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, and is one of the major risk factors for thromboembolism. 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 and in Japan. 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. AF-related cardioembolism is the most common cause of stroke in elderly patients. Ischemic stroke causes neurologic deficits and increases the mortality rate in patients with AF. It is well known that proper anticoagulation therapy is highly effective in preventing thromboembolism or death in patients with AF. 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.

Several studies of anticoagulation therapy in the elderly AF population have been reported from Western and Asian countries. However, few prospective cohort studies have compared the clinical course, risk factors for...
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. 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), 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. 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 mortality (n=44), death certificate data (n=4), and/or unconfirmed AF diagnosis (n=48). 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 CHADS2 and CHA2DS2-VASc stroke risk scores were recorded as the baseline stroke risk. The components of the CHADS2 score were congestive heart failure (CHF), hypertension, age ≥75 years, diabetes, and stroke/transient ischemic attack (TIA; doubled). The components of the CHA2DS2-VASc score were CHF, hypertension, age ≥75 years (doubled), diabetes, stroke/TIA (doubled), vascular disease, age 65–74 years, and female sex. 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 (diabetes 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 the therapeutic range (TTR) <60%), age (≥65 years), use of anti-platelet or non-steroidal anti-inflammatory drugs, and excessive consumption of alcohol. 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. 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).

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 inappropriate 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, as follows:

$$eGFR = 194 \times \frac{Cr^{-1.094}}{Age^{-0.287}}$$  

(×0.739 if female)

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

**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. To investigate the cumulative ratio for adverse events, considering competing risk, the Gray method was used. 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.

**Results**

**Baseline Characteristics and Outcomes**

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

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/m²)                | 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 |
| CHADS² score               | 1.95±1.30              | 1.35±1.08                | 2.70±1.15           | <0.0001 |
| CHA²DS²-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 m²)      | 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±19.8           | 0.29    |
| HAS-BLED score             | 1.80±1.06              | 1.55±1.06                | 2.12±1.00           | <0.0001 |
| Prior bleeding             | 28 (2.1)               | 12 (1.6)                 | 16 (2.7)            | 0.25    |
| 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 CHADS², CHA²DS²-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).
Elderly and Younger 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                            | 1.06 (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 | 1.08 (0.66–1.77) 0.76 |
| Persistent or permanent AF | 1.13 (0.59–2.16) 0.72 | 1.08 (0.66–1.77) 0.76 | 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) 0.36 |
| 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).
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<sub>2</sub>, CHA<sub>2</sub>DS<sub>2</sub>-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**

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

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

| Variables                        | Non-elderly NVAF       | Elderly NVAF          |
|----------------------------------|-------------------------|-----------------------|
|                                  | Warfarin (n=371)        | DOAC (n=243)          | Warfarin (n=338)        | DOAC (n=186)          |
| Age (years)                      | 67.1±5.90               | 65.9±6.80             | 80.8±4.30               | 80.2±4.00             |
| Male sex                         | 0.02                    | 0.69                  | 0.08                   | 0.63                  |
| BMI (kg/m²)                      | 24.2±3.60               | 24.2±4.00             | 23.3±3.50               | 23.0±3.40             |
| Persistent or permanent AF       | 0.0006                  | 0.09                  | 244 (72.2)              | 108 (58.1)            |
| CHADS<sub>2</sub> score          | 125 (33.7)              | 69 (28.4)             | 145 (42.9)              | 57 (30.7)             |
| HAS-BLED score                   | 233 (62.8)              | 151 (62.1)            | 238 (70.4)              | 127 (68.3)            |
| Diabetes                         | 114 (30.7)              | 58 (23.9)             | 117 (34.6)              | 52 (28.0)             |
| Prior stroke or TIA              | 50 (13.5)               | 26 (10.7)             | 55 (16.3)               | 28 (15.1)             |
| Vascular disease                 | 71 (19.1)               | 34 (14.0)             | 102 (30.2)              | 41 (22.0)             |
| CHADS<sub>2</sub>-VASc score     | 1.54±1.08               | 1.36±1.01             | 2.81±1.18               | 2.57±1.07             |
| LA diameter (mm)                 | 45.3±7.90               | 42.9±7.30             | 46.1±8.80               | 44.1±8.40             |
| Hemoglobin (g/dL)                | 14.2±1.70               | 14.0±1.60             | 12.9±1.90               | 13.0±1.70             |
| eGFR (mL/min/1.73m²)             | 66.1±19.7               | 69.6±15.9             | 52.9±18.1               | 59.6±16.5             |
| Prior bleeding                   | 9 (2.4)                 | 1 (0.4)               | 9 (2.7)                 | 2 (1.1)               |
| HAS-BLED score                   | 1.77±1.07               | 1.37±0.97             | 2.21±1.01               | 1.82±0.94             |
| Post PCI                         | 26 (7.0)                | 13 (5.4)              | 37 (11.0)               | 18 (9.7)              |
| Cancer                           | 24 (6.5)                | 19 (7.8)              | 42 (12.4)               | 25 (13.4)             |
| Antiplatelet drugs               | 92 (24.8)               | 26 (10.7)             | 113 (33.4)              | 39 (21.0)             |

Unless indicated otherwise, data are given as the mean ± SD or n (%). Abbreviations as in Table 1.
The SAKURA AF Registry, 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. 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 the present study.

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.
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. 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, frailty, and multimorbidity, 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. 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 reported that in an analysis of the elderly population with a high incidence of death before 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 recommended the use of the incidence curve using cumulative incidence functions (Gray method) and the Fine-Gray regression model 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. 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. In other recent cohort studies, DOAC use was shown to lead to a lower rate of intracranial hemorrhage than warfarin use, and to improve quality-adjusted life years 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 DOAC 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.

References
1. Chugh SS, Havmoeller R, Narayanam K, Singh D, Rienstra M, Benjamin EJ, et al. Worldwide epidemiology of atrial fibrillation: A Global Burden of Disease 2010 Study. Circulation 2014; 129: 837 – 847.
2. Krijthe H, Fujiki A, Orgasa H, Ogawa S, Okumura K, Kubota I, et al. Prevalence of atrial fibrillation in the general population of Japan: An analysis based on periodic health examination. Int J Cardiol 2009; 137: 102 – 107.
3. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: The Framingham Study. Stroke 1991; 22: 983 – 988.
4. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, et al. Prevalence of diagnosed atrial fibrillation in adults: National implications for rhythm management and stroke prevention: The Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA 2001; 285: 2370 – 2375.
5. Ohsawa M, Okayama A, Sakata K, Kato K, Itai K, Onoda T, et al. Rapid increase in estimated number of persons with atrial fibrillation in Japan: An analysis from national surveys on cardiovascular diseases in 1980, 1990 and 2000. J Epidemiol 2005; 15: 194 – 196.
6. Yamashita Y, Hamatani Y, Esato M, Chun YH, Tsuji H, Wada H, et al. Clinical characteristics and outcomes in extreme elderly (age ≥85 years) Japanese patients with atrial fibrillation: The Fushimi AF Registry. Chest 2016; 149: 401 – 412.
7. Nishida T, Okumura Y, Yokoyama K, Matsumoto N, Tachibana E, Kuronuma K, et al. Oral anticoagulant use and clinical outcomes in elderly Japanese patients: Findings from the SAKURA AF Registry. Heart Vessels 2019; 34: 2021 – 2030.
8. Kato Y, Hayashi T, Tanahashi N, Kobayashi S. Cardioembolic stroke is the most serious problem in the aging society: Japan standard stroke registry study. J Stroke Cerebrovasc Dis 2015; 24: 811 – 814.
9. Fang MC, Go AS, Chang Y, Borowsky LH, Pomernacki NK, Udaltsova N, et al. Long-term survival after ischemic stroke in patients with atrial fibrillation. JAMA Cardiology 2014; 82: 1033 – 1037.
10. Hylek EM, Go AS, Chang Y, Jansvold NG, Henault LE, Selby JV, et al. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. N Engl J Med 2003; 349: 1019 — 1026.
11. Korotsune Y, Yamashita T, Akao M, Atarashi H, Ikeda K, Okumura K, et al. Baseline demographics and clinical characteristics in the All nip AF in the Elderly (ANAFIE) Registry. Circ J 2019; 83: 1538 – 1545.
12. Beyth RJ, Antani MR, Covinsky KE, Miller DG, Chren MM, Quinn LM, et al. When is warfarin prescribed to patients with nonhemorrhagic atrial fibrillation? J Gen Intern Med 1996; 11: 721 – 728.
13. Wallis CJD, Juvet T, Lee Y, Matta R, Herschorn S, Kodama R, et al. Association between use of antithrombotic medication and hematutia-related complications. JAMA Intern Med 2017; 17: 1260 – 1271.
14. Ohta M, Hayashi K, Mori Y, Sato H, Noto T, Kawahatsu K, et al. Impact of frailty on bleeding events related to anticoagulation therapy in patients with atrial fibrillation. Circ J 2021; 85: 235 – 242.
15. Halperin JL, Hankey GJ, Wojdyla DM, Piccini JP, Lokhnygina Y, Patel MR, et al. Efficacy and safety of rivaroxaban compared with warfarin among elderly patients with nonvalvular atrial fibrillation in the Rivaroxaban Once Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF). Circulation 2014; 130: 138 – 146.
16. Patti G, Lucerna M, Pecen L, Siller-Matula JM, Cavallari I, Kirchhof P, et al. Thromboembolic risk, bleeding outcomes and effect of different antithrombotic strategies in very elderly patients with atrial fibrillation: A sub-analysis from the PREFER in AF (PREvervention of Thromboembolic Events-European Registry in Atrial Fibrillation) trial. J Am Heart Assoc 2017; 6: e005657.
17. Chao TF, Liu CJ, Lin YJ, Chang SL, Lo LW, Hu YF, et al. Oral anticoagulation in very elderly patients with atrial fibrillation: A nationwide cohort study. Circulation 2018; 138: 37 – 47.
18. Yamashita T, Suzuki S, Inoue H, Akao M, Atarashi H, Ikeda T, et al. Two-year outcomes of more than 30,000 elderly patients with atrial fibrillation: Results from the All nip AF study. J Am Heart Assoc 2022; 11: 377 – 384.
19. Abdel-Qadir H, Fang J, Lee DS, Tu JV, Amir E, Austin PC, et al. Importance of considering competing risks in time-to-event
analyses: Application to stroke risk in a retrospective cohort study of elderly patients with atrial fibrillation. Circ Cardiovasc Qual Outcomes 2018; 11:e004580.
20. Hayashi K, Tsuda T, Nomura A, Fujino N, Nohara A, Sakata K, et al. Impact of B-type natriuretic peptide level on risk stratification of thromboembolism and death in patients with nonvalvular atrial fibrillation: The Hokuriku-Plus AF Registry. Circ J 2018; 82: 1271 – 1278.
21. Tsuda T, Hayashi K, Fujino N, Konno T, Tada H, Nomura A, et al. Effect of hypertrophic cardiomyopathy on the prediction of thromboembolism in patients with nonvalvular atrial fibrillation. Heart Rhythm 2019; 16: 829 – 837.
22. Yamagishi M, Tsuda T, Kato T, Furusuo H, Hayashi K. Cost-effectiveness for prevention of thromboembolism by antiocoagu-lants in non-valvular atrial fibrillation: Additional analysis from the Hokuriku-Plus AF Registry. Heart Vessels 2019; 34: 1024 – 1030.
23. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: Results from the National Registry of Atrial Fibrillation. JAMA 2001; 285: 2864–2870.
24. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: The Euro Heart Survey on atrial fibrillation. Chest 2010; 137: 263–272.
25. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ. Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: The Euro Heart Survey. Chest 2010; 138: 1093–1100.
26. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briët E. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost 1993; 69: 236–239.
27. Yasaka M, Minematsu K, Yamaguchi T. Optimal intensity of international normalized ratio in warfarin therapy for secondary prevention of stroke in patients with non-valvular atrial fibrillation. Intern Med 2001; 40: 1183–1188.
28. Yamagishi M, Tsuda T, Kato T, Furusuo H, Hayashi K. Cost-effectiveness for prevention of thromboembolism by antiocoagu-lants in non-valvular atrial fibrillation: Additional analysis from the Hokuriku-Plus AF Registry. Heart Vessels 2019; 34: 1024 – 1030.
29. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999; 94: 496–509.
30. Kanda Y. Investigation of the freely available easy-to-use software ‘EZR’ for medical statistics. Bone Marrow Transplant 2013; 48: 452–458.
31. Lip GY, Clementy N, Pericart L, Banerjee A, Fauchier L. Stroke and major bleeding risk in elderly patients aged ≥75 years with atrial fibrillation: The Loire Valley atrial fibrillation project. Stroke 2015; 46: 143–150.
32. Akao M, Chun YH, Wada H, Esato M, Hashimoto T, Abe M, et al. Current status of clinical background of patients with atrial fibrillation in a community-based survey: The Fushimi AF Registry. J Cardiol 2013; 61: 260–266.
33. Okumura Y, Yokoyama K, Matsumoto N, Tachibana E, Kuronuma K, Oiwa K, et al. Current use of direct oral anticoag-ulants for atrial fibrillation in Japan: Findings from the SAKURA AF Registry. J Arrhythm 2017; 33: 289–296.
34. Bogam A, Kuriita T, Abe H, Ando K, Ishikawa T, Imai K, et al. JCS/JHRS 2019 guideline on non-pharmacotherapy of cardiac arrhythmias. Circ J 2021; 85: 1104–1244.
35. Piccini JP, Hellkamp AS, Washam JB, Becker RC, Breithardt G, Berkowitz SD, et al. Polyparmacy and the efficacy and safety of rivaroxaban versus warfarin in the prevention of stroke in patients with nonvalvar atrial fibrillation. Circulation 2016; 133: 352–360.
36. Alexander KP, Brouwer MA, Mulder H, Vinereanu D, Lopes RD, Proietti M, et al. Outcomes of apixaban versus warfarin in patients with atrial fibrillation and multi-morbidity: Insights from the ARISTOTLE trial. Am Heart J 2019; 208: 123–131.
37. Livingstone S, Morales DR, Donnan PT, Payne K, Thompson AJ, Youn JH, et al. Effect of competing mortality risks on pre-dictive performance of the QRSK3 cardiovascular risk prediction tool in older people and those with comorbidity: External validation population cohort study. Lancet Healthy Longev 2021; 2: e352–e361.
38. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009; 361: 1139–1151.
39. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvar atrial fibrillation. N Engl J Med 2011; 365: 883–891.
40. Hori M, Matsumoto M, Tanahashi N, Momomura S, Uchiyama S, Goto S, et al. Rivaroxaban vs. warfarin in Japanese patients with atrial fibrillation: The J-ROCKET AF study. Circ J 2012; 76: 2104–2111.
41. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011; 365: 981–992.
42. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Apixaban vs. warfarin in patients with atrial fibrillation. N Engl J Med 2013; 369: 2093–2104.
43. Koretsune Y, Hoshino H, Matsuoy S, Ibuki T, Morimoto T. Comparative safety and effectiveness of apixaban vs. warfarin in oral anticoagulant-naive Japanese patients with non-valvular atrial fibrillation: A retrospective chart review study. Circ J 2022; 86: 213–221.
44. Shah SJ, Singer DE, Fang MC, Reynolds K, Go AS, Eckman MH. Net clinical benefit of oral anticoagulation among older adults with atrial fibrillation. Circ Cardiovasc Qual Outcomes 2019; 12: e006212.

Supplementary Files
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