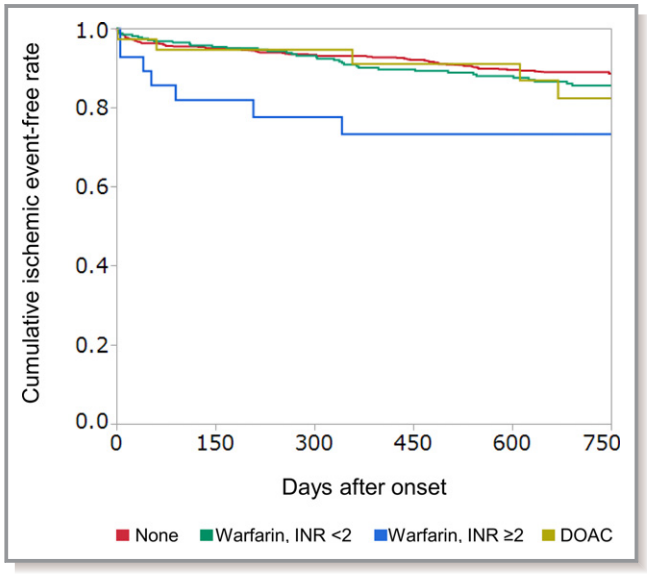

Figure. Cumulative ischemic event-free rates according to prior anticoagulation. DOAC indicates direct oral anticoagulant; INR, international normalized ratio.

Table 5. Association Between Prior Anticoagulation and Ischemic Events Within 2 Years in Cox Proportional Hazards Models

	Crude			Minimally Adjusted*			Fully Adjusted†		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Ischemic events within 2 years									
None (n=813)	1.00	…	…	1.00	…	…	1.00	…	…
Warfarin, INR <2 (n=310)	1.32	0.89–1.93	0.158	1.33	0.88–1.97	0.169	1.30	0.85–1.94	0.222
Warfarin, INR ≥2 (n=28)	2.96	1.24–5.98	0.017	3.18	1.31–6.60	0.013	2.94	1.20–6.15	0.021
DOAC (n=38)	1.46	0.51–3.26	0.438	1.41	0.49–3.21	0.481	1.42	0.49–3.26	0.479

DOAC indicates direct oral anticoagulant; HR, hazard ratio; INR, international normalized ratio; TIA, transient ischemic attack.
*Adjusted for age; sex; congestive heart failure; hypertension; diabetes mellitus; prior stroke, TIA, or thromboembolism; prior modified Rankin Scale score; and acute reperfusion therapy.
†Adjusted for age; sex; congestive heart failure; hypertension; diabetes mellitus; prior stroke, TIA, or thromboembolism; vascular disease; dyslipidemia; current smoking; creatinine clearance on admission; prior antiplatelet therapy; prior modified Rankin Scale score; and acute reperfusion therapy.

Few studies have shown associations between prior anticoagulation and long-term clinical outcomes in patients with ischemic stroke. A previous study has shown that prior therapeutic warfarin treatment was associated with a lower risk of 2-year mortality.[21] However, another has shown that there was no significant association between prior therapeutic warfarin treatment and long-term mortality (mean follow-up: 38 months).[22] In the present study, prior warfarin treatment was associated with a lower risk of death or disability at 3 months but was not associated with a lower risk of death or disability at 2 years. The high incidence of subsequent ischemic events in patients developing ischemic stroke or TIA during therapeutic warfarin treatment may contribute to this result. In the present study, prior therapeutic warfarin treatment was associated with a higher risk of subsequent ischemic events even after adjusting for components of CHA_2DS_2-VASc score (age; sex; congestive heart failure; hypertension; diabetes mellitus; prior stroke, TIA, or thromboembolism; and vascular disease).[14] Thus, patients developing ischemic stroke or TIA during therapeutic warfarin treatment could possess risk factors for ischemic events such as malignancy and antiphospholipid syndrome. Warfarin has low efficacy for prevention of ischemic events due to these risk factors.[23–26] Further studies are required to verify this hypothesis because these risk factors were uncaptured in the present study.

Several studies have shown that prior DOAC treatment also reduced stroke severity.[5–8] Hellwig et al, for example, reported that prior DOAC treatment was associated with lower risk of severe neurological deficit (NIHSS score ≥11) and death or disability (mRS score ≥3) at discharge in ischemic stroke patients with atrial fibrillation.[7] In the present study, however, there were no significant associations between prior DOAC treatment and initial severity or death or disability at 3 months or 2 years. This result may be due to a small number of patients with prior DOAC treatment.

This study has several limitations. First, it is at risk for being statistically underpowered because of the small numbers of patients with prior therapeutic warfarin treatment and DOAC treatment. The number of patients developing ischemic events during the follow-up period was also small. Second, patients with prior apixaban or edoxaban treatment were not enrolled in the SAMURAI-NVAF study given the study period. Third, 4.8% of the participants were lost to follow-up at 3 months, and 13.0% were lost to follow-up at 2 years.

Conclusions

Prior warfarin treatment was associated with a lower risk of death or disability at 3 months but was not associated with a lower risk of death or disability at 2 years in ischemic stroke or TIA patients with NVAF. Prior warfarin treatment with an INR ≥2 on admission was associated with a higher risk of ischemic events within 2 years. Patients developing ischemic stroke or TIA during therapeutic warfarin treatment should receive close follow-up in case ischemic events recur.

Appendix

Sites and Investigators Participating in the SAMURAI Study

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SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Clinical Characteristics According to Completion of 2-Year Follow-Up

Clinical characteristics according to completion of 2-year follow-up were compared using the Pearson chi-squared test, the unpaired t-test, or the Mann-Whitney U test, as appropriate.

Association between Prior Anticoagulation and Hemorrhagic Events within 2 Years

According to the definition of major bleeding in the International Society on Thrombosis and Haemostasis statement,[1] hemorrhagic events were defined as intracerebral hemorrhage, subarachnoid hemorrhage, subdural hemorrhage, intraspinal bleeding, intraocular bleeding, retroperitoneal bleeding, intraarticular bleeding, pericardial bleeding, intramuscular bleeding with compartment syndrome, bleeding causing a fall in hemoglobin level of ≥2.0 g/dL, and bleeding leading to transfusion of ≥2 units of whole blood or red blood cells. Any other bleeding requiring discontinuation of antithrombotic therapy was also included in hemorrhagic events. The association between prior anticoagulation and hemorrhagic events within 2 years was assessed using crude and the following multivariable models: the minimally-adjusted model adjusted for age, sex, congestive heart failure, hypertension, diabetes mellitus, prior stroke/TIA/thromboembolism, prior mRS score, and acute reperfusion therapy and the fully-adjusted model adjusted for age, sex, congestive heart failure,

hypertension, diabetes mellitus, prior stroke/TIA/thromboembolism, vascular disease, dyslipidemia, current smoking, creatinine clearance on admission, prior antiplatelet therapy, prior mRS score, and acute reperfusion therapy. In these multivariable models, Cox regression analysis was used.

Table S1. Clinical characteristics according to completion of 2-year follow-up.

Clinical characteristic	Complete (n=1,034)	Incomplete (n=155)	P value
Age, mean±SD, years	78±10	79±10	0.277
Women, n (%)	435 (42)	92 (59)	<0.001
Congestive heart failure, n (%)	216 (21)	33 (21)	0.909
Hypertension, n (%)	760 (74)	109 (70)	0.405
Diabetes mellitus, n (%)	222 (21)	22 (14)	0.037
Prior stroke/TIA/thromboembolism, n (%)	274 (27)	37 (24)	0.488
Vascular disease, n (%)	148 (14)	19 (12)	0.492
Dyslipidemia, n (%)	349 (34)	42 (27)	0.100
Current smoking, n (%)	165 (16)	22 (14)	0.574
Creatinine clearance on admission, mean±SD, mL/min	57±27	56±25	0.695
Prior antiplatelet therapy, n (%)	255 (25)	34 (22)	0.461
Prior modified Rankin Scale score, median [IQR]	0 [0-1]	0 [0-1]	0.894
NIHSS score on admission, median [IQR]	8 [2-18]	10 [4-20]	0.043
Acute reperfusion therapy, n (%)	232 (22)	33 (21)	0.749

SD indicates standard deviation; TIA, transient ischemic attack; IQR, interquartile range; and NIHSS, National Institutes of Health Stroke Scale.

Table S2. Association between prior anticoagulation and hemorrhagic events within 2 years in Cox proportional hazards models.

	Crude			*Minimally-adjusted			† Fully-adjusted		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Hemorrhagic events within 2 years									
None (n=813)	1.00	-	-	1.00	-	-	1.00	-	-
Warfarin, INR <2 (n=310)	0.75	0.38-1.38	0.365	0.75	0.37-1.42	0.389	0.62	0.30-1.19	0.157
Warfarin, INR ≥2 (n=28)	0.68	0.04-3.11	0.682	0.65	0.04-3.08	0.649	0.52	0.03-2.52	0.483
DOAC (n=38)	1.06	0.17-3.45	0.936	1.04	0.17-3.45	0.960	0.95	0.15-3.28	0.941

INR indicates international normalized ratio; DOAC, direct oral anticoagulant; HR, hazard ratio; and CI, confidence interval.

*Adjusted for age, sex, congestive heart failure, hypertension, diabetes mellitus, prior stroke/transient ischemic attack/thromboembolism, prior modified Rankin Scale score, and acute reperfusion therapy. † Adjusted for age, sex, congestive heart failure, hypertension, diabetes mellitus, prior stroke/transient ischemic attack/thromboembolism, vascular disease, dyslipidemia, current smoking, creatinine clearance on admission, prior antiplatelet therapy, prior modified Rankin Scale score, and acute reperfusion therapy.

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