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Clinical Characteristics, Outcomes, and Risk Factors for Adverse Events in Elderly and Non-Elderly Japanese Patients With Non-Valvular Atrial Fibrillation

— Competing Risk Analysis From the Hokuriku-Plus AF Registry —

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Background: Few studies in Japan have reported on follow-up data regarding the clinical course and risk factors for adverse outcomes in elderly patients with non-valvular atrial fibrillation (NVAF), vs. younger patients, when considering the competing risk of death.

Methods and Results: We prospectively studied 1,328 patients with NVAF (965 men; mean [±SD] age 72.4±9.7 years) from the Hokuriku-Plus AF Registry with a median follow-up of 5.0 years (interquartile range 3.5–5.3 years) and evaluated the incidence of thromboembolism or major bleeding in elderly (age ≥75 years; n=595) and non-elderly (age <75 years; n=733) patients. Analysis using the Gray method showed no significant difference in the incidence of thromboembolism; however, the incidence of major bleeding was significantly higher in the elderly than non-elderly group. The Fine-Gray model, after adjustment for age and sex in the elderly group, showed that age (hazard ratio [HR] 1.08; 95% confidence interval [CI] 1.02–1.13; P=0.004) and warfarin use (HR 1.87; 95% CI 1.12–3.14; P=0.02) were significantly associated with major bleeding. In the elderly group, those using warfarin had a higher incidence of thromboembolism and major bleeding than those using direct oral anticoagulants (DOACs).

Conclusions: The efficacy and safety of DOACs were remarkable in elderly compared with non-elderly patients with NVAF considering the competing risk of death. DOACs may be a favorable choice in elderly patients with NVAF.

Key Words: Anticoagulants; Atrial fibrillation; Bleeding; Competing risk; Thromboembolism

Atrial fibrillation (AF) is one of the most common arrhythmias, particularly in the elderly population,[1,2] and is one of the major risk factors for thromboembolism.[3] As a result of increased life expectancy and a rapidly growing elderly population, the number of elderly patients with AF is expected to rise in Western countries[4] and in Japan.[5]

The higher prevalence of AF and the higher risk of thromboembolism in the elderly AF population have resulted in a higher incidence of thromboembolism in the elderly than younger population.[6,7] AF-related cardioembolism is the most common cause of stroke in elderly patients.[8] Ischemic stroke causes neurologic deficits and increases the mortality rate in patients with AF.[9] It is well known that proper anticoagulation therapy is highly effective in preventing thromboembolism or death in patients with AF.[10] However, the use of anticoagulants in elderly patients with non-valvular AF (NVAF) raises concerns about adverse events such as bleeding, because these patients may have bleeding risk factors, including low body weight, susceptibility to falls, renal dysfunction, polypharmacy, and cognitive dysfunction.[11–14]

Several studies of anticoagulation therapy in the elderly AF population have been reported from Western[15,16] and Asian countries.[11,17,18] However, few prospective cohort studies have compared the clinical course, risk factors for

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adverse outcomes, and the efficacy and safety of oral anticoagulants (OAC) in elderly and younger patients with NVAF in Japan. In addition, among elderly NVAF patients with multiple non-cardiovascular morbidities, the incidence of thromboembolism or major bleeding may be affected by death from other causes.[19] Previous studies have used the traditional method of time-to-event analysis, which can overestimate the incidence of these non-fatal events in the presence of competing risks. Using data derived from Japanese multicenter prospective cohorts (i.e., the Hokuriku-Plus AF registry[20–22]), the present study compared clinical characteristics and outcomes between elderly (age ≥75 years) patients with NVAF and those aged <75 years, and investigated the risk factors for adverse outcomes considering competing risks of death.

Methods

Study Population

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki and all participants provided written informed consent.

The Hokuriku-Plus AF Registry is a multicenter population-based prospective cohort study, and a detailed study design has been published elsewhere.[20] Briefly, 1,492 participants aged 30–94 years were recruited from a total of 19 institutions in the Hokuriku and Yokohama areas in Japan. All patients with AF were carefully treated by cardiologists. Baseline enrollment took place between January 2013 and May 2014, and follow-up examinations were conducted annually for 5 years. Of the 1,492 patients with AF, 96 were excluded from the present study because of mitral stenosis and/or mechanical prosthetic valve implantation, and another 68 were excluded because of insufficient data. Thus, the present study included 1,328 patients with NVAF. These 1,328 patients were divided into 2 groups: an elderly AF group (age ≥75 years) and a non-elderly AF group (age <75 years).

Risk Factor Definitions and Anticoagulation Therapy

The $CHADS_2$ and CHA_2DS_2-VASc stroke risk scores were recorded as the baseline stroke risk. The components of the $CHADS_2$ score were congestive heart failure (CHF), hypertension, age ≥75 years, diabetes, and stroke/transient ischemic attack (TIA; doubled).[23] The components of the CHA_2DS_2-VASc score were CHF, hypertension, age ≥75 years (doubled), diabetes, stroke/TIA (doubled), vascular disease, age 65–74 years, and female sex.[24] The diagnostic criteria for CHF, hypertension, diabetes, and vascular disease have been reported previously.[20]

The HAS-BLED bleeding risk score was recorded as the baseline bleeding risk. The components of the HAS-BLED score were hypertension (systolic blood pressure >160 mmHg), abnormal renal function (dialysis or serum creatinine ≥2.26 mg/dL), abnormal liver function (aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase concentrations 3-fold higher than the upper limit of normal, or a bilirubin level 2-fold higher than the upper limit of normal), stroke history, bleeding history, labile international normalized ratio (INR) data (time in therapeutic range [TTR] <60%), age (>65 years), use of antiplatelet or non-steroidal anti-inflammatory drugs, and excessive consumption of alcohol.[25] Anemia was defined as a hemoglobin level <13.0 g/dL for men and <12.0 g/dL for women. The prothrombin time (PT)-INR and TTR were measured, as reported previously, to evaluate the intensity of anticoagulation by warfarin.[26] The optimal intensity of anticoagulation was defined in terms of PT-INR: 1.6–2.6 for older patients (≥70 years) and 2.0–3.0 for younger patients (<70 years).[27]

In the evaluation of direct OAC (DOAC) use, we defined "off-label use of DOAC" as under- or over-dosing of DOACs. DOAC under-dosing was defined as inappropriately low dosing, corresponding to the administration of low-dose DOACs despite a recommendation for a standard dose, except in the case of dabigatran administration dosing 110 mg, b.i.d. DOAC over-dosing was defined as inappropriate standard dosing, corresponding to the administration of standard-dose DOACs despite a recommendation for a low dose.

Regarding examination findings, the estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet Renal Disease study equation modified for the Japanese population,[28] as follows:

$$eGFR = 194 \times Cr^{-1.094} \times Age^{-0.287} \ (\times 0.739 \text{ if female})$$

Echocardiographic data were collected at the time of entry into the registry. Left atrial diameter was recorded in the parasternal view.

Study Endpoints

The endpoint of this analysis was the incidence of death, thromboembolism, and major bleeding. Thromboembolism included ischemic or hemorrhagic stroke, TIA, and systemic embolism. Stroke was defined as a sudden onset of focal deficit lasting >24 h and was further categorized as ischemic or hemorrhagic. Systemic embolism was defined as an acute vascular occlusion outside the brain. Major bleeding included intracranial hemorrhage, bleeding treated with transfusion, and bleeding with a reduction in hemoglobin >2 g/dL.

Statistical Analysis

Normally distributed continuous variables are presented as the mean±SD, continuous variables that were not normally distributed are presented as the median with interquartile range (IQR), and categorical variables are presented as percentages. Continuous variables were compared using Student's t-test for paired data and categorical variables were compared using Fisher's exact test. Adjusted hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) of each variable associated with adverse events were calculated using the Fine-Gray regression model.[29] To investigate the cumulative ratio for adverse events, considering competing risk, the Gray method was used.[19] Two-sided $P<0.05$ was considered statistically significant. All statistical analyses were performed using JMP®, Pro version 14 (SAS Institute, Cary, NC, USA) or EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/). More precisely, EZR is a modified version of R commander designed to add statistical functions frequently used in biostatistics.[30]

Results

Baseline Characteristics and Outcomes

Using the Hokuriku-Plus AF Registry data, we prospectively studied 1,328 patients with NVAF (965 men; mean

Table 1. Baseline Characteristics of the Entire Cohort, and the Elderly (Age ≥75 Years) and Non-Elderly (Age <75 Years) NVAF Groups Separately

Variables	Entire cohort (n=1,328)	Non-elderly NVAF (n=733)	Elderly NVAF (n=595)	P value
Age (years)	72.4±9.7	65.7±7.2	80.8±4.3	<0.0001
Male sex	965 (72.7)	572 (78.0)	393 (66.1)	<0.0001
BMI (kg/m^2)	23.7±3.6	24.1±3.6	23.2±3.4	<0.0001
Persistent or permanent AF	825 (62.1)	448 (61.1)	377 (63.4)	0.43
CHF	424 (31.9)	202 (27.6)	222 (37.3)	0.0002
Hypertension	845 (63.6)	609 (61.0)	236 (71.7)	0.0005
Diabetes	371 (27.9)	186 (25.4)	185 (31.2)	0.02
Prior stroke or TIA	179 (13.5)	84 (11.5)	95 (16.0)	0.02
Vascular disease	293 (22.1)	125 (17.1)	168 (28.2)	<0.0001
$CHADS_2$ score	1.95±1.30	1.35±1.08	2.70±1.15	<0.0001
CHA_2DS_2-VASc score	3.27±1.74	2.35±1.43	4.41±1.37	<0.0001
LA diameter (mm)	44.1±8.4	43.5±7.9	44.9±8.8	0.005
Hemoglobin (g/dL)	13.6±1.8	14.1±1.6	12.9±1.8	<0.0001
eGFR (mL/min/1.73 m^2)	62.7±19.4	68.5±18.5	55.6±18.0	<0.0001
TTR (warfarin users; %)	71.5±19.8	70.7±20.6	72.3±18.9	0.29
Prior bleeding	28 (2.1)	12 (1.6)	16 (2.7)	0.25
HAS-BLED score	1.80±1.06	1.55±1.06	2.12±1.00	<0.0001
Post-PCI	115 (8.7)	48 (6.6)	67 (11.3)	0.003
Cancer	123 (9.3)	49 (6.7)	74 (12.4)	0.0004
Any oral anticoagulants	1,138 (85.7)	614 (83.8)	524 (88.1)	0.03
Warfarin	709 (53.4)	371 (50.6)	338 (56.8)	0.03
Any DOAC	429 (32.3)	243 (33.2)	186 (31.3)	0.45
Dabigatran	190 (14.3)	112 (15.3)	78 (13.1)	0.27
Rivaroxaban	203 (15.3)	114 (15.6)	89 (15.0)	0.82
Apixaban	36 (2.7)	17 (2.3)	19 (3.2)	0.40
Off-label use of DOAC	77 (5.8)	39 (5.3)	38 (6.4)	0.41
Antiplatelet drugs	350 (26.4)	154 (21.0)	196 (32.9)	<0.0001

Unless indicated otherwise, data are given as the mean±SD or n (%). AF, atrial fibrillation; BMI, body mass index; CHF, congestive heart failure; DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate; LA, left atrium; NVAF, non-valvular atrial fibrillation; PCI, percutaneous coronary intervention; TIA, transient ischemic attack; TTR, time in therapeutic range.

age 72.4±9.7 years) for a median of 5.0 years (IQR 3.5–5.3 years), and evaluated the incidence of thromboembolism, major bleeding, and death in 595 elderly (≥75 years) and 733 non-elderly (<75 years) patients.

The baseline characteristics of the patients in the entire cohort and in the elderly and non-elderly AF groups separately are presented in **Table 1**. Compared with the non-elderly AF group, patients in the elderly AF group were more likely to: be female, have concomitant cancer and a history of coronary intervention, and be using antiplatelet drugs; have a lower body mass index, hemoglobin, and eGFR; have higher $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores; and have a greater left atrium diameter. Among the entire cohort, 85.7% were receiving OACs, with 53.4% of patients being prescribed warfarin and 32.3% being prescribed DOACs (14.3% dabigatran, 15.3% rivaroxaban, and 2.7% apixaban). The TTR in warfarin users in the entire cohort was 71.5%, and there was no significant difference in TTR between the elderly and non-elderly groups (72.3±18.9% vs. 70.7±20.6%; P=0.29).

In the entire cohort, over the median follow-up period of 5.0 years (IQR 3.5–5.3 years), 156 patients died from any cause (2.7 per 100 person-years), thromboembolism occurred in 76 patients (1.4 per 100 person-years), and major bleeding occurred in 108 patients (1.9 per 100 person-years). Regarding the cases of thromboembolism, 68.4% were stroke, 10.5% were TIA, and 21.1% were systemic embolism other than in the brain. With regard to major bleeding, 36.0% of cases were intracranial hemorrhage and 64.0% were bleeding that required transfusion or bleeding associated with a reduction in hemoglobin >2 g/dL. In the elderly group, 104 (17.5%) patients died without thromboembolism and 87 (14.6%) patients died without major bleeding. In the non-elderly group, 37 patients (5.1%) died without thromboembolism and 38 (5.2%) died without major bleeding (**Supplementary Figure**).

Because death without thromboembolism or bleeding was frequently seen, particularly in the elderly group, we decided to perform an analysis considering the competing risk of death. The Gray method showed no significant difference in the incidence of thromboembolism between the elderly and non-elderly groups (HR 1.18; 95% CI 0.75–1.85; P=0.46 by Fine-Gray model and Gray test; **Figure 1A**). In contrast, the rate of major bleeding was significantly higher in the elderly than non-elderly group (HR 2.32; 95% CI 1.57–3.42; P<0.0001 by Fine-Gray model and Gray test; **Figure 1B**).

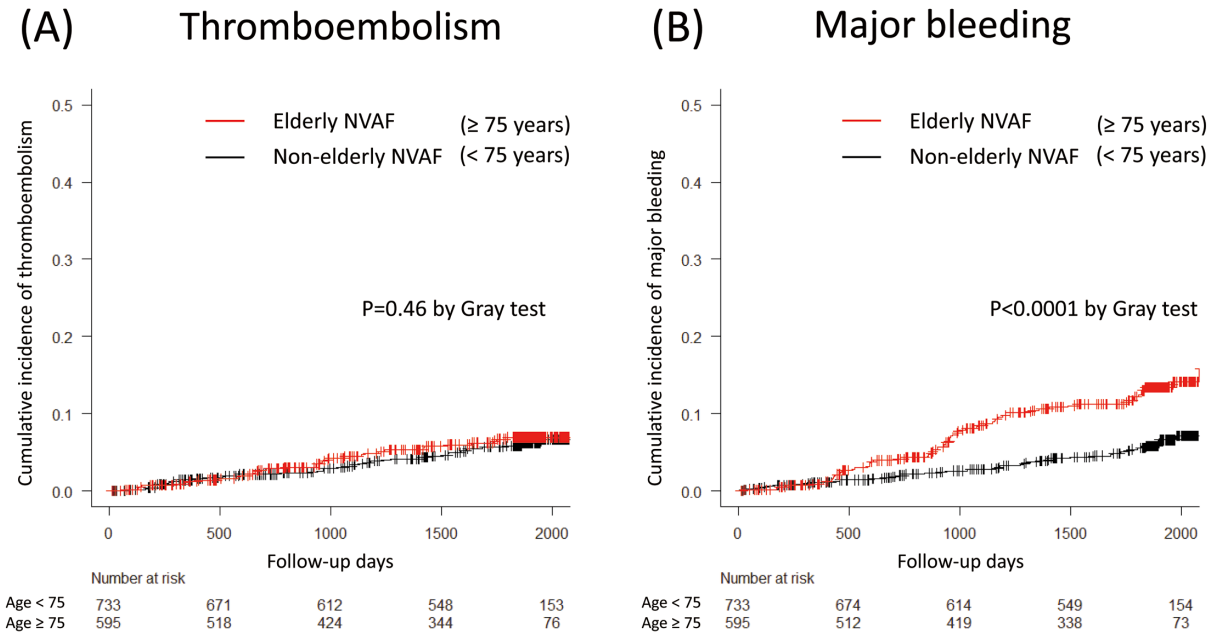

Figure 1. Results of the Gray test for the incidence of (**A**) thromboembolism and (**B**) major bleeding in elderly (age ≥75 years) and non-elderly (age <75 years) patients with non-valvular atrial fibrillation (NVAF).

Table 2. Fine-Gray Models Predicting the Risk Factors for Major Bleeding in the Cohort

Variable	Univariate analysis		Multivariate analysis (Model 1)		Multivariate analysis (Model 2)	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.06 (1.03–1.08)	<0.0001	1.05 (1.02–1.08)	<0.0001		
Male sex	1.08 (0.70–1.66)	0.74	1.19 (0.77–1.84)	0.35	1.00 (0.65–1.55)	1.00
BMI	0.97 (0.92–1.03)	0.35				
Persistent or permanent AF	1.10 (0.74–1.63)	0.63				
CHF	1.59 (1.08–2.33)	0.02	1.22 (0.81–1.84)	0.35	1.41 (0.95–2.08)	0.09
Hypertension	1.19 (0.79–1.78)	0.41				
Diabetes	1.12 (0.75–1.69)	0.58				
Prior stroke	1.22 (0.73–2.05)	0.45				
Vascular disease	1.07 (0.68–1.66)	0.78				
Cancer	1.22 (0.67–2.21)	0.51				
Anemia	1.96 (1.33–2.88)	0.0006	1.42 (0.94–2.15)	0.10		
Creatinine (mg/dL)	1.21 (1.04–1.40)	0.02	1.05 (0.84–1.33)	0.65		
Warfarin use	1.86 (1.24–2.79)	0.003	1.68 (1.11–2.53)	0.01	1.62 (1.07–2.47)	0.02
Any DOAC use	0.69 (0.44–1.07)	0.09				
Off-label use of DOAC	0.85 (0.34–2.07)	0.71				
Antiplatelet drug use	1.42 (0.96–2.12)	0.08				
HAS-BLED score	1.33 (1.12–1.59)	0.001			1.27 (1.06–1.53)	0.01

Model 1 was adjusted for covariables other than the HAS-BLED score. Model 2 was adjusted for the HAS-BLED score and covariables other than the components of the HAS-BLED score. CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.

Comparison of Predictors for Major Bleeding in Elderly and Non-Elderly NVAF

To evaluate the predictors for major bleeding, we used the Fine-Gray model in the entire cohort (**Table 2**). Model 1 adjusted for covariables other than the HAS-BLED score and Model 2 adjusted for the HAS-BLED score and covariables other than the components of the HAS-BLED score. In the entire cohort, high age and the use of warfarin at baseline were independent predictors for major bleeding in Model 1, whereas the use of warfarin and the HAS-BLED score were independent predictors for major bleeding in Model 2.

We also evaluated differences in the predictors of major bleeding in the elderly and non-elderly groups. **Table 3** pres-

Table 3. Fine-Gray Models Predicting the Risk Factors for Major Bleeding in the Elderly (Age ≥75 Years) and Non-Elderly (Age <75 Years) NVAF Groups

Variables	Non-elderly NVAF				Elderly NVAF			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.03 (0.99–1.07)	0.16			1.08 (1.02–1.13)	0.004	1.08 (1.02–1.13)	0.004
Male sex	1.40 (0.62–3.18)	0.42	1.29 (0.57–2.94)	0.53	1.13 (0.68–1.90)	0.64	1.18 (0.71–2.00)	0.52
BMI	0.95 (0.87–1.04)	0.27			1.01 (0.94–1.09)	0.83		
Persistent or permanent AF	1.13 (0.59–2.16)	0.72			1.08 (0.66–1.77)	0.76		
CHF	1.91 (1.02–3.57)	0.04	1.87 (1.00–3.51)	0.05	1.30 (0.80–2.11)	0.28		
Hypertension	0.93 (0.50–1.74)	0.82			1.19 (0.70–2.04)	0.53		
Diabetes	1.73 (0.92–3.27)	0.09			0.78 (0.45–1.33)	0.36		
Prior stroke	1.99 (0.92–4.29)	0.08			0.80 (0.40–1.61)	0.53		
Vascular disease	1.20 (0.56–2.59)	0.64			0.84 (0.48–1.45)	0.52		
Post PCI	1.05 (0.33–3.38)	0.93			0.60 (0.24–1.47)	0.26		
Cancer	1.52 (0.54–4.23)	0.43			0.94 (0.45–1.94)	0.86		
Anemia	1.70 (0.83–3.49)	0.15			1.60 (0.99–2.56)	0.05		
Creatinine (mg/dL)	1.34 (1.00–1.79)	0.05			1.08 (0.93–1.26)	0.31		
Warfarin use	1.67 (0.87–3.19)	0.12			1.90 (1.13–3.20)	0.01	1.87 (1.12–3.14)	0.02
Any DOAC use	0.83 (0.42–1.66)	0.60			0.61 (0.35–1.09)	0.09		
Off-label use of DOAC	1.02 (0.24–4.24)	0.98			0.70 (0.22–2.21)	0.54		
Antiplatelet drug use	2.22 (1.17–4.18)	0.01			0.92 (0.56–1.55)	0.77		
HAS-BLED score	1.51 (1.14–2.01)	0.004	1.49 (1.11–1.99)	0.007	1.07 (0.82–1.39)	0.63		

CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.

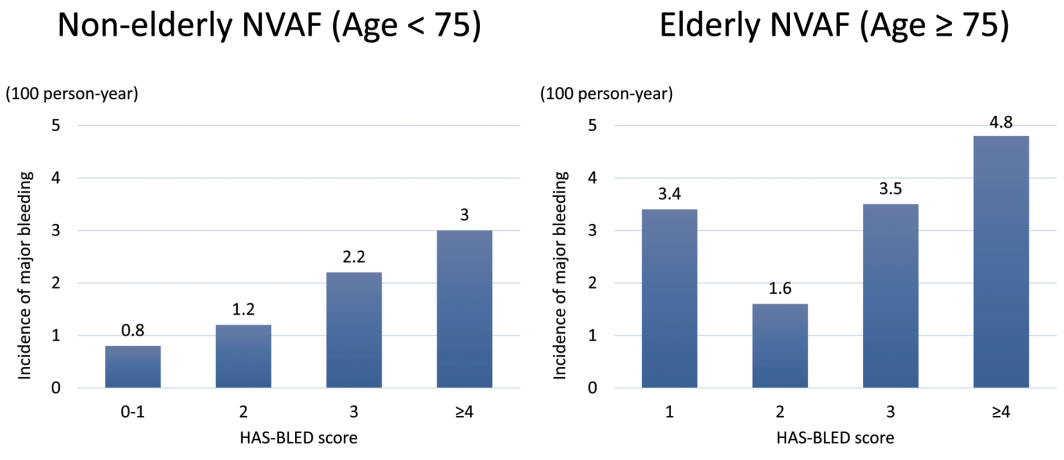

Figure 2. Incidence of major bleeding by HAS-BLED scores in elderly and non-elderly patients with non-valvular atrial fibrillation (NVAF).

Table 4. Baseline Characteristics of Warfarin and DOAC Users in the Elderly (Age ≥75 Years) and Non-Elderly (Age <75 Years) NVAF Groups

Variables	Non-elderly NVAF			Elderly NVAF		
	Warfarin (n=371)	DOAC (n=243)	P value	Warfarin (n=338)	DOAC (n=186)	P value
Age (years)	67.1±5.90	65.9±6.80	0.02	80.8±4.30	80.2±4.00	0.08
Male sex	292 (78.7)	188 (77.3)	0.69	226 (66.9)	120 (64.5)	0.63
BMI (kg/m^2)	24.2±3.60	24.2±4.00	0.93	23.3±3.50	23.0±3.40	0.19
Persistent or permanent AF	271 (73.1)	145 (59.7)	0.0006	244 (72.2)	108 (58.1)	0.001
CHF	125 (33.7)	69 (28.4)	0.18	145 (42.9)	57 (30.7)	0.007
Hypertension	233 (62.8)	151 (62.1)	0.93	238 (70.4)	127 (68.3)	0.62
Diabetes	114 (30.7)	58 (23.9)	0.07	117 (34.6)	52 (28.0)	0.14
Prior stroke or TIA	50 (13.5)	26 (10.7)	0.32	55 (16.3)	28 (15.1)	0.80
Vascular disease	71 (19.1)	34 (14.0)	0.10	102 (30.2)	41 (22.0)	0.05
$CHADS_2$ score	1.54±1.08	1.36±1.01	0.04	2.81±1.18	2.57±1.07	0.03
CHA_2DS_2-VASc score	2.62±1.39	2.37±1.34	0.03	4.52±1.40	4.26±1.29	0.04
LA diameter (mm)	45.3±7.90	42.9±7.30	0.0004	46.1±8.80	44.1±8.40	0.02
Hemoglobin (g/dL)	14.2±1.70	14.0±1.60	0.17	12.9±1.90	13.0±1.70	0.53
eGFR (mL/min/1.73 m^2)	66.1±19.7	69.6±15.9	0.02	52.9±18.1	59.6±16.5	<0.0001
Prior bleeding	9 (2.4)	1 (0.4)	0.09	9 (2.7)	2 (1.1)	0.34
HAS-BLED score	1.77±1.07	1.37±0.97	<0.0001	2.21±1.01	1.82±0.94	<0.0001
Post PCI	26 (7.0)	13 (5.4)	0.50	37 (11.0)	18 (9.7)	0.77
Cancer	24 (6.5)	19 (7.8)	0.52	42 (12.4)	25 (13.4)	0.78
Antiplatelet drugs	92 (24.8)	26 (10.7)	<0.0001	113 (33.4)	39 (21.0)	0.003

Unless indicated otherwise, data are given as the mean±SD or n (%). Abbreviations as in Table 1.

ents the results of the Fine-Gray model in the 2 groups. In patients with NVAF aged <75 years, a high HAS-BLED score at baseline was an independent predictor of major bleeding after adjusting for sex and congestive failure. In contrast, in the elderly group, high age and warfarin use were independent predictors of major bleeding after adjusting for sex. We also evaluated the incidence of major bleeding according to HAS-BLED score in the elderly and non-elderly groups (**Figure 2**). In the non-elderly group, the incidence of major bleeding increased with increasing HAS-BLED score, but this did not occur in the elderly group.

Incidence of Thromboembolism or Major Bleeding in Warfarin and DOAC Users

We next compared warfarin and DOAC users in each group to evaluate the incidence of thromboembolism and major bleeding. The baseline characteristics of warfarin and DOAC users in the elderly and non-elderly groups are presented in **Table 4**. In both groups, warfarin users had higher $CHADS_2$, CHA_2DS_2-VASc and HAS-BLED scores than DOAC users, indicating a higher risk of thromboembolism and bleeding.

To compare the cumulative incidence of major bleeding and thromboembolism in warfarin and DOAC users, we used the Gray method with anticoagulation therapy at baseline. As shown in **Figure 3A**,**B**, there was no significant difference in the incidence of thromboembolism and major bleeding between warfarin and DOAC users in the non-elderly group. However, in the elderly group, DOAC users had a significantly lower incidence of thromboembolism and major bleeding than warfarin users (**Figure 3C**,**D**). Furthermore, we evaluated the cumulative incidence of thromboembolism (**Figure 4A**) and major bleeding (**Figure 4B**) in DOAC users. Remarkably, there were no significant differences in the incidence of thromboembolism and major bleeding between the elderly and non-elderly groups. From these results, the efficacy and safety of DOAC were more remarkable in elderly than non-elderly patients with NVAF.

Discussion

Main Findings

This prospective real-world cohort study, conducted by cardiologists, evaluated the clinical characteristics and outcomes of elderly (age ≥75 years) compared with non-elderly (age <75 years) patients with NVAF. The main findings of the study were: (1) although the incidence of thromboembolism was comparable in the elderly and non-elderly groups, major bleeding occurred more frequently in the elderly group; (2) warfarin use was an independent predictor for major bleeding in the elderly group, whereas the HAS-BLED score was an independent predictor in the non-elderly group; (3) warfarin users had a significantly higher rate of thromboembolism and major bleeding than DOAC users in the elderly group, but the incidence of these events were similar in the non-elderly group; and (4) among DOAC users, there was no significant difference in the incidence of thromboembolism and major bleeding between the elderly and non-elderly groups, probably due to the lower rate of major bleeding, particularly in the elderly group.

Thromboembolism and Major Bleeding in Elderly Patients With AF

Previous cohort studies of elderly patients with AF in Western countries reported that although elderly patients with AF have a high risk of both stroke and bleeding, the

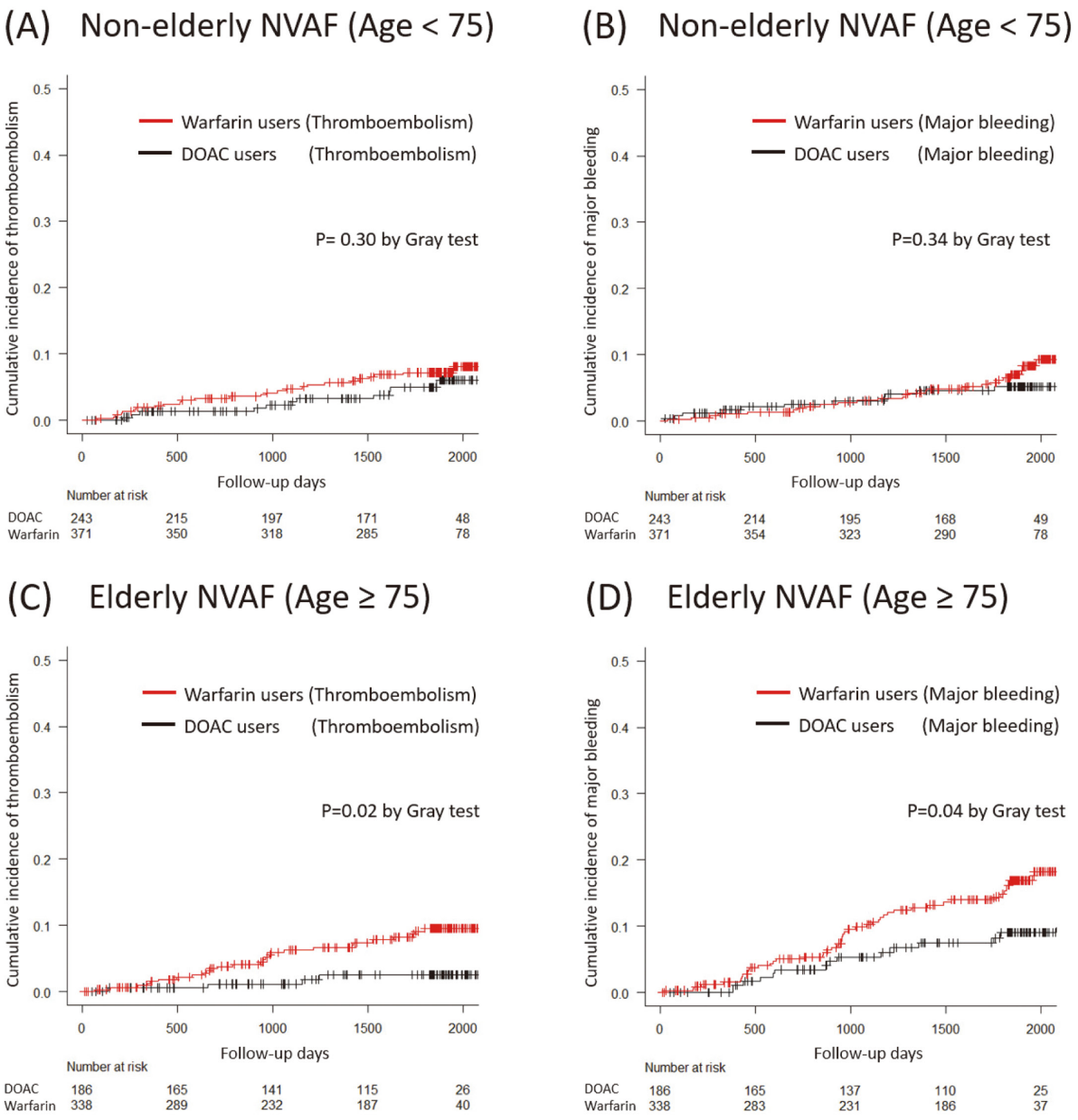

Figure 3. Results of the Gray test for the cumulative incidence of (**A**,**C**) thromboembolism and (**B**,**D**) major bleeding in non-elderly (age <75 years; **A**,**B**) and elderly (age ≥75 years; **C**,**D**) patients with non-valvular atrial fibrillation (NVAF) according to warfarin or direct oral anticoagulant (DOAC) use considering the competing risk of death.

benefits of anticoagulant therapy are present regardless of increasing age.[16,31] The Fushimi AF registry,[32] which is a community-based prospective study of a Japanese AF cohort, reported that the elderly (age ≥85 years) AF cohort had a higher rate of thromboembolism and a similar rate of major bleeding compared with the younger AF cohort.[6] The results of the Fushimi AF Registry differed from those of the present study, but it should be noted that the definition of the "elderly" group differs between the 2 studies. Another reason for this discrepancy may be the difference in the prescription rate of OACs (41.3% of elderly patients in the Fushimi AF registry vs. 88.1% in the present study). The SAKURA AF Registry,[33] a large prospective cohort of Japanese AF patients on OACs, showed a higher rate of thromboembolism in very elderly patients (≥85 years) with AF and bleeding in elderly patients (75–84 years) with AF.[7] The discrepancy in the rate of thromboembolism between the SAKURA AF Registry and the present study may be due to differences in the TTR or the proportion of patients with appropriate DOAC dosing. The percentage of warfarin users aged 75–84 years who had TTR levels >60% was 69% in the SAKURA AF Registry and 82% in the present study. The percentage of DOAC users aged 75–84 years who received an appropriate dose was 70% in

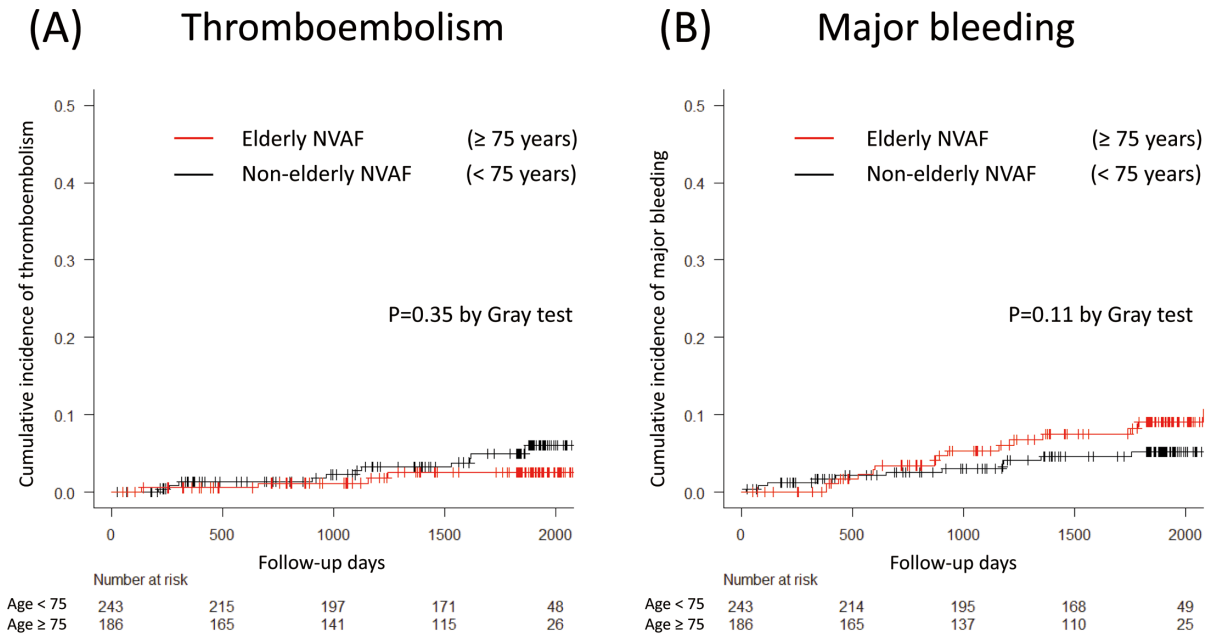

Figure 4. Results of the Gray test for the incidence of (**A**) thromboembolism and (**B**) major bleeding in elderly (age ≥75 years) and non-elderly (age <75 years) non-valvular atrial fibrillation (NVAF) patients using direct oral anticoagulants (DOACs).

the SAKURA AF Registry, compared with 78% in the present study. In the SAKURA AF Registry, 76.8% of patients were treated in cardiovascular centers or affiliated/community hospitals and 23.2% were treated in general practice clinics; in comparison, in the present study, 99.1% of patients were treated in cardiovascular centers or affiliated/community hospitals and only 0.9% were treated in general practice clinics. From these results, a high rate of OAC administration and favorable control of OAC therapy could effectively prevent thromboembolism even in the elderly population, but may increase major bleeding in the elderly compared with younger population. Therefore, in elderly patients with AF, it is important to predict and reduce bleeding events during anticoagulation therapy.

HAS-BLED Score in Elderly and Non-Elderly Patients With AF

The Japanese Circulation Society guideline has recommended the HAS-BLED score to evaluate the risk of bleeding.[34] From our results, the impact of the HAS-BLED score on the prediction of bleeding was different in the elderly and non-elderly AF populations. The elderly population has many clinical problems, such as polypharmacy,[35] frailty,[14] and multimorbidity,[36] which have been reported to be associated with bleeding events and are not included in the HAS-BLED score. This may be the reason for the difference in the impact of the HAS-BLED score between the younger and elderly AF populations. A recent report also showed that the current risk prediction tool performed poorly in the elderly population because of a high rate of multimorbidity.[37] The HAS-BLED score was a useful risk prediction tool for bleeding in the non-elderly population; however, in the elderly population, even if the HAS-BLED score is low, physicians should pay careful attention to clinical problems not included in the HAS-BLED score.

Competing Risk Analysis in the Elderly Population

In the elderly group in the present study, almost 15–18% of NVAF patients died without adverse outcomes, which is higher than the occurrence rate of adverse outcomes. The traditional time-to-event method (Kaplan-Meier method) is used to estimate the cumulative incidence of events, whereas the Cox regression model is used to estimate the predictors of the future occurrence of events. However, Abdel-Qadir et al[19] reported that in an analysis of the elderly population with a high incidence of death without non-fatal events, the incidence of non-fatal events and the effect of covariates for predicting events were overestimated if the competing risk of death was not considered. Abdel-Qadir et al[19] recommended the use of the incidence curve using cumulative incidence functions (Gray method)[19] and the Fine-Gray regression model[29] for multivariate analysis to generate more precise estimates of the incidence and predictors of non-fatal events in the population with competing risk of death. Accordingly, competing risk analysis should be performed to estimate the incidence or predictors for non-fatal events, particularly in elderly populations with a high rate of death before events.

DOACs for Elderly Patients

From our results, warfarin use was an independent risk factor for major bleeding in the elderly population. In addition, DOAC users had a lower rate of major bleeding than warfarin users in the elderly population. Several studies reported that use of DOACs resulted in a lower rate of fatal bleeding events, including intracranial hemorrhage, compared with warfarin use.[38–43] Recently, the All Nippon AF In the Elderly (ANAFIE) Registry, a large cohort

study of the elderly AF population, reported that the incidences of stroke, bleeding, and death were lower in DOAC than warfarin users.[18] In other recent cohort studies, DOAC use was shown to lead to a lower rate of intracranial hemorrhage than warfarin use,[17] and to improve quality-adjusted life years[44] when considering the competing risk of death. Our results additionally showed that the favorable efficacy and safety of DOAC compared with warfarin was more pronounced in elderly than younger AF populations. DOACs may be a favorable choice for anticoagulation therapy in the elderly NVAF population with high mortality and high risk of bleeding. It may be better for the elderly warfarin users with NVAF to switch to DOACs from warfarin.

Study Limitations

This study had some limitations. First, it included a relatively small sample size compared with other AF studies, particularly in the elderly AF population. This limitation may have affected the results regarding the incidence of thromboembolism in elderly AF patients. Second, the Hokuriku-Plus AF Registry did not evaluate polypharmacy, frailty, and multimorbidity, which may affect the clinical course, including major bleeding or mortality in the elderly population. Third, because the Hokuriku-Plus AF Registry enrolled patients with AF from January 2013 to May 2014, edoxaban was not included in the DOACs at baseline. Finally, we did not evaluate the effects of adherence to OACs, changing to other OACs, or withdrawing OACs during follow-up. In the warfarin group, 32.5% of patients with warfarin at baseline were changed to any DOACs during follow-up, whereas in the DOAC group 1.5% of patients with DOAC at baseline were changed to warfarin during follow-up.

Conclusions

The incidence of thromboembolism was similar between elderly and non-elderly patients with NVAF with favorable control of anticoagulation. Major bleeding events were frequent in elderly patients with NVAF, particularly among warfarin users under the consideration of the competing risk of death. From the aspect of both efficacy and safety, DOACs may be a favorable choice in elderly patients with NVAF.

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Disclosures

The authors declare that there are no conflicts of interest.

IRB Information

This study was approved by the Ethics Committee for Medical Research of Kanazawa University Graduate School of Medical Science (1394-4).

Data Availability

The deidentified participant data will not be shared.

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Supplementary Files

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