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Clinical Benefits of Oral Anticoagulants for Elderly Patients With Cardioembolic Stroke at High Bleeding Risk

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Abstract. *Background/Aim: The relationship between the severity of cardioembolic stroke (CES) and oral anticoagulant (OAC) treatment before stroke onset in very elderly (≥80 years) patients with nonvalvular atrial fibrillation (NVAF) at high bleeding risk remains unknown. Patients and Methods: A total of 364 consecutive patients (≥80 years) with CES and NVAF within 48 h following stroke onset were investigated. High bleeding risk was defined as follows: Bleeding history, renal dysfunction (creatinine clearance <30 ml/min), low body weight (≤45 kg), and antiplatelet or nonsteroidal anti-inflammatory drug use. Patients were divided into two groups: High bleeding risk (n=214) and non-high bleeding risk (n=150). We assessed stroke severity and functional outcome between the two groups, and evaluated the effect of therapy with direct OAC (DOAC) on stroke severity in the high-risk group. Results: The high-risk group had a worse modified Rankin Scale (mRS) at discharge than the non-high-risk group [median: 4 (range=2-5) vs. 3 (range=1-4); p=0.02]. Patients in the high-risk group were categorized according to OAC treatment before stroke onset: No OAC (n=148), warfarin (n=46), and DOAC (n=20). The numbers of patients with National Institutes of Health Stroke Scale score (NIHSS) ≥8 on admission in these groups were 104 (70%), 30 (65%), and 8 (40%) (p=0.03), respectively. Multivariate analysis confirmed that DOAC therapy had a lower odds ratio (OR) for severe stroke (NIHSS ≥8) on admission (OR relative to no OAC=0.22, 95% confidence interval=0.08-0.62; p=0.005) and poor functional outcome (mRS ≥4) at discharge (OR=0.31, 95% confidence interval=0.11-0.90; p=0.03). Conclusion: Very elderly patients with CES at high bleeding risk have unfavorable functional outcomes. DOAC administration may be associated with reduced stroke severity.*

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Key Words: Atrial fibrillation, high bleeding risk, elderly patients, cardioembolic stroke, stroke severity, functional outcome.

Currently, the prevalence of atrial fibrillation (AF) increases with age, and the rate of AF-related cardioembolic stroke (CES) is increasing as the population ages (1). Thus, clinical guidelines for stroke prevention in patients with nonvalvular AF (NVAF) recommend the use of direct oral anticoagulants (DOACs), including in elderly patients (2, 3). A recent large-scale Japanese registry, the All Nippon AF In the Elderly (ANAFIE) Registry, showed that most elderly patients (≥75 years) with NVAF were administered anticoagulation therapy, and 66% of these patients were administered a DOAC (4).

However, DOACs are not frequently prescribed for very elderly (≥80 years) patients with NVAF at high risk of bleeding. A recent study, the Edoxaban Low-Dose for Elder Care Atrial Fibrillation Patients (ELDERCARE-AF) trial, showed that the administration of 15 mg edoxaban once daily in very elderly patients (≥80 years) at high bleeding risk reduced stroke or systemic embolism and did not significantly increase events of major bleeding (5). This trial included patients with NVAF who were inappropriate for OAC therapy at the recommended therapeutic strength or approved doses owing to one or more of the following reasons: Low creatinine clearance (CCr) (15-30 ml/min), low body weight (≤45 kg), history of bleeding from a vital organ or gastrointestinal bleeding, antiplatelet use, or continuous nonsteroidal anti-inflammatory drug (NSAID) use (5). The

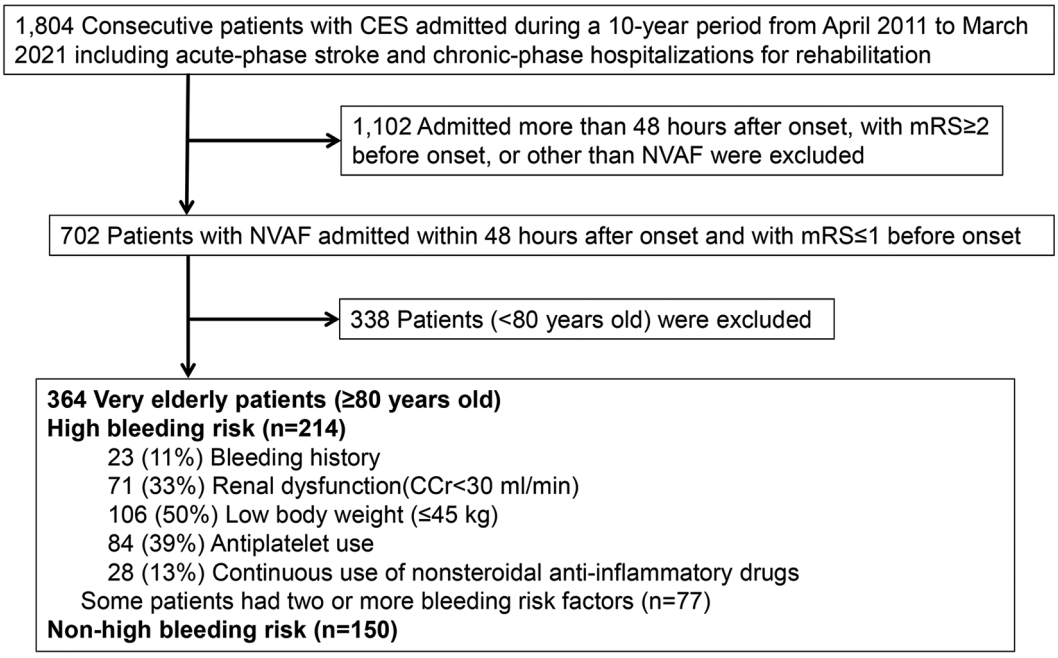

Figure 1. *Flowchart of study patients. CES: Cardioembolic stroke; mRS: modified Rankin Scale; NVAF: nonvalvular atrial fibrillation; CCr: creatinine clearance.*

results of this trial led to an increase in DOAC prescription for very elderly patients at high bleeding risk.

CES is a significant factor in defining healthy life expectancy as the population ages in Japan. Although anticoagulant therapy for very elderly patients with NVAF at high bleeding risk has been shown to reduce embolism, the severity and prognosis of CES in very elderly (≥80 years) patients with NVAF at high bleeding risk remain unknown. Therefore, this study aimed to evaluate the stroke severity and prognosis of very elderly patients with CES with NVAF at high bleeding risk.

Patients and Methods

Study patients. The Hirosaki Stroke and Rehabilitation Center provides acute therapy in a stroke care unit and rehabilitation therapy in a recovery rehabilitation ward. A total of 1,804 consecutive patients with CES were admitted to the Hirosaki Stroke and Rehabilitation Center for acute or chronic rehabilitation therapy within 60 days following CES onset during a 10-year period from April 2011 to March 2021. Of them, 702 patients with CES with NVAF who were admitted to the Center within 48 h following CES onset and who had modified Rankin Scale (mRS) scores of 0 or 1 before stroke onset were initially selected. In this study, following the exclusion of patients aged <80 years (n=338), we finally examined the very elderly group aged ≥80 years (n=364).

Patients were further divided into the following two groups according to bleeding risk: High-risk group (n=214) and non-high-risk group (n=150). The high-risk group consisted of patients with any of the following factors: Bleeding history, renal dysfunction (CCr <30 ml/min), low body weight (≤45 kg), antiplatelet use, or continuous NSAID use, and who were eligible under the criteria of the ELDERCARE-AF trial (5) (Figure 1). Clinical characteristics, stroke severity on admission, and functional outcome at discharge were compared between the two risk groups.

This study was approved by the Ethics Committees of the Hirosaki University Graduate School of Medicine (approval number: 2022-129).

Diagnosis, stroke severity, and functional outcome. On admission, all patients underwent computed tomography of the brain. Subsequently, magnetic resonance imaging was performed, including transversal diffusion-weighted imaging, T2-weighted imaging, fluid-attenuated inversion recovery, and magnetic resonance angiography (Signa Excite HD 1.5T; GE Medical System, Waukesha, WI, USA), when intracerebral hemorrhage was not detected. All patients underwent chest X-ray, 12-lead electrocardiogram, 24-h Holter electrocardiography, carotid ultrasonography, and standard blood tests. As required, some patients underwent transesophageal echocardiography. CES was diagnosed according to the Trial of Org 10172 in Acute Stroke Treatment classification (6).

OAC treatment before stroke onset was evaluated. Thrombolysis therapy with intravenous recombinant tissue plasminogen activator (rt-PA) and/or mechanical thrombectomy was performed according to the Japanese guidelines (3). Using the National Institutes of Health Stroke Scale (NIHSS), stroke severity on admission was assessed; severe stroke was defined as an NIHSS score of 8 points or higher (7, 8). Using the mRS, functional outcome at discharge was assessed. Thromboembolism risk before stroke onset was determined using the $CHADS_2$ score [considering congestive heart failure (CHF), hypertension, age (≥75 years), diabetes mellitus,

Table I. *Clinical characteristics of the study patients*.

		Bleeding risk		
		Non-high (n=150)	High (n=214)	*p*-Value
Basic characteristics	Age (years)	84 (82-87)	85 (82-88)	0.008
	Female	69 (46%)	144 (67%)	<0.0001
	Body weight (kg)	54 (48.5-60.6)	45.6 (42-55)	<0.0001
	BMI (kg/m^2)	22.5 (21.2-24.5)	21.1 (19.1-23.6)	<0.0001
	AF type (PAF)	55 (37%)	76 (36%)	0.82
Risk stratification	$CHADS_2$ score	3 (2-4)	4 (3-4)	0.002
	CHA_2DS_2-VASc score	5 (4-6)	6 (5-6)	<0.0001
	HAS-BLED score	2 (2-3)	3 (3-4)	<0.0001
	Congestive heart failure	50 (33%)	103 (48%)	0.005
	Hypertension	118 (79%)	170 (79%)	0.86
	Diabetes mellitus	31 (21%)	58 (27%)	0.16
	Prior cerebral infarction or TIA	62 (41%)	110 (51%)	0.06
	Vascular disease	30 (20%)	65 (30%)	0.03
	Antiplatelet use	0	84 (39%)	<0.0001
	Continuous use of NSAIDs	0	28 (13%)	<0.0001
	Prior bleeding episode	0	23 (11%)	0.0002
Blood chemistry	Cre (mg/dl)	0.79 (0.66-1.02)	0.86 (0.70-1.16)	0.02
	CCr (ml/min)	48.8 (39.8-56.1)	36.8 (27.5-46.9)	<0.0001
	PT-INR	0.98 (0.91-1.07)	0.99 (0.91-1.07)	0.95
Treatment	OAC before onset			0.20
	None	109 (73%)	148 (69%)	
	WF	22 (15%)	46 (22%)	
	DOAC	19 (13%)	20 (9%)	
	rt-PA thrombolysis	32 (21%)	31 (14%)	0.09
	Mechanical thrombectomy	5 (3%)	2 (1%)	0.10

AF: Atrial fibrillation; CCr: creatinine clearance which was estimated by the Cockcroft-Gault equation; BMI: body mass index; DOAC: direct oral anticoagulant; NSAIDs: nonsteroidal anti-inflammatory drugs; OAC: oral anticoagulant; PAF: paroxysmal AF; PT-INR: prothrombin time-international normalized ratio for warfarin-treated patients; rt-PA: recombinant tissue plasminogen activator; TIA: transient ischemic attack; WF: warfarin. Data are shown as medians (25^{th}-75^{th} percentiles) or frequencies (%).

stroke or transient ischemic attack (TIA)] and the CHA_2DS_2-VASc score [CHF, hypertension, age (≥75 years), diabetes mellitus, stroke or TIA, vascular disease, age (65-74 years), and sex category (female sex)] for each patient. Bleeding risk before stroke onset was determined using the HAS-BLED score [for hypertension, abnormal renal/liver function, stroke, bleeding history, labile international normalized ratio (INR), elderly (≥65 years), and drugs/alcohol] for each patient (9-11).

The following were considered risk factors: CHF (New York Heart Association class II or higher, left ventricular ejection fraction <40%, and heart failure symptoms within 6 months before stroke onset), hypertension (antihypertensive treatment or documented blood pressure ≥140/90 mmHg), diabetes mellitus (insulin or antidiabetic treatment or at least two determinations of diabetic type on separate days evaluated by fasting blood glucose ≥126 mg/dl, casual blood glucose ≥200 mg/dl, oral glucose tolerance test, or hemoglobin A1c ≥6.5%), and vascular disease (coronary artery disease, aortic plaque, or ankle-brachial index ≤0.9).

Statistical analysis. Data were expressed as medians (interquartile ranges), or frequencies (%). A statistical analysis of differences between the two groups was performed using the Kruskal-Wallis test or chi-square test. Multivariate logistic regression analyses for stroke severity on admission and functional outcome at discharge were performed after adjusting for age, sex, CHF, hypertension, diabetes mellitus, prior cerebral infarction or TIA, rt-PA thrombolysis, and mechanical thrombectomy. Statistical analyses were performed using JMP Pro 16 software (SAS, Cary, NC, USA). A value of $p<0.05$ was considered statistically significant.

Results

Patient profiles. A comparison of the clinical characteristics of patients between the two groups is shown in Table I. The high-risk group had higher median age and percentage of females than the non-high-risk group [85 (range=82-88) *vs*. 84 (range=82-87) years; $p=0.008$, and 144 (67%) *vs*. 69 females (46%); $p<0.0001$). The percentages of paroxysmal AF were similar in the two groups. The high-risk group had significantly lower body weight and body mass index (BMI) than the non-high-risk group. The high-risk group showed significantly higher $CHADS_2$ [4 (range=3-4) *vs*. 3 (range=2-4); $p=0.002$], CHA_2DS_2-VASc [6 (range=5-6) *vs*. 5 (range=4-6); $p<0.0001$], and HAS-BLED scores [3 (range=3-

Table II. *Comparison of stroke severity on admission and outcomes at discharge between the two groups based on bleeding risk.*

	Bleeding risk		
	Non-high risk (n=150)	High risk (n=214)	*p*-Value
NIHSS on admission	11 (5-20)	14 (5-22)	0.23
mRS at discharge	3 (1-4)	4 (2-5)	0.02
Period of hospitalization (days)	70 (21-120)	76.5 (23.5-115)	0.99
Mortality (mRS: 6)	12 (8%)	29 (14%)	0.10

mRS: Modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale. Data are shown as frequencies (%) or medians (25^{th}-75^{th} percentiles).

Table III. *Multivariate logistic regression analysis for National Institutes of Health Stroke Scale (NIHSS) ≥8 on admission and modified Rankin Scale (mRS) ≥4 at discharge in the high bleeding risk group.*

		OR	95% CI	*p*-Value
NIHSS ≥8 on admission	No OAC	Reference		
	WF	0.74	0.34-1.60	0.44
	DOAC	0.22	0.08-0.62	0.005
mRS ≥4 at discharge	No OAC	Reference		
	WF	0.99	0.45-2.15	0.98
	DOAC	0.31	0.11-0.90	0.03

CI: Confidence interval; DOAC: direct oral anticoagulant; OAC: oral anticoagulant; OR: odds ratio; WF: warfarin. ORs were calculated using no oral anticoagulant (OAC) therapy as a reference after adjusting for age, sex, congestive heart failure, hypertension, diabetes mellitus, prior cerebral infarction, or transient ischemic attack in the analysis for NIHSS on admission. In the analysis for mRS at discharge, adjustments were made for recombinant tissue plasminogen activator thrombolysis and mechanical thrombectomy in addition to variables for NIHSS.

4) *vs.* 2 (range=2-3); $p<0.0001$] than the non-high-risk group. Hypertension, diabetes mellitus, prior cerebral infarction or TIA were similar for the two groups. The high-risk group had a significantly higher proportion of CHF and vascular disease than the non-high-risk group. The high-risk group also had significantly higher antiplatelet use, continuous NSAID use, and prior bleeding episodes than the non-high-risk group. The high-risk group had higher serum creatinine values [0.86 (range=0.7-1.16) *vs.* 0.79 (range=0.66-1.02) mg/dl; $p=0.02$]; additionally, the CCr was lower for the high-risk group [36.8 (range=27.5-46.9) *vs.* 48.8 (range=39.8-56.1) ml/min; $p<0.0001$].

Regarding OAC use before stroke onset, no differences were observed between the two groups. The high-risk group had lower rates of rt-PA thrombolysis and mechanical thrombectomy than the non-high-risk group; however, no significant differences between the two groups were noted.

Comparison of stroke severity on admission and functional outcome at discharge. The NIHSS and mRS scores were used to assess stroke severity on admission and functional outcome at discharge, respectively (Table II). The high-risk group had a higher NIHSS score on admission and proportion of mortality (mRS=6) than the non-high-risk group; however, no significant differences between the two groups were observed. However, the mRS score at discharge was significantly worse in the high-risk group [4 (range=2-5) *vs.* 3 (range=1-4); $p=0.02$] (Figure 2). The period of hospitalization did not differ between the two groups.

When only the patients in the high-risk group were analyzed, they were divided into the following three groups on the basis of OAC treatment before stroke onset: no OAC (n=148), warfarin therapy (n=46), and DOAC therapy (n=20). The number of patients with NIHSS scores (≥8) on admission was 104 (70%), 30 (65%), and 8 (40%) for these three groups, respectively ($p=0.03$) (Figure 3A). Patients with DOAC therapy had lower mRS scores at discharge than those with no OAC or warfarin therapy, with borderline significance [3 (range=1-4) *vs.* 4 (range=2-5) or 5 (range=1-5); $p=0.06$] (Figure 3B). Furthermore, multivariate analysis confirmed that DOAC therapy was associated with a lower odds ratio (OR) for severe stroke (NIHSS score ≥8) on admission (OR=0.22, 95% confidence interval=0.08-0.62; $p=0.005$) when no OAC was used as a reference (Table III). Moreover, DOAC therapy had a lower OR for unfavorable functional outcomes (mRS score ≥4) at discharge (OR=0.31, 95% confidence interval=0.11-0.90; $p=0.03$) when no OAC was used as a reference (Table III).

Next, patients with warfarin treatment in the high-risk group were further divided into the following two groups on the basis of the prothrombin time (PT)-INR value on admission based on the Japanese guidelines (3): those below the therapeutic range (PT-INR <1.6, n=41) and those within the therapeutic range group (PT-INR ≥1.6, n=5). NIHSS scores on admission and mRS scores at discharge in patients with PT-INR ≥1.6 were similar to those of patients treated with DOAC; however, these represented only a small number of patients (Figure 4). Multivariate analysis for severe stroke (NIHSS score ≥8) on admission and unfavorable functional outcome (mRS score ≥4) at discharge also supported these results (Table IV).

Discussion

Major findings. In this study, more than half of all study patients were very elderly (≥80 years) with CES at high bleeding risk. The NIHSS score on admission was not significantly higher, whereas the mRS score at discharge was significantly higher in patients with CES at high bleeding

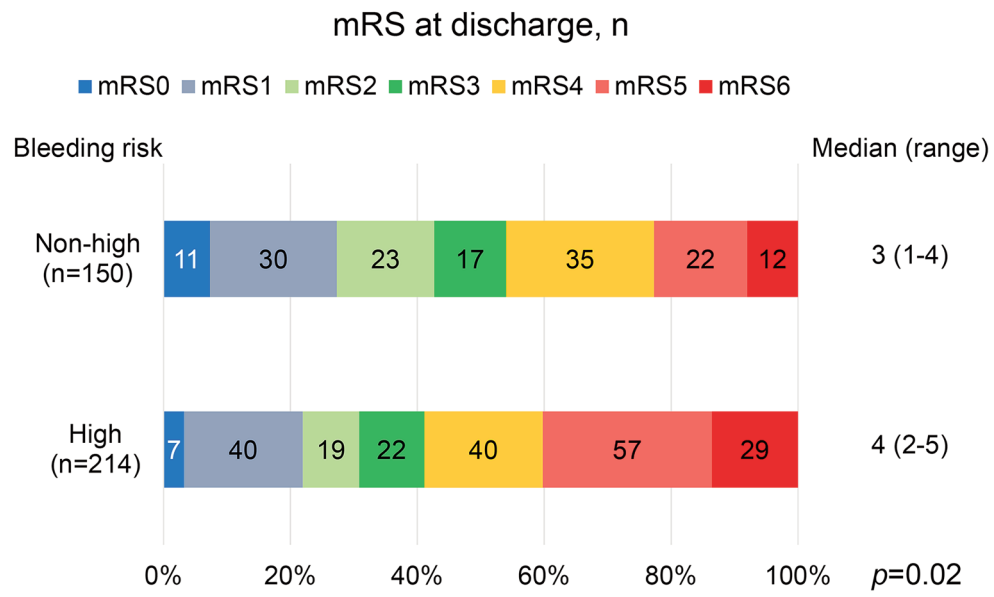

Figure 2. *Comparison of modified Rankin Scale (mRS) score at discharge according to bleeding risk. Non-high: Non-high bleeding risk group; High: high bleeding risk group. Median values and 25th-75th percentiles are shown in each group. Numbers in the graph indicate the number of patients.*

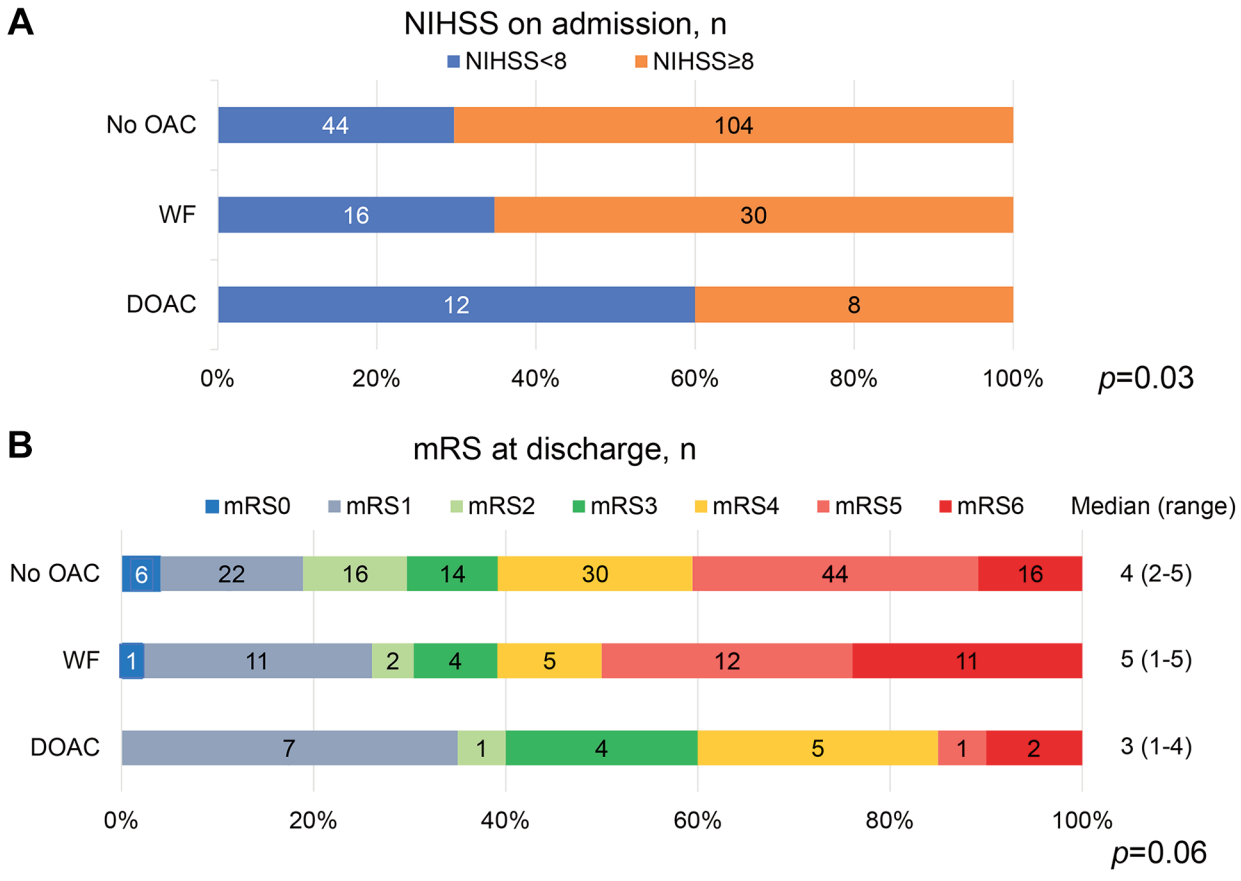

Figure 3. *National Institutes of Health Stroke Scale (NIHSS) score (A) and modified Rankin Scale (mRS) score (B) in the high bleeding risk group stratified by oral anticoagulant (OAC) therapy. DOAC: Direct oral anticoagulant; WF: warfarin.*

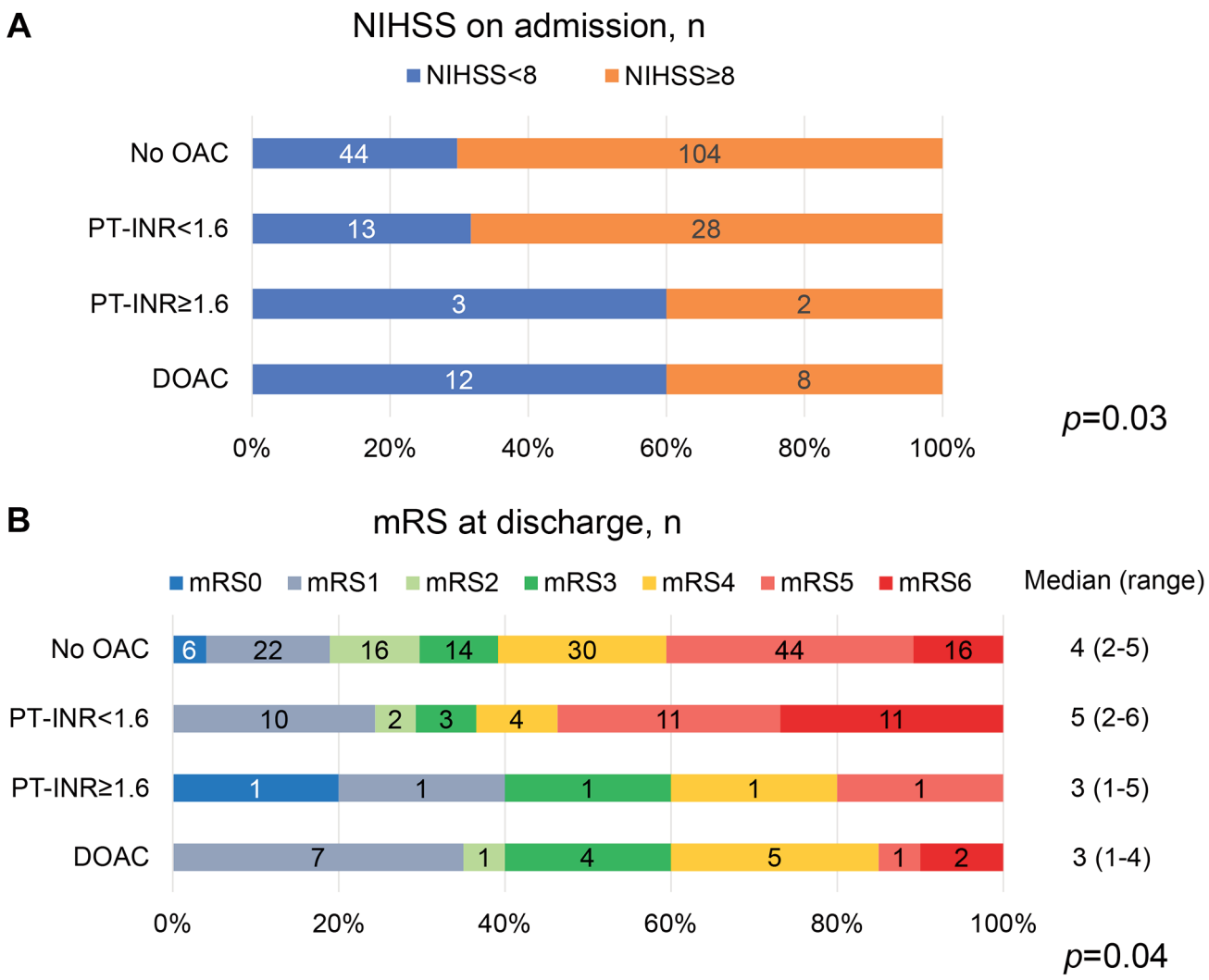

Figure 4. *National Institutes of Health Stroke Scale (NIHSS) score on admission (A) and modified Rankin Scale (mRS) score at discharge (B) in the high bleeding risk group stratified by oral anticoagulant (OAC) therapy before stroke onset. Patients with warfarin treatment in the high-risk group were divided into the following two groups on the basis of the prothrombin time-international normalized ratio (PT-INR) value on admission: those below the therapeutic range (PT-INR <1.6, n=41) and those within the therapeutic range (PT-INR ≥1.6, n=5). DOAC: Direct oral anticoagulant.*

risk than in those at non-high bleeding risk; however, no difference in the hospitalization period was noted between the two groups. These results indicate that patients with CES at high bleeding risk have more severe stroke and unfavorable functional outcomes than those at non-high bleeding risk. When the analysis was focused on OAC treatment before stroke onset in the high-risk group, the proportion of those with NIHSS scores ≥8 on admission was significantly lower and mRS scores at discharge tended to be lower in these with DOAC therapy than those without OAC or treated with WF therapy. Furthermore, multivariate analysis supported these results. To our knowledge, this is the first report showing that treatment with DOAC before stroke onset may be associated with reduced stroke severity on admission and favorable functional outcomes at discharge in very elderly patients with CES at high bleeding risk.

Stroke severity in very elderly (≥80 years) patients with CES at high bleeding risk. Our study patients at high bleeding risk had more advanced age, female preponderance, lower BMI, higher $CHADS_2$, CHA_2DS_2-VASc and HAS-BLED scores, and lower CCr than those at non-high bleeding risk (Table I). Tanaka *et al*. previously showed that patients with CES aged ≥80 years had higher NIHSS scores at admission and higher mRS scores and mortality rates at 3 months than those aged <80 years (12), suggesting a poor functional outcome in patients of advanced age with CES. We further reported that female sex, low BMI and low CCr are associated with

Table IV. *Multivariate logistic regression analysis for National Institutes of Health Stroke Scale (NIHSS) ≥8 on admission and modified Rankin Scale (mRS) ≥4 at discharge in the high-risk group (n=214) with focus on oral anticoagulant (OAC) use.*

		OR	95% CI	*p*-Value
NIHSS ≥8	No OAC	Reference		
on admission	PT-INR <1.6	0.83	0.37-1.88	0.66
	PT-INR ≥1.6	0.27	0.04-1.87	0.19
	DOAC	0.22	0.08-0.62	0.005
mRS ≥4	No OAC	Reference		
at discharge	PT-INR <1.6	1.13	0.50-2.54	0.77
	PT-INR ≥1.6	0.32	0.05-2.28	0.26
	DOAC	0.31	0.11-0.90	0.03

CI: Confidence interval; DOAC: direct oral anticoagulant; OR: odds ratio; PT-INR: prothrombin time-international normalized ratio for warfarin-treated patients. ORs were calculated using no OAC therapy as a reference after adjusting for age, sex, congestive heart failure, hypertension, diabetes mellitus, prior cerebral infarction, or transient ischemic attack in the analysis for NIHSS on admission. In the analysis for mRS at discharge, adjustments were made for recombinant tissue plasminogen activator thrombolysis and mechanical thrombectomy in addition to variables for NIHSS.

severe stroke at admission and unfavorable functional outcomes at discharge (8, 13, 14). Moreover, functional outcomes evaluated using the mRS at 3 months worsened as the $CHADS_2$ score increased (15). Thus, most factors characterizing patients with CES at high bleeding risk are associated with poor functional outcomes following stroke onset. Therefore, considering this characterization of patients with CES at high bleeding risk in the present study, it is expected that such patients have severe stroke at admission and unfavorable functional outcomes at discharge compared with those at non-high bleeding risk.

Favorable outcome of DOAC therapy before onset for very elderly patients with CES at high bleeding risk. Ide *et al*. reported clinical outcomes of patients with NVAF at high bleeding risk by analyzing the Fushimi AF Registry (16). The patients with high bleeding risk (mean $CHADS_2$ score, 3.2) had a higher incidence of stroke and systemic embolism, and major bleeding than those with non-high bleeding risk. Although OAC should be ideally administered to these patients, OAC therapy was only administered to 48.8% of their patients with high bleeding risk. This may be a knowledge gap in OAC therapy for elderly patients with NVAF at high bleeding risk (17).

As for this significant issue, the clinical characteristics of elderly patients with NVAF without OAC therapy were investigated. Akao *et al*. reported that 8.1% (n=2,645) of elderly Japanese patients with NVAF (≥75 years) registered in the ANAFIE Registry were not treated with OAC, and female sex, age ≥85 years, history of major bleeding, and antiplatelet use were associated with a lack of OAC therapy (18). Of note, most of these factors are consistent with those comprising a high bleeding risk. To overcome this knowledge gap, Okumura *et al*. performed the ELDERCARE-AF trial, which showed the efficacy and safety of a once-daily dose of 15 mg edoxaban compared with placebo in very elderly patients (≥80 years) at high bleeding risk (5). Furthermore, Chao *et al*. showed that DOAC therapy for very elderly patients (≥80 years) with AF significantly reduced the incidence of ischemic stroke compared with no OAC and that the risks of intracranial hemorrhage and major bleeding were similar for those from the Taiwan National Health Insurance Research Database treated with DOAC therapy and those treated with no-OAC (19). Moreover, DOAC therapy for ELDERCARE-AF trial-eligible patients in the ANAFIE Registry was associated with reduced incidence of stroke and systemic embolism without a significant increase in major bleeding compared to non-eligible patients (20). These findings indicate that DOAC therapy for very elderly patients with NVAF at high bleeding risk is associated with reduced ischemic stroke incidence without increasing major bleeding.

However, to the best of our knowledge, there has been no report investigating functional outcomes in patients at high bleeding risk who had CES during DOAC therapy. We and others previously showed that patients with CES that occurred during treatment with DOAC had a lower NIHSS score on admission and a favorable functional outcome at discharge, similar to those with therapeutic warfarin treatment (21, 22). In the present study, we firstly showed that very elderly patients with CES at high bleeding risk treated with DOAC have a reduced stroke severity on admission and favorable functional outcomes at discharge. We further showed that patients with PT-INR ≥1.6 had a lower NIHSS score on admission and a more favorable functional outcome at discharge than those in the non-OAC and PT-INR <1.6 groups; however, a small number of patients was noted for the PT-INR ≥1.6 group. These findings indicate that treatment with DOAC is associated with not only reduced CES incidence in very elderly patients with NVAF at high bleeding risk but also led to favorable functional outcomes in very elderly patients with CES at high bleeding risk. DOAC treatment may contribute to extending life expectancy in this regard, particularly in a hyper-aging society such as in Japan.

Study limitations. This study had several limitations. Firstly, since this was a single-center retrospective observational study, the generalizability of our findings may be limited. However, consecutive patients admitted to our hospital during the study period were examined, thereby minimizing potential biases caused by an observational study. Secondly, the relatively small number of very elderly patients with CES

in this study, particularly those with DOAC therapy and PT-INR ≥1.6, puts it at risk of being statistically underpowered. Finally, the precise mechanism by which very elderly patients with CES at high bleeding risk treated with DOAC showed a reduced stroke severity and a favorable functional outcome remains largely unknown. Further prospective large-scale studies are warranted.

Conclusion

Very elderly patients with CES (≥80 years) and NVAF at high bleeding risk have more severe stroke and unfavorable functional outcomes than those at non-high bleeding risk. DOAC administration before stroke onset may be associated with reduced stroke severity on admission and favorable functional outcomes at discharge in this population.

Conflicts of Interest

Dr. Tomita received research funding from Boehringer Ingelheim, Bayer, Daiichi-Sankyo, and Speakers' Bureau/Honorarium from Boehringer Ingelheim, Bayer, Daiichi-Sankyo, and Bristol-Myers Squibb. The rest of the Authors have no relevant disclosures.

Authors' Contributions

Conception: Kazumasa Saito and Hirofumi Tomita. Study design: Kazumasa Saito, Joji Hagii, and Hirofumi Tomita. Data collection and processing: Kazumasa Saito, Joji Hagii, Takanobu Soma, Shota Washima, Natsumi Yamada, Hiroshi Shiroto, Shin Saito, Takaatsu Kamada, and Shingo Takanashi. Article writing: Kazumasa Saito. Critical review: Joji Hagii and Hirofumi Tomita.

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