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Original article

Assessment of the bleeding risk of anticoagulant treatment in non-severe frail octogenarians with atrial fibrillation

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ABSTRACT

Background: Physicians estimate the frailty in elderly patients with atrial fibrillation (AF) to aid in the decision making with respect to oral anticoagulant (OAC) therapy. There are limited data on the safety of OAC therapy in non-severe frail elderly patients. We evaluated the risk factors of bleeding among non-severe frail octogenarians with AF taking OACs.

Methods: Among 430 consecutive AF patients aged 80 years and over with non-severe frailty, we enrolled 346 patients [167 men, 83.7 (81.0–85.0) years] who were newly initiated on OACs: dabigatran, rivaroxaban, apixaban, edoxaban, or warfarin. To measure the frailty, the clinical frailty scale (CFS) was used. Non-severe frailty was defined as a CFS score of <7. The clinical factors were compared between the patients with and without bleeding during the OAC therapy.

Results: Out of the 346 patients enrolled, 266 (76.9%) received direct OACs (DOACs) and 80 (23.1%) warfarin. Of the 266 patients receiving DOACs, there were 204 (76.7%) prescribed appropriately adjusted-dose DOACs based on the approved Japanese recommendations. Of the 80 warfarin-treated patients, 52 (65.0%) were prescribed appropriately adjusted-dose warfarin. During a follow-up of 32.7 (14.0–51.0) months, bleeding events were detected in 59 patients (17.1%). Among the clinical factors, a multivariate analysis found that having a low body mass index (BMI) (<18.5 kg/m^2) was associated with the development of bleeding [hazard ratio (HR): 3.26, 95% confidence interval (CI): 1.65–6.50, $p < 0.01$)]. Moreover, having a low BMI remained an independent risk factor for bleeding in the patients treated with appropriately adjusted-dose OACs (HR: 2.17, 95% CI: 1.01–4.70, $p = 0.048$).

Conclusions: In non-severe frail octogenarians with AF taking OACs, having a low BMI was the most significant factor associated with the development of bleeding.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice. With the aging population, the burden of AF among patients aged 80 years and over is expected to rise 4-fold by the year 2050, representing more than half of all cases of AF [1]. Patients with AF have a five-fold increased risk of thromboembolism complications, such as an ischemic stroke [2] and it is estimated that AF is associated with approximately 30% of ischemic strokes in patients over the age of 80 years [3].

Frailty, as a clinical state of elderly populations, is confirmed as an independent risk factor of poor clinical outcomes associated with medical management [4]. So, physicians estimate the frailty in elderly patients with AF to aid in the decision making with respect to the oral anticoagulant (OAC) therapy for preventing ischemic strokes. The frailty status is one of the possible reasons why elderly patients with AF are not prescribed OACs. In severe frail elderly patients with AF, it may be appropriate to use no anticoagulation for ischemic stroke prevention [5]. However, there are limited data on the safety of an OAC therapy in non-severe frail elderly patients with AF. It is essential that they are not under-anticoagulated for unfounded fear of bleeding complications.

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The objective of this study was to evaluate the risk factors of bleeding among non-severe frail octogenarians with AF who were newly initiated with OACs. Also, we assessed the risk factors of bleeding among those treated with an appropriately adjusted-dose OAC.

Methods

Study population

Among 430 consecutive patients aged 80 years and over with non-severe frailty who were diagnosed with AF and were not anticoagulated under regular outpatient care or under admission, we enrolled 346 patients who were initiated with direct OACs (DOACs): dabigatran, rivaroxaban, apixaban, edoxaban, or warfarin between January 2011 and January 2017. Patients were categorized into DOAC or warfarin groups (dabigatran, rivaroxaban, apixaban, or edoxaban) based on their administered OAC. The first recorded OAC prescription date was designated as the index date. The reasons why 84 patients were not prescribed OACs were no justification provided (23.7%), a history of bleeding (16.7%), patient refusal (16.7%), severe renal dysfunction (14.3%), active bleeding (11.9%), or a poor patient condition (16.7%). The study flow chart is shown in Fig. 1.

Assessment of frailty

Frailty was assessed with the Clinical FrailtyScale (CFS) of the Canadian Study on Health & Aging. The CFS is a method for identifying frail individuals and classifying their degree of frailty, with scores ranging from 1 (very fit) to 9 (terminally ill) [6]. Each patient was attributed a CFS score by cardiologists when AF was diagnosed. Non-severe frailty was defined as a CFS score of <7.

OAC administration protocol

The choice of the OACs, whether the four DOACs or warfarin, for stroke prevention depended on the decision of each physician. We attempted to prescribe an appropriately adjusted-dose of DOACs based on the approved Japanese recommendations: either dabigatran 150 mg twice daily [110 mg twice daily in patients with a creatinine clearance (CrCl) of 30–49 ml/min or aged 70 years and older], rivaroxaban 15 mg once daily (10 mg once daily in patients with a CrCl of 15–49 ml/min), apixaban 5 mg twice daily [2.5 mg twice daily in patients with two or more of the following criteria: age $\geq$80 years, body weight (BW) $\leq$60 kg, and serum creatinine $\geq$1.5 mg/dl], or edoxaban 60 mg once daily (30 mg once daily in patients with BW $\leq$60 kg or a CrCl of 15–49 ml/min], or adjusted-dose warfarin for the management of the anticoagulant therapy. The warfarin dose was adjusted to a target international normalized ratio (INR) of 1.6–2.6 in accordance with the Japanese guidelines for patients with non-valvular AF [7]. The time in a therapeutic INR range (TTR) was calculated using the linear interpolation method, expressed as a percentage of the observation time [8]. The appropriate dose adjustment of warfarin was defined as a TTR with an INR value between 1.6 and 2.6 for over more than 65% of the entire treatment period.

Follow-up

Patients were followed until their first bleeding event, discontinuation of the treatment, a treatment switch, patient death, or end of the study period (January 2018), whichever occurred earliest. To monitor the adverse effects due to OACs, interviewing and examining the patients or usual blood tests, were performed every 1–3 months during the OAC therapy. Additional testing was performed as necessary when a bleeding complication was suspected.

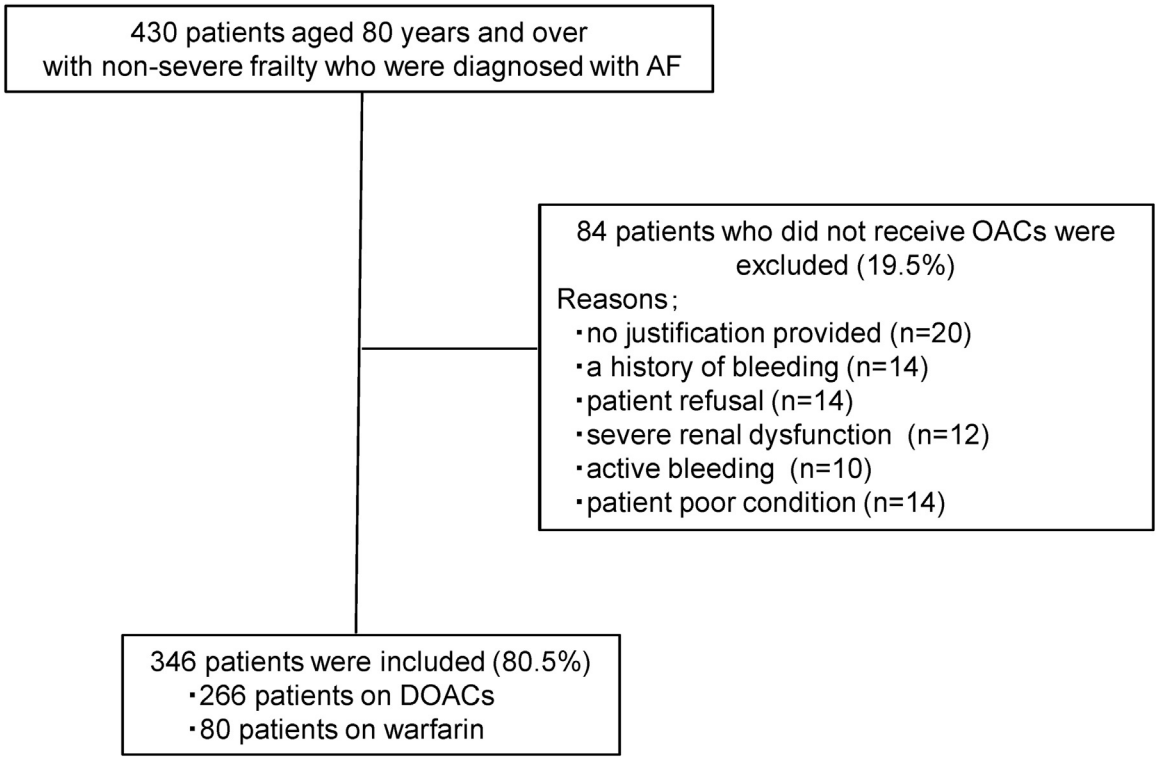

Fig. 1. Flow chart of the study. Three hundred forty-six consecutive non-severe frail octogenarians who were newly initiated on OACs were included in the present study. AF, atrial fibrillation; (D)OAC, (direct) oral anticoagulant.

In the present study, we categorized bleeding into three categories: major bleeding, clinically relevant non-major bleeding, and minor bleeding. Major bleeding was defined as bleeding requiring hospitalization, bleeding requiring a transfusion of ≥2 units of blood, or bleeding that was life-threatening during the use of OACs. Clinically relevant non-major bleeding was defined as bleeding not meeting the criteria for major bleeding, but requiring medical intervention, unscheduled consultation with a physician, temporary discontinuation of the study treatment, pain, or impairment of daily activities. Minor bleeding was defined as bleeding not meeting the criteria for major or clinically relevant non-major bleeding.

Statistical analysis

Data analyses were performed using EZR on R-commander version 1.24 software (Saitama Medical Center, Jichi Medical University, Saitama, Japan). All continuous variables were tested for the normality of the distribution using the Kolmogorov–Smirnov test. Continuous variables with a normal distribution were described as the mean ± standard deviation (SD), continuous variables with a skewed distribution were described as the median (quartile: 25–75%), and categorical variables were described as frequencies and percentages. Comparisons between patients with and without bleeding were analyzed using a univariate logistic regression analysis (Fisher's exact test, Unpaired *t*-test, or Mann–Whitney test). A multivariate logistic regression analysis using a Cox proportional hazard model was constructed to assess the most significant indices as clinical factors for the development of bleeding. In all tests, a *p*-value of 0.05 was considered as the cut-off for statistical significance.

Ethical consideration

The present study was approved by the Toho University Omori Medical Center Ethical Committee (approval no.: M17139), and informed consent was obtained from all patients before participation.

Results

Patient characteristics

One hundred sixty-seven patients (48.3%) were male and the mean age was 83.7 (81.0–85.0) years, mean BW 52.1 (43.3–60.0) kg, and mean body mass index (BMI) 21.6 (18.8–24.2) kg/m^2. Seventy-nine patients (22.8%) had a low BMI of less than 18.5 kg/m^2. The CFS was 1, 2, 3, 4, 5, and 6 in 2, 7, 101, 143, 68, and 25 of the 346 patients, respectively. The mean duration of the follow-up period was 32.7 (14.0–51.0) months. The baseline characteristics are listed in Table 1.

Table 1
Baseline characteristics.

All patients (n = 346)	
Male, number (%)	167 (48.3%)
Age (years)	83.7 (81.0–85.0)
Body mass index (kg/m^2)	21.6 (18.8–24.2)
Body weight (kg)	52.1 (43.3–60.0)
Hypertension, number (%)	266 (76.9%)
Diabetes mellitus, number (%)	77 (22.3%)
Congestive heart failure, number (%)	116 (33.5%)
Ischemic stroke, number (%)	70 (20.2%)
Coronary artery disease, number (%)	47 (13.6%)
PCI using stents (+)	35 (10.2%)
Smoking, number (%)	149 (43.1%)
Paroxysmal AF, number (%)	193 (55.8%)
Dementia (%)	53 (15.3%)
COPD (%)	17 (4.9%)
History of bleeding (%)	20 (5.8%)
CHADS2score	2.7 (2.0–3.0)
CHA_2DS_2-VASc score	5.3 (4.0–6.0)
Clinical Frailty Scale	4.0 (3.0–5.0)
HAS-BLED score	2.3 (2.0–3.0)
Serum creatinine (mg/dl)	0.9 (0.7–1.1)
eGFR (ml/min/1.73 m^2)	55.2 (43.9–63.8)
Creatinine clearance (ml/min)	44.6 (33.6–53.0)
Hemoglobin (ng/dl)	12.3 ± 1.8
Use of warfarin, number (%)	80 (23.1%)
Antiplatelet therapy, number (%)	79 (22.8%)
Aspirin	41 (11.8%)
ADP receptor inhibitors	19 (5.5%)
PDE3 inhibitors	12 (3.5%)
Others	24 (6.9%)
Treatment follow up (in months)	32.7 (14–51)

PCI, percutaneous coronary intervention; AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; ADP, adenosine diphosphate; PDE3, phosphodiesterase enzyme 3.
Data are expressed as the mean ± SD, median (25–75%), or number (%).

OAC prescription

There were 266 (76.9%) prescribed with DOACs, and 80 (23.1%) with warfarin. The number of patients who were prescribed dabigatran, ribaroxaban, apixaban, and edoxaban were 64, 80, 95, and 27, respectively. Of the 266 patients receiving DOACs, those prescribed an appropriately adjusted-dose of dabigatran, rivaroxaban, apixaban, and edoxaban were 46 (71.9%), 59 (73.7%), 72 (75.8%), and 24 (88.9%), respectively, those prescribed inappropriately low doses of dabigatran, rivaroxaban, apixaban, and edoxaban were 10 (15.6%), 13 (16.3%), 16 (16.8%), and 2 (7.4%), respectively, and those prescribed inappropriately high doses of dabigatran, rivaroxaban, apixaban, and edoxaban were 8 (12.5%), 8 (10.0%), 7 (7.4%), and 1 (3.7%), respectively. Of the 80 warfarin-treated patients, 52 (65.0%) were prescribed an appropriately adjusted-dose of warfarin. The mean TTR in the patients with an appropriate dose adjustment of warfarin was 69.7%. Two hundred fifty-six (74.0%) were treated with appropriately adjusted-dose OACs based on the approved Japanese recommendations out of the 346 patients administered OACs. When comparing the DOAC and warfarin-groups, the CrCl level was significantly lower in the warfarin-group than DOAC-group [DOAC group: 46.7 (35.9–54.8) versus the warfarin group: 37.3 (26.4–46.0), $p < 0.01$). On the other hand, the CrCl level did not differ significantly between the patients prescribed each of the four DOACs ($p = 0.77$).

Incidence of bleeding events

All patients

During the follow-up of 32.7 (14.0–51.0) months, bleeding events were detected in 59 patients (17.1%) while on anticoagulation. Of them, major bleeding was seen in 12 patients, clinically relevant non-major bleeding in 4, and minor bleeding in 43 (Fig. 2). Among the 12 major bleeding events, there was 1 involving hemoptysis, 1 hepatic bleeding, and 10 gastrointestinal bleeding. One patient prescribed warfarin, died from massive hematemesis due to a peptic ulcer. Gastrointestinal bleeding was the most common type of bleeding event.

Patients prescribed an appropriately adjusted-dose OAC

In 256 patients prescribed an appropriately adjusted-dose OAC, 43 (16.8%) had bleeding events. Among them, major bleeding occurred in 7 patients, clinically relevant non-major bleeding in 1, and minor bleeding in 35.

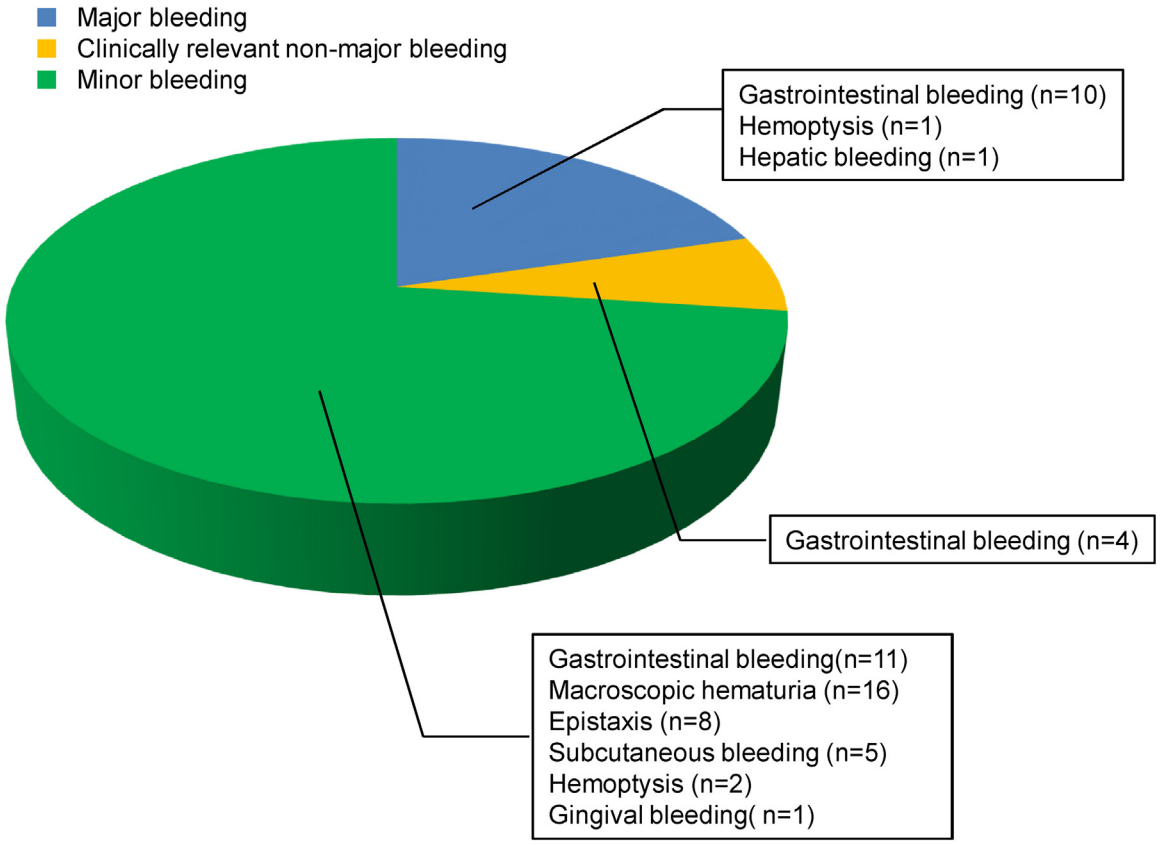

Fig. 2. The details of the bleeding events associated with the OAC therapy. The colors of the circles show the proportions of major bleeding, clinically relevant non-major bleeding, or minor bleeding. Gastrointestinal bleeding was the most common type of bleeding event.

Comparison of DOACs to warfarin

In the patients receiving DOACs 16.9% (45/266) had bleeding events, as did 17.5% (14/80) of those receiving warfarin ($p = 0.87$). Moreover, in the patients with DOACs, bleeding events were detected in 12.5% of patients (8/64) receiving dabigatran as compared to 22.5% (18/80) of those receiving rivaroxaban, 15.8% (15/95) receiving apixaban, and 14.8% (4/27) receiving edoxaban ($p = 0.44$).

Incidence of strokes/systemic embolisms and mortality

Overall, strokes/systemic embolisms (SEs) occurred in 10 patients (2.9%) during the follow-up period. Of the patients receiving DOACs, strokes/SEs occurred in 2.3% (6/266), as compared to 5.0% (4/80) in those receiving warfarin ($p = 0.25$). Further, strokes/SEs were detected in 4.7% of patients (3/64) receiving dabigatran as compared to 1.3% (1/80) of those receiving rivaroxaban, 1.1% (1/95) receiving apixaban, and 3.7% (1/27) receiving edoxaban ($p = 0.34$).

On the other hand, the mortality rate of the patients with OACs was 17.6% (61/346) during the follow-up period. The mortality rate did not differ significantly between the patients prescribed DOACs (16.2%) and warfarin (22.5%) ($p = 0.24$).

Risk factors for the development of bleeding

All patients

We divided the 346 patients into two groups, the bleeding group and non-bleeding group, and the patient characteristics were compared between the patients with and without bleeding. When comparing the two groups, the bleeding group had a significantly lower BMI [20.2 (17.5–22.6) vs. 21.9 (19.1–24.5) kg/m^2, $p < 0.01$], BW [49.5 (42.6–55.0) vs. 52.6 (44.0–60.5) kg, $p = 0.039$)], and hemoglobin level (11.9 ± 1.7 ng/dl vs. 12.4 ± 1.8 ng/dl, $p = 0.025$) (Table 2). The CrCl level and HAS-BLED scores were similar between those patients who experienced bleeding complications and those who did not. To test which risk factor was associated with bleeding, we performed a multivariate logistic regression analysis using a Cox proportional hazards model. Among the patient characteristics, having a low BMI (<18.5 kg/m^2) was significantly associated with the development of bleeding [hazard ratio (HR): 3.26, 95% confidence interval (CI): 1.65–6.50, $p < 0.01$] (Table 3a). The freedom rate from the occurrence of the bleeding events was compared between the BMI <18.5 kg/m^2 group and BMI ≥18.5 kg/m^2 group by a Kaplan–Meier model, and the rates differed significantly ($p < 0.01$) (Fig. 3).

Patients with appropriately adjusted-dose OACs

We divided the 256 patients with appropriately adjusted-dose OACs into two groups, the bleeding group and non-bleeding group, and the patient characteristics were compared between the patients with and without bleeding. Univariate logistic regression analyses revealed that the patients who developed bleeding had a significantly lower BMI [20.1 (17.5–22.5) kg/m^2 vs. 21.6 (18.9–24.2) kg/m^2, $p = 0.018$). A multivariate logistic regression analysis in the patients treated with appropriately adjusted-dose OACs showed that having a low BMI (<18.5 kg/m^2) remained an independent risk factor for bleeding (HR: 2.17, 95% CI: 1.01–4.70, $p = 0.048$) (Table 3b).

Discussion

Main findings

The main finding of the present study was that having a low BMI (<18.5 kg/m^2) was the most significant factor associated with the

Table 2
Comparison of the patient characteristics between bleeding and non-bleeding.

	Bleeding ($n=59$)	Non-bleeding ($n=287$)	p value
Male, number (%)	33 (55.9%)	134 (46.7%)	0.20**
Age (years)	84.0 (81–86)	83.6 (81–85)	0.56***
Body mass index (kg/m^2)	20.2 (17.5–22.6)	21.9 (19.1–24.4)	$<$ 0.01***
Body weight (kg)	49.5 (42.6–55.0)	52.6 (44.0–60.5)	0.039***
Hypertension, number (%)	47 (79.7%)	219 (76.3%)	0.78**
Diabetes mellitus, number (%)	13 (22.0%)	64 (22.3%)	1.0**
Congestive heart failure, number (%)	22 (37.3%)	94 (32.8%)	0.55**
Ischemic stroke, number (%)	14 (23.7%)	56 (19.5%)	0.48**
Coronary artery disease, number (%)	10 (16.9%)	37 (12.9%)	0.41**
PCI using stents (+)	8 (13.6%)	27 (9.4%)	0.35**
Smoking, number (%)	31 (52.5%)	118 (41.1%)	0.15**
Paroxysmal AF, number (%)	35 (59.3%)	158 (55.1%)	0.57**
Dementia (%)	12 (20.3%)	41 (14.3%)	0.24**
COPD (%)	3 (5.1%)	14 (4.9%)	1.0**
History of bleeding (%)	4 (6.8%)	16 (5.6%)	0.76**
$CHADS_2$ score	2.8 (2.0–4.0)	2.7 (2.0–3.0)	0.34***
CHA_2DS_2-VASc score	5.4 (5.0–6.0)	5.3 (4.0–6.0)	0.43***
Clinical Frailty Scale	4.2 (3.0–5.0)	4.0 (3.0–5.0)	0.48***
HAS-BLED score	2.4 (2.0–3.0)	2.2 (2.0–3.0)	0.16***
Serum creatinine (mg/dl)	0.95 (0.7–1.2)	0.94 (0.7–1.0)	0.95***
eGFR (ml/min/1.73 m^2)	54.6 (44.1–62.6)	55.3 (43.7–63.8)	0.87***
Creatinine clearance (ml/min)	41.4 (31.8–50.1)	45.2 (34.2–53.8)	0.43***
Hemoglobin (ng/dl)	11.9 ± 1.7	12.4 ± 1.8	0.025*
Use of warfarin, number (%)	14 (23.7%)	66 (23.0%)	0.87**
Antiplatelet therapy, number (%)	18 (30.5%)	61 (21.3%)	0.13**
Aspirin	10 (16.9%)	31 (10.8%)	0.19**
ADP receptor inhibitors	5 (8.5%)	14 (4.9%)	0.34**
PDE3 inhibitors	4 (6.8%)	8 (2.8%)	0.13**
Others	5 (8.5%)	19 (6.6%)	0.58**

PCI, percutaneous coronary intervention; AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; ADP, adenosine diphosphate; PDE3, phosphodiesterase enzyme 3. Data are expressed as the mean ± SD, median (25–75%), or number (%). p-values were determined by an *unpaired t-test, **Fisher's exact test, or ***Mann–Whitney test.

development of bleeding in non-severe frail octogenarians with AF who were newly initiated on OACs.

Anticoagulation in frail older patients with AF

The evaluation of frailty is important to help assess the suitability of an aggressive medical treatment, as it can result in dependency, poor outcomes, and/or mortality. A broadly defined scale, the CFS, was used, which has been verified as a useful rapid assessment tool of frailty [9,10] and an adverse outcome [11] and/or mortality predictor [12].

A previous study reported that patients classified as non-frail to only moderately frail measured with the CFS were 3.5 times more likely to receive anticoagulant therapy than the severe frail patients [13]. However, there are no definite guidelines for the prescription of OACs in elderly patients with AF that take their frailty into consideration. While the proposed algorithm provides guidance for the prescription of anticoagulation, including with

Table 3a
Risk factors for bleeding in the patients treated with oral anticoagulants by a Cox proportional hazard model.

Variable	HR (95%CI)	p-value
BMI $<$18.5 (kg/m^2)	3.26 (1.65–6.50)	$<$ 0.01
BW $\leq$50 (kg)	0.85 (0.42–1.71)	0.64
Age $\geq$85 (years)	1.14 (0.65–1.99)	0.64
HAS-BLED score $\geq$3	1.34 (0.70–2.55)	0.38
Chronic kidney disease	1.17 (0.66–2.08)	0.59
Hemoglobin $<$10.0 (ng/dl)	1.38 (0.78–2.45)	0.27
Use of warfarin (%)	0.80 (0.43–1.47)	0.47
Antiplatelet therapy (%)	1.32 (0.66–2.66)	0.44

BMI, body mass index; BW, body weight; HR, hazard ratio; CI, confidence interval.

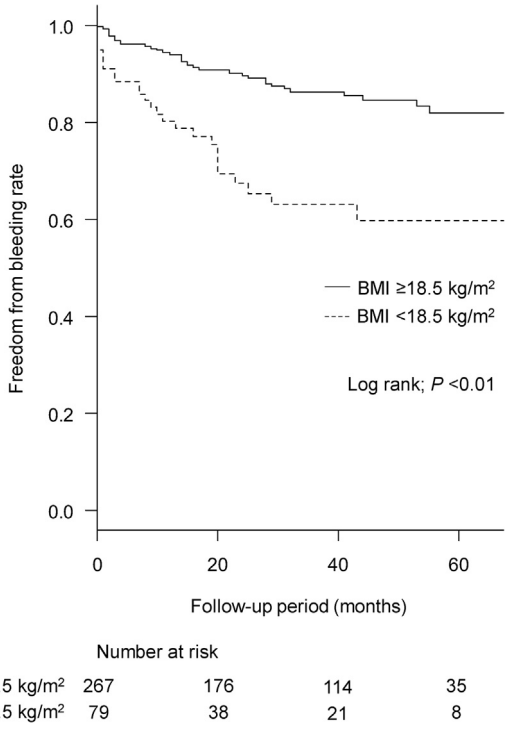

Fig. 3. Kaplan–Meier curves regarding the bleeding events during the follow-up period. This figure shows the comparison of the bleeding events between the patients with a body mass index (BMI) $<$18.5 kg/m^2 and BMI $\geq$18.5 kg/m^2. The rate differed significantly in the log-rank test between the two groups.

Table 3b
Risk factors for bleeding in the patients treated with appropriately adjusted-dose oral anticoagulants by a Cox proportional hazard model.

Variable	HR (95%CI)	*p*-value
BMI <18.5 (kg/m^2)	2.17 (1.01–4.70)	0.048
BW ≤50 (kg)	1.12 (0.51–2.48)	0.78
Age ≥85 (years)	1.11 (0.57–2.15)	0.75
HAS-BLED score ≥3	2.03 (0.97–4.25)	0.06
Chronic kidney disease	1.14 (0.56–2.32)	0.71
Hemoglobin <10.0 (ng/dl)	1.21 (0.62–2.36)	0.57
Use of warfarin (%)	0.57 (0.26–1.27)	0.17
Antiplatelet therapy (%)	1.07 (0.48–2.39)	0.87

BMI, body mass index; BW, body weight; HR, hazard ratio; CI, confidence interval.

DOACs or warfarin in frail elderly populations [5], it is important to note that the validity of this guidance has not been confirmed. To the best of our knowledge, this study is the first survey to estimate the incidence and risk factors of bleeding associated with OACs among non-severely frail octogenarians with AF.

Relationship between a low BMI and the development of bleeding

A low BMI is associated with frailty [14] and frail elderly populations are at greater risk of malnutrition. Although no agreed gold standard method exists to measure malnutrition, approximately 40% of elderly populations are at risk of malnutrition [15]. Renal and hepatic clearance of various drugs have been reported to be related to BMI [16]. Therefore, a low BMI and malnutrition are important considerations in elderly populations taking medications due to the potential for an altered drug metabolism. A retrospective study conducted in Korea reported that having a low BMI (<18.5 kg/m^2) was significantly associated with an increased risk of major bleeding compared to having a normal weight or being overweight to obese in AF patients receiving DOACs [17]. Our study also showed that the patients who had a low BMI had more bleeding events than those that did not despite an appropriate dose of OACs in accordance with the approved recommendations. A potential overdose of DOACs or warfarin has to be considered for AF octogenarians with a lower BMI, especially for a BMI <18.5 kg/m^2, even if their frailty is not so severe.

Comparison of the safety of DOACs to warfarin

A recent meta-analysis and real-world data demonstrated that DOACs have a favorable risk-benefit profile compared with warfarin in patients with AF [18,19]. On the other hand, a meta-analysis that compared DOACs and warfarin in elderly patients (≥75 years) with AF or venous thromboembolisms (VTE) showed that there was no significant difference in the safety outcome for both indications with DOACs compared with warfarin [20]. However, the relationship between the frailty and safe prescription of OACs was not studied sufficiently in those meta-analyses. Therefore, it is difficult to translate those outcomes to an older and particularly frail population.

Approximately 75% of OACs in the present study consisted of DOACs, and approximately 75% of OACs were given with appropriate doses. Under that condition, the type of OACs was not a risk factor for the development of bleeding whether its dose was appropriately adjusted or not. Actually, the rate of the incidence of bleeding events did not differ significantly between the DOACs and warfarin groups. These findings suggest that DOAC use in non-severe frail octogenarians with AF may be as safe as warfarin therapy. It is likely physically difficult for older patients with AF to go to regular INR checks at warfarin clinics even if their frailty is not so severe. This makes the older population prone to difficulties in keeping up with variable warfarin dosages. On the other hand, DOACs have the potential difficulty of monitoring and a currently limited availability of specific reversal agents. The choice of OACs, whether DOACs or warfarin, should be discussed with not only the patients, but also their caregivers.

Other risks of bleeding

Risk factors for bleeding among patients with AF or VTE who were prescribed OACs have been reported [21] and included renal dysfunction, low BW, and the HAS-BLED score as the common risk factors. We considered the reasons why those factors were not related to the OAC-associated bleeding in our study.

Renal dysfunction

In the present study, the CrCl level, besides the serum creatinine and estimated glomerular filtration rate, was not related to OAC-associated bleeding. We tended to avoid the administration of OACs in patients with severe renal dysfunction because renal impairment is a well-recognized risk factor for bleeding [22]. Even if OACs were administered, those patients stopped receiving OACs early before developing bleeding complications. As a result, the renal dysfunction may not have been associated with the development of bleeding.

Having a low BW

Large clinical trials of DOACs, for example, the RE-LY trial of dabigatran [23] and ARISTOTLE trial that compared apixaban with warfarin [24] demonstrated that major bleeding was more often observed in patients with a lower BW, especially if it was ≤50 or 60 kg. However, those studies were performed mainly in Western countries, and people in Western countries tend to be taller and have a heavier BW compared to those in Asia. Therefore, whether the definition of a low BW, that is, 50 or 60 kg, would be appropriate in Asian people is unclear. In such circumstances, the Fushimi AF Registry AF cohort conducted in Japan showed that the incidence of major bleeding was comparable between the low BW (≤50 kg) and non-low BW groups (>50 kg) among AF patients prescribed DOACs or warfarin [25]. In our study also, having a low BW was not an independent risk factor of bleeding events. Because of the global disparities among countries and the height difference among the various populations, the BW alone might not properly reflect the body composition for a drug titration, unlike the BMI.

HAS-BLED score

The HAS-BLED score is a widely accepted assessment tool for predicting the risk of bleeding in patients with warfarin treatment [26,27]. While this score defines an age over 65 years as a risk factor, it is well recognized that the bleeding risk continues to increase with an advancing age beyond 65 years. Therefore, it may be important to consider the frailty and other factors, such as a low BMI, which were confirmed as a risk factor of bleeding in the present study. Therefore, it may be difficult to translate the use of the HAS-BLED score for very elderly patients, particularly frail populations.

Limitations

This study had some potential limitations. First, a single measure of frailty was used, so patients may have been misclassified based on other definitions of frailty. Second, it was a retrospective study conducted at a single institute. Treatment with DOACs or warfarin was selected by the attending physician, and the baseline characteristics of the patients and differences in the cost (DOACs are more expensive than warfarin) may have

influenced the choice of the medications. Third, this study had a small sample size, which might have resulted in statistical bias. In particular, there were only 27 patients taking edoxaban when our survey was conducted (January 2011 to January 2017), because of the limited spread within the market during that early period after it obtained approval. Fourth, the follow-up duration was relatively short. Further research is necessary with more patients and long-term follow-up. Nevertheless, the results were found to be clear and statistically significant.

Conclusions

In non-severely frail octogenarians with AF taking OACs, having a low BMI was the most significant factor associated with the development of bleeding. Particular consideration should be given to the decision on an anticoagulant therapy in non-severe frail octogenarians with a lower BMI.

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Conflicts of interest

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