Anticoagulants, Reperfusion Therapy, and Outcomes in Ischemic Stroke Patients With Non-Valvular Atrial Fibrillation — A Single-Center, 6-Year Experience of 546 Consecutive Patients —

Satoshi Suda, MD, PhD; Yuki Sakamoto, MD; Seiji Okubo, MD, PhD; Junya Aoki, MD, PhD; Takashi Shimoyama, MD, PhD; Takuya Kanamaru, MD, PhD; Kentaro Suzuki, MD; Akihito Kutsuna, MD; Noriko Matsumoto, MD, PhD; Chikako Nito, MD, PhD; Yasuhiro Nishiyama, MD, PhD; Masahiro Mishina, MD, PhD; Kazumi Kimura, MD, PhD

Background: This study investigated changes in anticoagulant use, treatment, and functional outcomes in acute ischemic stroke (AIS) patients with non-valvular atrial fibrillation (NVAf) over a 6-year period.

Methods and Results: Patients with AIS and NVAF admitted to our department from April 2011 to March 2017 were analyzed retrospectively. Patients were divided into 3 groups based on the time of the initial visit (Periods 1–3, corresponding to April 2011–March 2013, April 2013–March 2015, and April 2015–March 2017, respectively). Associations between prescribed medication prior to event and stroke severity, reperfusion therapy, and outcomes were assessed. There was no significant change in the rate of insufficient warfarin and inappropriately lowered doses of direct oral anticoagulant (DOAC) treatment over time. The number of patients receiving prior DOAC treatment increased, but neurological severity on admission was milder than in the other 2 groups. The rate of reperfusion therapy increased from 19.9% (Period 1) to 42.7% (Period 3) for moderate-to-severe stroke patients. Multivariate logistic regression analysis revealed that reperfusion therapy was independently positively associated with good functional outcomes, but negatively associated with mortality (odds ratios [95% confidence intervals] 7.14 [3.34–15.29] and 0.13 [0.008–0.69], respectively).

Conclusions: Inappropriate anticoagulant use for stroke patients with NVAF did not decrease over time. An increase in reperfusion therapy was a strong factor in improved functional outcomes and mortality.

Key Words: Non-valvular atrial fibrillation; Oral anticoagulants; Reperfusion therapy

Atrial fibrillation (AF) is the most common cardiac arrhythmia in developed countries. It is known to increase the risk of stroke and death. The number of patients with AF is gradually and steadily increasing in Japan because of the increase in the aging population.^{1,2} It was reported that patients with AF develop severe ischemic stroke and have poorer outcomes after stroke, including mortality, than those without AF.^{3,4}

The concept and tools of oral anticoagulant (OAC) therapy for preventing stroke in patients with non-valvular atrial fibrillation (NVAf) and acute therapy for large-vessel occlusive stroke have changed in the past 10 years. A meta-analysis of the RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE AF-TIMI 48 trials showed a favorable risk-benefit profile with significant reductions in stroke, intracranial hemorrhage, and mortality.⁵ Direct OAC (DOAC) therapy was approved in Japan in 2011, thereby increasing the anticoagulation therapy options for

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NVAf patients. The Japanese government approved a 4.5-h time window for recombinant tissue-type plasminogen activator (rt-PA) in August 2012. Furthermore, an analysis of 5 pooled trials (MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND IA), performed between December 2010 and December 2014, demonstrated that endovascular thrombectomy is beneficial for most patients with acute ischemic stroke (AIS) due to anterior circulation large vessel occlusion.⁶

These major changes may have affected the initial stroke characteristics and outcomes of patients with NVAF; however, temporal trend reports in Japan are scarce. The aim of this study was to investigate the changes in OAC status and reperfusion therapy, as well as changes in the initial clinical characteristics and outcomes of AIS

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Department of Neurological Science, Graduate School of Medicine, Nippon Medical School, Tokyo, Japan

Mailing address: Satoshi Suda, MD, PhD, Department of Neurological Science, Graduate School of Medicine, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo 113-8603, Japan. E-mail: suda-sa@nms.ac.jp

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Table 1. Clinical Background Characteristics of the Patients Over the 6-Year Study Period

	Total (n=546)	Period 1 (n=136)	Period 2 (n=206)	Period 3 (n=204)	P-value
Female	230 (45.1)	55 (40.4)	83 (40.3)	92 (45.1)	0.5538
Age (years)	77 [69–85]	72 [65–84]	79 [71–86]	77 [70–85]	0.411
CHADS ₂ score	2 [1–3]	2 [1–3]	2 [1–3]	2 [1–3]	0.0503
CHA ₂ DS ₂ -VASc score	4 [2–5]	3 [2–4]	4 [2–5]	4 [3–5]	0.014
Preadmission mRS	0 [0–2]	0 [0–0]	0 [0–2]	0 [0–2]	0.012
NIHSS score on admission	9 [3–20]	9 [3–19]	12 [5–23]	7 [2–18]	0.0745
Biochemistry at admission					
Blood glucose (mg/dL)	118 [102–144]	116 [101–147]	121 [104–144]	116 [99–138]	0.6259
eGFR (mL/min/1.73m ²)	61 [48–76]	64 [51–80]	63 [48–77]	58 [45–71]	0.0057
Anticoagulant status prior to the event					
No anticoagulant therapy	391 (71.6)	101 (74.3)	154 (74.8)	136 (66.7)	0.1403
Warfarin	98 (18.0)	30 (22.1)	37 (18.0)	31 (15.2)	0.2712
DOAC	57 (10.4)	5 (3.7)	15 (7.3)	38 (18.6)	<0.0001
Onset to arrival (h)	4.5 [2–14]	7 [3.0–14]	4.5 [2.0–13.0]	3.3 [1.1–16.2]	0.0019
Reperfusion therapy	172 (31.5)	26 (19.1)	63 (30.6)	83 (40.7)	0.0001
rt-PA	55 (10.1)	12 (8.8)	23 (11.2)	20 (9.8)	0.7703
Endovascular therapy	63 (11.5)	7 (5.2)	19 (9.2)	37 (18.1)	0.0005
rt-PA plus endovascular therapy	54 (9.9)	7 (5.2)	21 (10.2)	26 (12.8)	0.0699
Parenchymal hemorrhage	45 (8.2)	8 (5.9)	17 (8.3)	20 (9.8)	0.4362
mRS at discharge	3 [1–5]	3 [1–5]	3 [1–5]	3 [1–4]	0.8795
NIHSS score on discharge	3 [0–13]	4 [1–18]	3 [0–14]	2 [0–9]	0.0276
Mortality during hospitalization	41 (7.5)	15 (11.0)	19 (9.2)	7 (3.4)	0.0167

The study was divided into 3 periods, based on the time of the initial visit: Period 1, April 2011–March 2013; Period 2, April 2013–March 2015; Period 3, April 2015–March 2017. Data are given as the median [interquartile range] or as n (%). DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; rt-PA, recombinant tissue-type plasminogen activator.

patients with NVAf over a 6-year period.

Methods

Subjects

From April 2011 (when dabigatran, the first DOAC available in Japan, was introduced to the market) through March 2017, consecutive AIS or transient ischemic attack (TIA) patients with NVAf who were admitted to our institute within 7 days from symptom onset were retrospectively recruited from a prospective registry. Patients with a history of rheumatic heart disease and prosthetic mechanical heart valves were excluded. This study was approved by the ethics committee of Nippon Medical School and conformed to the tenets of the Declaration of Helsinki. All participants or participant family members provided written informed consent prior to study participation.

Clinical Characteristics

AF at the initial visit was diagnosed using a 12-lead surface electrocardiogram and 24-h Holter recordings. AF was also diagnosed on the basis of any medical history of AF recorded by referring physicians. Clinical background characteristics, including sex, age, prestroke CHADS₂ score or CHA₂DS₂-VASc score, blood glucose concentrations, estimated glomerular filtration rate (eGFR), and OAC status, were recorded on admission. However, aortic plaques were not assessed as a component of the score because transesophageal echocardiography was performed for approximately only one-quarter of patients included in

the present study. Insufficient treatment with warfarin (corresponding to warfarin treatment and a prothrombin time-international normalized ratio [PT-INR] on admission of <2.0 for patients <70 years of age and a PT-INR <1.6 for patients aged ≥70 years) was determined based on previous studies in Japan and on domestic guidelines.^{7–9} Inappropriately lowered doses of DOAC were defined as the administration of low-dose DOAC despite the standard dosage criteria being met based on the domestic label (Table S1). Magnetic resonance imaging (MRI) studies, including diffusion-weighted imaging and time-of-flight magnetic resonance angiography (MRA), were performed on admission using a commercially available echo planar instrument operating at 1.5 T (Echelon Oval; Hitachi Medical Systems, Tokyo, Japan). Patients with MRI contraindications were evaluated with computed tomography (CT) angiography or conventional angiography. CT was performed at least once within 48 h after admission, and parenchymal hemorrhagic transformation was defined as a hematoma that was ≤30% of the infarcted area with some slight space-occupying effects (PH-1) or as a dense hematoma when it was >30% of the infarcted area with substantial space-occupying effect or as any hemorrhagic lesion outside the infarcted area (PH-2).¹⁰ Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) score on admission. Initial stroke severity was defined as mild (NIHSS score 0–9), moderate (NIHSS score 10–19), or severe (NIHSS score ≥20). Functional outcomes were assessed using the modified Rankin scale (mRS) score and NIHSS score at the time of discharge. A good discharge outcome was defined as an mRS score of

Figure. (A–D) Changes in oral anticoagulants status (A) and insufficient warfarin therapy and inappropriately lowered doses of direct oral anticoagulants (DOAC) over time (B), as well as in the relationship between reperfusion therapy and mortality over time in all patients (C) and in patients with moderate-to-severe stroke severity (D), defined as those with an initial National Institutes of Health Stroke Scale (NIHSS) score ≥ 10 . The study was divided into 3 periods: first, April 2011–March 2013; second, April 2013–March 2015; third, April 2015–March 2017. (E,F) Differences in modified Rankin scale (mRS) scores with and without reperfusion therapy at discharge in all patients (E) and in patients with moderate-to-severe stroke severity (F), defined as an initial NIHSS score ≥ 10 .

Table 2. Multiple Logistic Regression Analysis of Predictors of Mild or Mild-Moderate (Not Severe) Stroke on Admission

	Mild stroke		Mild-moderate stroke	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age (per 10 years)	0.67 (0.51–0.87)	0.0024	0.75 (0.56–1.01)	0.0560
Female	0.88 (0.57–1.36)	0.5646	0.73 (0.45–1.18)	0.1977
Pre-mRS score (per 1 point)	0.74 (0.63–0.86)	<0.0001	0.78 (0.67–0.91)	0.0012
CHA ₂ DS ₂ -VASc score (per 1 point)	1.04 (0.96–1.21)	0.6520	0.99 (0.84–1.17)	0.8950
Blood glucose level (per 10 mg/dL)	0.91 (0.86–0.96)	0.0003	0.95 (0.90–1.00)	0.0741
eGFR <60 mL/min/1.73 m ²	0.88 (0.59–1.32)	0.5445	0.84 (0.75–1.88)	0.4590
Prescribed DOAC	2.48 (1.21–5.08)	0.0130	3.35 (1.24–9.03)	0.0168

CI, confidence interval; OR, odds ratio. Other abbreviations as in Table 1.

0–2, and a poor outcome was defined as an mRS score of 3–5 or death (mRS score of 6).

Statistical Analysis

Patients were divided into 3 groups based on the year of the initial visit: Period 1, April 2011–March 2013 (n=136); Period 2, April 2013–March 2015 (n=206); and Period 3, April 2015–March 2017 (n=204). We initially compared demographics and clinical characteristics between the 3 time periods. Then, patients were divided into 3 groups based on the prescribed medication prior to the index event: no OAC, warfarin treatment, and DOAC treatment. The association between the admission NIHSS score and anticoagulant status prior to stroke was assessed using multivariate logistic models. Furthermore, we compared clinical characteristics of all patients and patients who experienced moderate-to-severe stroke (initial NIHSS

score ≥ 10) in accordance with discharge outcomes and mortality during hospitalization.¹¹ Age, sex, and variables with $P < 0.05$ in the univariate analysis were entered into a multivariate logistic regression model to identify variables independently associated with poor functional outcome and mortality. Data are presented as the median (interquartile range [IQR]) or as number (%). Odds ratios (ORs) are presented with corresponding 95% confidence intervals (CIs). All analyses were performed using JMP version 13 (SAS Institute, Cary, NC, USA) and $P < 0.05$ was considered significant.

Results

In all, 546 consecutive patients with NVAF and AIS or TIA (230 females; median age 77 years [IQR 69–85 years]; median NIHSS score 9 [IQR, 3–20]) were enrolled in the

Table 3. Clinical Background Characteristics Over the 6-Year Study Period Among Patients With Moderate to Severe Stroke (Admission National Institutes of Health Stroke Scale Score ≥ 10)

	Total (n=269)	Period 1 (n=66)	Period 2 (n=113)	Period 3 (n=90)	P-value
Female	129 (48.0)	32 (48.4)	55 (48.7)	42 (46.7)	0.9557
Age (years)	80 [72–87]	82 [73–89]	80 [74–87]	79 [72–86]	0.2551
CHADS ₂ score	2 [1–3]	2 [1–3]	2 [1–3]	2 [1–3]	0.9360
CHA ₂ DS ₂ -VASc score	4 [3–5]	4 [3–5]	4 [3–5]	4 [3–5]	0.8728
Preadmission mRS	0 [0–2]	0 [0–3]	0 [0–3]	0 [0–3]	0.4403
NIHSS score on admission	20 [15–26]	20 [14–26]	21 [17–28]	19 [13–24]	0.0574
Biochemistry at admission					
Blood glucose (mg/dL)	125 [102–144]	123 [101–152]	124 [108–148]	126 [109–162]	0.3255
eGFR (mL/min/1.73 m ²)	58 [45–74]	62 [49–76]	57 [41–73]	56 [46–71]	0.578
Onset to arrival (h)	3.0 [1.7–9.7]	3.8 [2.5–12]	3.5 [2.0–10.0]	1.7 [0.9–6.0]	0.0001
Reperfusion therapy	123 (31.5)	20 (30.3)	51 (45.1)	52 (57.8)	0.0030
rt-PA	34 (12.6)	8 (12.1)	19 (16.8)	7 (7.8)	0.1552
Endovascular therapy	47 (17.4)	7 (10.6)	15 (13.3)	25 (27.8)	0.0062
rt-PA plus endovascular therapy	42 (15.6)	5 (7.6)	17 (15.0)	20 (22.2)	0.0440
Parenchymal hemorrhage	45 (8.2)	5 (7.6)	8 (7.1)	14 (15.6)	0.1016
mRS at discharge (IQR)	5 [4–5]	5 [4–5]	5 [4–5]	4 [3–5]	0.1043
NIHSS score on discharge	12 [4–22]	16 [8–30]	12 [4–23]	9 [3–16]	0.0002
Mortality during hospitalization	35 (13.0)	13 (19.7)	18 (15.9)	4 (4.4)	0.0096

The study was divided into 3 periods, based on the time of the initial visit: Period 1, April 2011–March 2013; Period 2, April 2013–March 2015; Period 3, April 2015–March 2017. Data are given as the median [IQR] or as n (%). IQR, interquartile range. Other abbreviations as in Table 1.

Table 4. Clinical, Laboratory, and Procedural Factors for Good Outcome Among Moderate-to-Severe Stroke Patients (Admission National Institutes of Health Stroke Scale Score ≥ 10) in Univariate and Multivariate Analyses

	Total (n=269)	Good outcome (n=44)	Poor outcome (n=225)	P-value	Multivariate analysis	
					OR (95% CI)	P-value
Female	129 (48.0)	13 (29.6)	116 (51.6)	0.0075	0.79 (0.33–1.90)	0.6040
Age (years)	80 [72–87]	77 [66–85]	81 [74–87]	0.0069	0.99 (0.94–1.04)	0.6372
CHADS ₂ score	2 [1–3]	2 [1–2]	2 [1–3]	0.0026		
CHA ₂ DS ₂ -VASc score	4 [3–5]	3 [2–5]	4 [3–5]	0.0005	0.79 (0.58–1.05)	0.1041
Preadmission mRS	0 [0–2]	0 [0–0]	0 [0–3]	0.0105	0.89 (0.65–1.18)	0.4284
NIHSS score on admission	20 [15–26]	18 [11–23]	21 [16–26]	0.0025	0.92 (0.86–0.97)	0.0042
Biochemistry at admission						
Blood glucose (mg/dL)	125 [102–144]	133 [103–159]	124 [106–153]	0.7553		
eGFR (mL/min/1.73 m ²)	58 [45–74]	62 [51–77]	57 [43–74]	0.1407		
Onset to arrival (h)	3.0 [1.7–9.7]	2.0 [0.8–3.4]	3.7 [2.0–10.0]	0.0005	1.01 (0.97–1.02)	0.6578
Reperfusion therapy	123 (31.5)	34 (77.3)	89 (39.6)	<0.0001	5.55 (2.39–12.87)	<0.0001
rt-PA	34 (12.6)	10 (22.7)	24 (10.7)	0.0277		
Endovascular therapy	47 (17.4)	8 (18.2)	39 (17.3)	0.8922		
rt-PA plus endovascular therapy	42 (15.6)	16 (36.4)	26 (11.6)	<0.0001		
Parenchymal hemorrhage	27 (10.0)	3 (6.8)	24 (10.7)	0.4372		

Unless indicated otherwise, data are given as the median [IQR] or as n (%). Abbreviations as in Tables 1–3.

present study. There were 136 (24.9%), 206 (37.7%), and 204 (37.4%) patients in the Period 1, 2, and 3 groups, respectively.

The clinical background characteristics of the patients in this study overall and for each period over the 6 years of the study are given in **Table 1** and **Figure**. There were significant differences in CHA₂DS₂-VASc scores ($P=0.0014$), preadmission mRS scores ($P=0.012$), and eGFR ($P=0.0057$) among the 3 groups. The proportion of reperfusion therapy increased steadily from 19.1% ($n=26$) during Period 1 to 40.7% ($n=83$) during Period 3 ($P<0.0001$). The occurrence

of hemorrhagic transformation increased slightly from 5.9% ($n=8$) during Period 1 to 9.8% ($n=20$) Period 3, but the difference was not statistically significant ($P=0.4362$). **Figure A** shows the change in OAC status over time. The proportion of patients not receiving OAC in Periods 1, 2, and 3 was 74.3%, 74.8%, and 66.7%, respectively ($P=0.1403$). The proportion of prior DOAC use increased significantly from 3.7% ($n=5$) in Period 1 to 18.1% ($n=37$) in Period 3 ($P<0.0001$), whereas warfarin use decreased slightly from 22.1% ($n=30$) in Period 1 to 15.2% ($n=31$) in Period 3 ($P=0.2712$). Furthermore, there were no significant changes

Table 5. Clinical, Laboratory, and Procedural Factors for Mortality Among Moderate-to-Severe Stroke Patients (Admission National Institutes of Health Stroke Scale Score ≥ 10) in Univariate and Multivariate Analyses

	Total (n=269)	No mortality (n=234)	Mortality (n=35)	P-value	Multivariate analysis	
					OR (95% CI)	P-value
Female	129 (48.0)	112 (47.9)	17 (48.6)	0.9377	1.53 (0.66–3.56)	0.31175
Age (years)	80 [72–87]	80 [72–87]	84 [74–88]	0.1265	1.48 (0.94–2.40)	0.0921
CHADS ₂ score	2 [1–3]	2 [1–3]	2 [2–3]	0.5985		
CHA ₂ DS ₂ -VASc score	4 [3–5]	4 [3–5]	4 [3–5]	0.9763		
Preadmission mRS	0 [0–2]	0 [0–3]	0 [0–3]	0.8597		
NIHSS score on admission	20 [15–26]	20 [14–25]	23 [18–30]	0.0094	1.08 (1.03–1.14)	0.0034
Biochemistry at admission						
Blood glucose (mg/dL)	125 [102–144]	124 [104–153]	130 [113–161]	0.1965		
eGFR (mL/min/1.73 m ²)	58 [45–74]	58 [45–73]	56 [38–76]	0.5802		
Onset to arrival (h)	3.0 [1.7–9.7]	3.0 [1.6–9.1]	4.0 [2.5–10.9]	0.1317		
Reperfusion therapy	123 (31.5)	110 (47.0)	13 (37.1)	0.2745		
rt-PA	34 (12.6)	29 (12.4)	5 (14.3)	0.7533		
Endovascular therapy	47 (17.4)	40 (17.1)	7 (20.0)	0.6728		
rt-PA plus endovascular therapy	42 (15.6)	41 (17.5)	1 (2.9)	0.0258	0.13 (0.008–0.69)	0.0111
Parenchymal hemorrhage	27 (8.2)	26 (11.1)	1 (2.9)	0.1296		

Unless indicated otherwise, data are given as the median [IQR] or as n (%). Abbreviations as in Tables 1–3.

Table 6. Clinical, Laboratory, and Procedural Factors for Good Outcome Among All Patients in Univariate and Multivariate Analyses

	Total (n=546)	Good outcome (n=227)	Poor outcome (n=319)	P-value	Multivariate analysis	
					OR (95% CI)	P-value
Female sex	230 (45.1)	71 (31.3)	159 (49.8)	<0.0001	0.97 (0.57–1.67)	0.9220
Age (years)	77 [69–85]	74 [67–81]	81 [74–87]	<0.0001	0.95 (0.92–0.98)	0.0031
CHADS ₂ score	2 [1–3]	2 [1–3]	2 [1–3]	<0.0001		
CHA ₂ DS ₂ -VASc score	4 [2–5]	3 [2–4]	4 [3–5]	<0.0001	0.94 (0.78–1.14)	0.5561
Preadmission mRS	0 [0–2]	0 [0–0]	0 [0–3]	<0.0001	0.57 (0.44–0.59)	<0.0001
NIHSS score on admission	3 [0–13]	3 [1–7]	17 [7–24]	<0.0001	0.87 (0.84–0.90)	<0.0001
Biochemistry at admission						
Blood glucose (mg/dL)	118 [102–144]	113 [98–138]	121 [104–151]	0.0087	1.00 (0.99–1.00)	0.3707
eGFR (mL/min/1.73 m ²)	61 [48–76]	65 [54–77]	59 [43–75]	0.0014	0.99 (0.98–1.00)	0.2249
Onset to arrival (h)	4.5 [2–14]	4.0 [2.0–17.1]	4.5 [2.0–13.3]	0.9286		
Reperfusion therapy	172 (31.5)	65 (28.6)	107 (33.5)	0.2237		
rt-PA	55 (10.1)	27 (11.9)	28 (8.8)	0.2330		
Endovascular therapy	63 (11.5)	16 (7.1)	47 (14.7)	0.0056	1.71 (0.70–4.18)	0.2356
rt-PA plus endovascular therapy	54 (9.9)	22 (9.7)	32 (10.0)	0.8957		
Parenchymal hemorrhage	45 (8.2)	12 (5.3)	33 (10.3)	0.0341	0.37 (0.15–0.94)	0.0358

Unless indicated otherwise, data are given as the median [IQR] or as n (%). Abbreviations as in Tables 1–3.

in the rate of insufficient warfarin therapy ($P=0.8955$) and inappropriately lowered DOAC doses over time ($P=0.4501$; **Figure B**). The mortality rate decreased significantly from 11.0% ($n=15$) in Period 1 to 3.4% ($n=7$) in Period 1 ($P=0.0167$; **Figure C**).

Clinical background characteristics of the patients according to prior OAC status are given in **Table S2**. Admission NIHSS scores were significantly lower in the DOAC than no OAC ($P=0.0370$) and warfarin ($P=0.0085$) groups, but there was no significant difference in NIHSS scores at admission between the no OAC and WF groups ($P=0.2591$). The percentage of patients with hemorrhagic transformation during the acute phase did not differ among the 3 groups ($P=0.9882$). Discharge mRS and NIHSS scores did not differ significantly among the 3

groups ($P=0.5111$ and $P=0.7004$, respectively). The clinical background characteristics of the patients according to stroke severity on admission are given in **Table S3**. There were significant differences in age ($P<0.0001$), sex ($P=0.0065$), CHADS₂ score ($P=0.0071$), CHA₂DS₂-VASc score ($P=0.0003$), preadmission mRS score ($P<0.0001$), blood glucose levels ($P=0.0002$), eGFR ($P=0.0077$), and prior DOAC use ($P=0.0458$) between those who experienced mild and moderate-to-severe strokes. Multivariate logistic analysis showed that prior DOAC treatment was independently associated with mild stroke (NIHSS score <10 ; OR 2.48; 95% CI 1.21–5.08; $P=0.0130$) and mild-moderate stroke on admission (NIHSS score <20 ; OR 3.35; 95% CI 1.24–9.03; $P=0.0168$; **Table 2**).

Table 3 lists the clinical background characteristics of

Table 7. Clinical, Laboratory, and Procedural Factors for Mortality Among All Stroke Patients in Univariate and Multivariate Analyses

	Total (n=546)	No mortality (n=505)	Mortality (n=41)	P-value	Multivariate analysis	
					OR (95% CI)	P-value
Female	230 (45.1)	209 (41.4)	21 (51.2)	0.2201	1.53 (0.66–3.56)	0.31175
Age (years)	77 [69–85]	80 [72–87]	84 [75–88]	0.0008	1.98 (1.24–3.23)	0.0042
CHADS ₂ score	2 [1–3]	2 [1–3]	3 [2–3]	0.2296		
CHA ₂ DS ₂ -VASc score	4 [2–5]	4 [2–5]	4 [3–5]	0.1757		
Preadmission mRS	0 [0–2]	0 [0–1]	0 [0–3]	0.0716	1.12 (0.89–1.41)	0.3191
NIHSS score on admission	3 [0–13]	8 [2–19]	22 [13–29]	<0.0001	1.08 (1.04–1.12)	<0.0001
Biochemistry at admission						
Blood glucose (mg/dL)	118 [102–144]	118 [101–144]	125 [113–160]	0.0745	1.01 (0.99–1.01)	0.1563
eGFR (mL/min/1.73 m ²)	61 [48–76]	62 [48–76]	56 [40–75]	0.1876		
Onset to arrival (h)	4.5 [2–14]	4.5 [2.0–15.0]	4.0 [2.5–10.5]	0.6108		
Reperfusion therapy	172 (31.5)	157 (31.1)	15 (36.6)	0.4662		
rt-PA	55 (10.1)	50 (9.0)	5 (12.2)	0.6388		
Endovascular therapy	63 (11.5)	56 (11.1)	7 (17.1)	0.2487		
rt-PA plus endovascular therapy	54 (9.9)	51 (10.1)	3 (7.3)	0.5661		
Parenchymal hemorrhage	45 (8.2)	43 (8.5)	2 (4.9)	0.4154		

Unless indicated otherwise, data are given as the median [IQR] or as n (%). Abbreviations as in Tables 1–3.

patients with moderate to severe stroke (initial NIHSS score ≥ 10) over the 6-year study period. There were no differences in admission NIHSS scores among the 3 groups (i.e., Periods 1–3; $P=0.0574$). The time from onset to hospital arrival was shortened ($P=0.0001$) and reperfusion therapy, especially endovascular treatment (EVT) alone ($P=0.0062$) and rt-PA plus EVT ($P=0.0440$), increased significantly. There was a significant difference in discharge NIHSS scores among the 3 groups (median values 16, 12, and 9 during Periods 1, 2, and 3, respectively; $P=0.0002$). Moreover, the mortality rate decreased significantly from 19.7% during Period 1 to 4.4% during Period 3 ($P=0.0096$; **Figure D**).

Tables 4,5 show the associations between baseline characteristics related to functional outcome at discharge and mortality during hospitalization for patients with moderate to severe stroke. Multivariate logistic regression analysis revealed that reperfusion therapy (OR 5.55; 95% CI 2.39–12.87) was independently and positively associated with good functional outcomes, whereas initial NIHSS score (OR 0.92; 95% CI 0.86–0.97) was negatively associated with good functional outcomes (**Table 4**). Moreover, rt-PA plus EVT (OR 0.13; 95% CI 0.0008–0.69) was independently and negatively associated with mortality, and NIHSS score on admission was positively associated with mortality (OR 1.08; 95% CI 1.03–1.14; **Table 5**). The distribution of mRS scores (0–6) across all patients in whom reperfusion was used was as follows: 0, 17.4%; 1, 13.4%; 2, 12.3%; 3, 14.2%; 4, 16.3%; 5, 19.3%; and 6, 7.1%. The distribution of mRS scores across all patients in whom reperfusion was not used was as follows: 0, 17.4%; 1, 13.1%; 2, 12.8%; 3, 14.7%; 4, 16.0%; 5, 19.0%; and 6, 7.0%. In patients with moderate to severe stroke (initial NIHSS score ≥ 10), the distribution of mRS scores across all patients in whom reperfusion was used was as follows: 0, 12.8%; 1, 11.0%; 2, 14.0%; 3, 15.7%; 4, 18.6%; 5, 19.2%; and 6, 8.7% (**Figure E**). Across all patients with moderate to severe stroke (initial NIHSS score ≥ 10) in whom reperfusion was not used, the distribution of mRS scores was as follows: 0, 0%; 1, 1.4%; 2, 5.5%; 3, 7.5%; 4, 26.0%; 5,

44.5%; and 6, 15.1%. The distribution of mRS scores in patients with moderate to severe stroke severity in whom reperfusion was used was as follows: 0, 6.5%; 1, 8.9%; 2, 12.2%; 3, 17.9%; 4, 20.3%; 5, 23.6%; and 6, 10.6% (**Figure F**). There was no independent association between reperfusion therapy and discharge outcome and mortality during hospitalization for all patients (**Tables 6,7**).

Discussion

The main finding of the present study is that there was no marked change in the prescription rate for those with prior use of non-OAC therapy, insufficient warfarin therapy, and inappropriately lowered doses of DOAC during the 6-year study period. The number of patients using DOAC therapy prior to stroke increased gradually, but this may have been associated with milder stroke severity for AIS patients with NVAF. In addition, reperfusion therapy increased steadily, and this increase could be a strong factor in the improved functional outcomes and decreased mortality rates for AIS patients with NVAF.

We found that approximately 60% of warfarin users with stroke were under-dosed over time. Several large AF registries in Japan have reported that approximately 30–40% of warfarin users are under-dosed.^{12,13} The present study investigated stroke patients, so the rate of under-dosed warfarin users should be relatively high. In addition, the mean age of prior warfarin users in this study was 79 years, which is older than that of patients in the J-RHYTHM Registry (69 years), SAKURA AF Registry (72 years), and FUSHIMI AF Registry (74 years).^{12–14} This may have been related to the physician's intention to avoid bleeding complications, especially intracranial hemorrhage. Conversely, the proportion of inappropriately lowered doses of DOAC was 27.3% and 35.5% during Periods 2 and 3 in this study, which is consistent with previous research.¹² The proportion of inappropriately lowered doses of DOAC during Period 1 was 66.7%, which is high compared with the proportion in Periods 2 and 3, although the difference did not reach statistical significance. Since

DOAC was first approved in March 2011, only a few DOAC users were enrolled (n=5).

Compared with no anticoagulation, sufficient warfarin therapy was reported to be associated with mild severity and good clinical outcomes for ischemic stroke in AF patients.^{15,16} However, the relationships between prior DOAC treatment and initial stroke severity, as well as functional outcomes, have not been fully investigated.^{17,18} The present study showed that DOAC medication prior to the event was independently associated with mild or non-severe stroke on admission. However, discharge NIHSS and mRS scores did not differ among those with prior OAC use. In the present study, the median PT-INR was 1.47 and 62 of 98 patients (63%) were in the PT-INR sub-therapeutic range, similar to previous reports.^{19,20} These results indicate that it is difficult to control the therapeutic range of warfarin for older patients with AF who are at high risk of stroke.

There was no significant difference in the initial stroke index during the 6-year period. Conversely, the CHA₂DS₂-VASc and preadmission mRS scores increased as time progressed. The proportion of patients with a history of stroke increased gradually from 21.3% in Period 1 to 28.9% in Period 3. In addition, there was an increase in the proportion of patients aged >75 years from 58.1% in Period 1 to 65.7% in Period 3. These 2 changes may have affected the CHA₂DS₂-VASc score and preadmission mRS. We found significant changes in the time from onset and the rate of reperfusion therapy, especially for EVT alone and rt-PA plus EVT; subsequently, functional outcomes, including mortality, improved markedly. Endovascular thrombectomy is beneficial for most patients with AIS caused by occlusion of the proximal anterior circulation, regardless of patient characteristics or geographic location.⁶ Recently, a retrospective case series showed a strong correlation between reperfusion and the outcomes of patients with vertebrobasilar occlusion strokes treated with EVT, with a 10-fold increase in the likelihood of attaining good functional outcomes if successful reperfusion is attained and twice as high mortality rates for non-recanalized patients. However, the present study was a single-center retrospective observational study. Therefore, interpretation of the present findings requires considerable caution.

The present study had several limitations. First, the mRS score at the time of hospital discharge did not necessarily reflect long-term prognosis. This may have led to the under- or overestimation of the effects of reperfusion therapy on discharge outcome. Second, anticoagulant status prior to stroke was defined based on prescription information, and information regarding drug adherence was not systematically collected. This may have led to underestimation of the effect of DOAC treatment on the initial stroke severity and hemorrhagic transformation after reperfusion therapy. Recently, the continuous prescription rate was reported to be significantly lower for DOAC than warfarin for Japanese patients with NVAf.²¹ The findings of the present study should be confirmed using a larger prospective cohort. Third, our institution is an EVT-capable comprehensive stroke center with a relatively high rate of reperfusion therapy, especially EVT.²² Patients were highly selected and bias may be present. Therefore, the results of the present study may not be generalizable.

Conclusions

Based on our experiences over a 6-year period, more appropriate OAC treatment and a greater increase in reperfusion therapy for AIS patients with AF are required to prevent stroke and improve outcomes.

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Supplementary Files

Supplementary File 1

Table S1. Direct oral anticoagulant dose reduction criteria in Japan

Table S2. Clinical background characteristics of patients according to prior oral anticoagulant status

Table S3. Associations between baseline characteristics and admission stroke severity

Please find supplementary file(s);
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