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ORIGINAL ARTICLE
Atrial Fibrillation

Impact of Frailty on Bleeding Events Related to Anticoagulation Therapy in Patients With Atrial Fibrillation

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Background: Although anticoagulation is the key treatment to prevent stroke in patients with atrial fibrillation (AF), including elderly patients, anticoagulation is sometimes withheld for elderly people because of concerns about frailty. However, it remains unknown whether frailty increases bleeding events.

Methods and Results: A total of 120 consecutive non-valvular AF patients admitted with symptoms of AF or congestive heart failure were included in this study. Frailty was assessed using the Cardiovascular Health Study (CHS) frailty index. We performed a retrospective analysis of the risk factors associated with major bleeding events. After a median follow-up of 518 days, major bleeding events occurred in 17 (14.2%) patients. Patients with major bleeding events had a higher CHS frailty index (P=0.015). The cutoff value for high-risk CHS frailty index was 2 (area under the ROC curve: 0.68 [95% confidence interval (CI): 0.57–0.78]). The event-free rates at 2 years were 97.6% (95% CI: 83.9–99.7) in patients with a CHS frailty index <2 and 59.6% (95% CI: 27.9–81.0) for those with a CHS frailty index ≥2 (P<0.001).

Conclusions: Frailty is associated with increased bleeding events related to anticoagulant therapy in patients previously hospitalized with AF. Greater care should be taken with patients with a CHS frailty index ≥2.

Key Words: Anticoagulation; Atrial fibrillation; Frailty; Hemorrhage

Atrial fibrillation (AF) is common, especially in the elderly, and associated with heart failure (HF), stroke, and death.[1] The management of AF in the elderly is important, not only because of its increasing prevalence with age but also because increasing age is an independent risk factor for HF, stroke, and death due to AF.[2]

Anticoagulation is one of the key treatments to prevent stroke in AF, but decision-making about whether to withhold or initiate anticoagulation is a growing challenge for physicians. Various guidelines recommend prescribing anticoagulants for people over 75 years old.[3,4] On the other hand, bleeding is the most important complication of anticoagulant therapy and a major concern for both physicians and patients. According to a recent study of a large cohort of patients with AF using a simulation model, the net clinical benefit of anticoagulation decreases in patients aged >75 years.[5]

In real world data, the absence or underdosing of anticoagulant drugs is not rare, especially among elderly AF patients.[6–8] Factors such as previous bleeding, frailty, and an overall high bleeding risk are the most frequently reported reasons for withholding anticoagulation.[9] A previous study demonstrated that approximately half of the hospitalized frail patients with AF did not receive anticoagulant therapy even without contraindications.[10]

A recent meta-analysis showed that frailty is associated with increased stroke incidence, mortality, symptom severity, and the length of hospital stay in patients with AF.[11] Although frailty is associated with bleeding events under several circumstances, such as previous acute coronary syndrome and the periprocedural period of transcatheter or surgical aortic valve replacement,[12,13] it remains unclear whether frailty increases bleeding events in patients with anticoagulant therapy for AF. The objective of this study was to investigate how frailty influences bleeding events related to anticoagulant therapy in patients with AF.

Methods

Study Design and Population

We retrospectively analyzed 120 consecutive non-valvular

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Table 1. Baseline Clinical Characteristics of Non-Valvular AF Patients With Anticoagulant Therapy Hospitalized for Symptoms of AF or Congestive Heart Failure, Before Follow-up for Major Bleeding Events Over a Median 518 Days

Characteristics	Overall (n=120)	No major bleeding event (n=103)	Major bleeding event (n=17)	P value
Age, years, mean (±SD)	77.7 (9.5)	77.3 (9.8)	80.5 (7.0)	0.189
<65, n (%)	10 (8.3)	10 (9.7)	0 (0.0)	0.534
65–74, n (%)	29 (24.2)	25 (24.3)	4 (23.5)	
≥75, n (%)	81 (67.5)	68 (66.0)	13 (76.5)	
Male sex, n (%)	72 (60.0)	61 (59.2)	11 (64.7)	0.792
Weight, kg, mean (±SD)	58.5 (12.9)	58.2 (13.1)	60.1 (12.0)	0.565
BMI, kg/m^2, mean (±SD)	23.3 (4.4)	23.1 (4.4)	24.4 (4.4)	0.286
Length of hospital stay, days, mean (±SD)	18.3 (15.3)	18.4 (16.0)	18.0 (10.7)	0.923
Paroxysmal AF, n (%)	59 (49.2)	52 (50.5)	7 (41.2)	0.603
Hypertension, n (%)	73 (60.8)	63 (61.2)	10 (58.8)	1.000
Dyslipidemia, n (%)	38 (31.7)	29 (28.2)	9 (52.9)	0.052
Coronary artery disease, n (%)	35 (29.2)	28 (27.2)	7 (41.2)	0.258
Diabetes, n (%)	28 (23.3)	24 (23.3)	4 (23.5)	1.000
Chronic kidney disease, n (%)	89 (74.2)	73 (70.9)	16 (94.1)	0.069
Dialysis, n (%)	3 (2.5)	2 (1.9)	1 (5.9)	0.370
Congestive heart failure, n (%)	113 (95.0)	96 (94.1)	17 (100.0)	0.592
Previous stroke or transient ischemic attack, n (%)	29 (24.2)	27 (26.2)	2 (11.8)	0.239
Previous major bleeding event, n (%)	9 (7.5)	9 (8.7)	0 (0.0)	0.356
$CHADS_2$ score, mean (±SD)	2.0 (1.2)	2.0 (1.2)	1.8 (1.0)	0.535
CHA_2DS_2-VASc score, mean (±SD)	3.1 (1.3)	3.1 (1.3)	3.4 (1.1)	0.385
NYHA, mean (±SD)	2.4 (0.9)	2.4 (0.9)	2.5 (0.8)	0.525
HAS-BLED score, mean (±SD)	3.1 (1.1)	3.0 (1.1)	3.2 (0.8)	0.449
Oral anticoagulant agent, n (%)				
Warfarin	49 (40.8)	40 (38.8)	9 (52.9)	0.297
Direct oral anticoagulant	71 (59.2)	63 (61.2)	8 (47.1)	
Underdosing of oral anticoagulant agent, n (%)				
Warfarin	15 (12.5)	13 (12.6)	2 (11.8)	0.667
Direct oral anticoagulant	17 (14.2)	15 (14.6)	2 (11.8)	
Coadministration of antiplatelet agent, n (%)				
Single-antiplatelet therapy	38 (31.7)	30 (29.1)	8 (47.1)	0.310
Dual-antiplatelet therapy	9 (7.5)	8 (7.8)	1 (5.9)	
No. of medications (±SD)	10.6 (3.9)	10.4 (3.8)	11.9 (4.4)	0.147
Alb, g/dL, mean (±SD)	3.6 (0.5)	3.5 (0.5)	3.7 (0.5)	0.175
Hb, g/dL, mean (±SD)	12.1 (1.9)	12.1 (1.9)	12.0 (1.7)	0.777
Cr, mg/dL, mean (±SD)	1.4 (1.2)	1.4 (1.3)	1.2 (0.4)	0.634
CCr, mL/min, mean (±SD)	44.4 (22.1)	45.1 (23.4)	40.1 (10.2)	0.390
BNP, pg/mL, mean (±SD)	744.8 (713.4)	787.2 (753.5)	495.8 (317.1)	0.120
LVEF, %, mean (±SD)	45.2 (18.6)	44.4 (18.7)	49.6 (17.9)	0.288
E/E', mean (±SD)	15.8 (7.3)	16.0 (7.2)	14.4 (7.7)	0.427
LAD, mm, mean (±SD)	50.8 (13.6)	50.4 (14.2)	53.3 (8.6)	0.427
LAVI, mL/m^2, mean (±SD)	73.3 (26.1)	71.9 (22.8)	81.6 (41.0)	0.159

P values were generated by Student's t-test for continuous variables and Chi-square test for categorical variables. $CHADS_2$=congestive heart failure, 1 point; hypertension, 1 point; ≥75 years old, 2 points; diabetes mellitus, 1 point; previous stroke, transient ischemic attack or thromboembolism, 2 points. CHA_2DS_2-VASc=congestive heart failure, 1 point; hypertension, 1 point; ≥75 years old, 2 points; diabetes mellitus, 1 point; previous stroke, transient ischemic attack or thromboembolism, 2 points; vascular disease, 1 point; 65–74 years old, 1 point; female sex, 1 point. HAS-BLED=hypertension, 1 point; >65 years old, 1 point; abnormal renal function, 1 point; abnormal liver function 1 point; stroke history, 1 point; bleeding history or predisposition, 1 point; labile international normalized ratio, 1 point; ethanol or drug abuse, 1 point; drug predisposing to bleeding, 1 point. AF, atrial fibrillation; BMI, body mass index; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; Cr, creatinine; CCr, creatinine clearance; Hb, hemoglobin; LAD, left atrial diameter; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

AF patients on anticoagulant therapy who were admitted with AF symptoms or congestive HF symptoms from December 1, 2016 to December 31, 2018. The patients included 72 (58.5%) males aged 77.7±9.5 years. Patients were excluded if they met any of the following criteria: other indication for anticoagulation, death during hospitalization, or hospitalization duration too short to assess frailty (<5 days). The study protocol was in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Teine Keijinkai Hospital (2-019231-00).

Table 2. Frailty Assessment of Non-Valvular AF Patients With Anticoagulant Therapy, Before Follow-up for Major Bleeding Events Over a Median 518 Days

Frailty assessment	Overall (n=120)	No major bleeding event (n=103)	Major bleeding event (n=17)	P value
Weight loss, n, (%)	36 (30.0)	31 (30.1)	5 (29.4)	1.000
Grip strength, kg, mean (±SD)	20.4 (9.6)	20.8 (9.9)	18.2 (6.9)	0.324
Gait speed, m/s, mean (±SD)	1.9 (1.3)	1.9 (1.3)	1.6 (1.2)	0.371
Exhaution, n, (%)	19 (15.8)	14 (13.6)	5 (29.4)	0.144
Katz, mean (±SD)	3.50 (2.06)	3.5 (2.1)	3.8 (2.0)	0.486
FIM, mean (±SD)	90.3 (25.3)	91.0 (25.5)	86.1 (24.4)	0.464
MMSE, mean (±SD)	26.3 (4.6)	26.3 (4.8)	26.4 (3.5)	0.895
CHS frailty index, mean (±SD)	1.9 (1.1)	1.8 (1.2)	2.5 (0.9)	0.015
0 point (non-frail), n, (%)	14 (11.7)	14 (13.6)	0 (0.0)	0.318
1–2 points (pre-frail), n, (%)	72 (60.0)	61 (59.2)	11 (64.7)	
3–5 points (frail), n, (%)	34 (28.3)	28 (27.2)	6 (35.3)	

P values were generated by Student's t-test for continuous variables and Chi-square test for categorical variables. AF, atrial fibrillation; CHS frailty index, Cardiovascular Health Study frailty index; FIM, Functional Independence Measure; MMSE, Mini-Mental Scale Examination.

Study Measurements

Baseline demographic, clinical, laboratory, and echocardiographic information were retrieved from the electronic medical records. The patients' renal function was estimated using the Cockcroft and Gault formula, and the creatinine clearance (CCr) was used to check the appropriateness of anticoagulant dosing. The appropriate doses of direct anticoagulants (DOACs) and the therapeutic range for warfarin were assessed, and underdosing was defined as a dose lower than the drug-specific recommended dose according to renal function (CCr or serum creatinine), age, weight, and concomitant interacting medications. Different dosages of rivaroxaban are used in Japan than in other countries: 15 mg QD for normal renal function and 10 mg QD for CCr <50 mL/min. The therapeutic range of warfarin was evaluated by the latest laboratory data before discharge based on Japanese AF guidelines: an international normalized ratio range of 1.6–2.6 for patients aged ≥70 years, and 2–3 for all others.[14]

Frailty was measured during hospitalization using the Cardiovascular Health Study (CHS) frailty index. The CHS frailty index defines the presence of frailty and pre-frailty by 5 core components: shrinking, weakness, exhaustion, slowness, and low physical activity.[15] Individuals with 3 components are considered frail, and those with 1 or 2 components are considered pre-frail. Each component was evaluated by physical therapists as follows. Shrinking was defined as unintentional weight loss ≥2–3 kg in the previous 6 months. This threshold is commonly accepted in Japan and was originally used by the Japan Ministry of Health, Labour and Welfare as an indicator of nutrition for identifying vulnerable community-dwelling older adults in the long-term care insurance system.[16,17] Weakness was defined by grip strength less than the exact value stratified by sex and body mass index (BMI) (kg/m^2). The cutoff values of grip strengths in males were ≤29 kg for BMI ≤24, ≤30 kg for BMI=24–28, and ≤32 kg for BMI >28. Those in females were ≤17 kg for BMI ≤23, ≤17.3 kg for BMI=23–26, ≤18 kg for BMI=26–29, and ≤21 kg for BMI >29. Exhaustion was indicated by an affirmative answer to 1 of the following 2 questions asked by a physical therapist "In the previous month, did you feel that everything you did was an effort?" and "Did you feel exhausted without any reason?" Slowness was defined as gait speed slower than the exact value stratified by sex and standing height, based on the time for a 5-m walking test at maximum walking speed. The cutoff values for walking velocity in males were ≥0.76 m/s for height <173 cm and ≥0.65 m/s for height ≥173 cm, and those in females were ≥0.76 m/s for height <159 cm and ≥0.65 m/s for height ≥159 cm. According to studies evaluating the effect of frailty on prognosis after transcatheter aortic valve replacement, instead of self-reported physical activity, independence in activities of daily living (ADL) was assessed by the Katz ADL survey.[18,19] The Katz survey defines dependence as needing assistance with any 1 of 6 specified ADLs. We also performed additional assessments, including serum albumin level as a marker of malnutrition, Functional Independence Measurement (FIM) for detailed assessment of ADL, and the Mini-Mental Scale Examination (MMSE) for evaluation of cognitive function.[20,21]

Study Outcomes

The primary outcome was a major bleeding event after discharge. Major bleeding was defined as reduction in hemoglobin by ≥2 g/dL, transfusion of ≥2 units of blood, or symptomatic bleeding in a critical area or organ, following the definition by the International Society on Thrombosis and Hemostasis.[22]

Statistical Analysis

We performed a retrospective analysis of the risk factors associated with bleeding events. Baseline characteristics of the patients were compared by Student's t-test for continuous variables and Chi-square test for categorical variables. On factors identified with P<0.01 by these methods, univariate and multivariate analyses with a Cox proportional hazard model were performed to define the independent predictors of bleeding risk. Receiver operating characteristic (ROC) analysis was performed to determine the optimal cutoff value of the independent predictor that exhibited optimal sensitivity and specificity. The value for the maximum of the Youden index was considered as the optimal cutoff point. The Kaplan-Meier method was used to create time-dependent cumulative event-free curves, which were compared using the log-rank test. P<0.05 was considered statistically significant. All statistical analyses were performed

Table 3. Univariate and Multivariate Analyses of Risk Factors for Major Bleeding Events in Non-Valvular AF Patients With Anticoagulant Therapy

	HR	95% CI		P value
		Lower	Upper	
Univariate analysis				
Chronic kidney disease	6.527	0.860	49.54	0.070
Dyslipidemia	2.414	0.930	6.266	0.070
CHS frailty index	2.057	1.338	3.164	0.001
Multivariate analysis				
Chronic kidney disease	5.232	0.687	39.87	0.110
Dyslipidemia	2.074	0.773	5.566	0.147
CHS frailty index	1.846	1.172	2.908	0.008

AF, atrial fibrillation; CHS frailty index, Cardiovascular Health Study frailty index; CI, confidence interval; HR, hazard ratio.

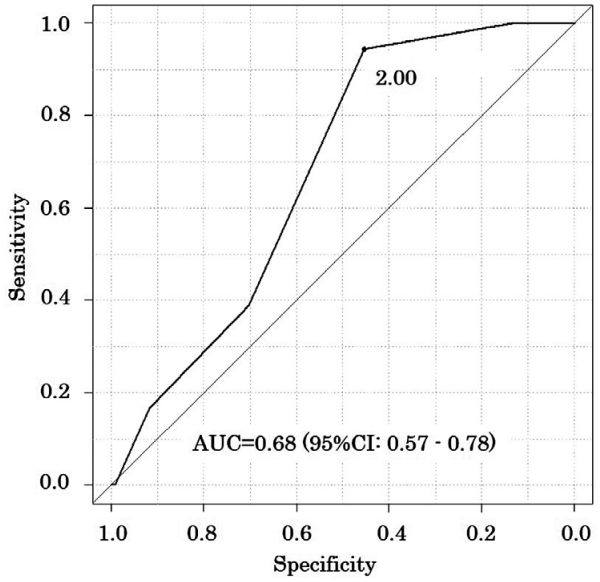

Figure 1. Receiver operating characteristic curve (ROC) for prediction of major bleeding events in elderly patients with atrial fibrillation based on the Cardiovascular Health Study frailty index. Determination of optimal cutoff values of the frailty index for identification of major bleeding events by ROC analysis. The cutoff value determined by the maximum Youden index was 2.00 (sensitivity, 0.494; specificity, 0.929). AUC, area under the curve; CI, confidence interval.

with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) designed to add statistical functions frequently used in biostatistics.[23]

Results

Primary Outcome and Patients' Characteristics

During a median follow-up of 518 days, major bleeding events occurred in 17 (14.2%) patients. The bleeding events included 8 (44.4%) gastrointestinal and 2 (13.3%) intracranial hemorrhages. The causes of gastrointestinal bleeding included angiodysplasia (n=4), diverticular disease (n=2), gastric ulcer (n=1), and gastric cancer (n=1). Intracranial hemorrhages were subdural hematoma (n=1) and intracerebral hemorrhage (n=1), and were caused by falls.

The baseline characteristics of all patients and the comparison between the bleeding and no bleeding groups are shown in **Table 1**. Several factors often associated with bleeding risk showed no significant differences between patients with and without bleeding events, such as the coadministration of antiplatelet agents, dialysis-dependent kidney disease, history of major bleeding, and the HAS-BLED score.

Relationship Between Frailty and Major Bleeding Events

In the whole group, the prevalence of pre-frailty and frailty evaluated by the CHS frailty index was 72 (60.0%) and 34 (28.3%), respectively. The patients with major bleeding events had higher CHS frailty index scores (P=0.015) than those without major bleeding (**Table 2**). Considering each component of the CHS frailty index separately, no factors were significantly different between the bleeding and no bleeding groups. The multivariate Cox proportional hazards model identified the CHS frailty index as the only significant determinant of major bleeding events (**Table 3**). Using the ROC curve, the cutoff value for CHS frailty index was 2.00 (area under the ROC curve: 0.68 [95% confidence interval (CI): 0.58–0.79]) (**Figure 1**). During the entire follow-up, major bleeding events occurred in 1 of 49 (2.0%) patients with a CHS frailty index <2 and in 16 of 71 (22.5%) patients with a CHS frailty index ≥2. The event-free rates at 2 years were 97.6% (95% CI: 83.9–99.7) in patients with a CHS frailty index <2 and 59.6% (95% CI: 27.9–81.0) in patients with a CHS frailty index ≥2 (P<0.001) (**Figure 2A**). When stratified by 3 groups, the event-free rates at 2 years were 100% (95% CI: 100.0–100.0) in non-frail patients (CHS frailty index=0), 79.0% (95% CI: 59.3–89.9) in pre-frail patients (CHS frailty index=1–2), and 73.5% (95% CI: 47.8–87.9) in frail patients (CHS frailty index=3–5) (P=0.087) (**Figure 2B**).

Comparison of Patients With CHS Frailty Index <2 and ≥2

Patients with CHS frailty index ≥2 were significantly older, weighed less and had lower BMI, with higher rates of hypertension, coronary artery disease, and chronic kidney disease, than patients with CHS frailty index <2 (**Table 4**).

Although the $CHADS_2$ and CHA_2DS_2-VASc scores were higher in patients with CHS frailty index ≥2 (**Table 4**), the event-free rates of thromboembolic events at 2 years

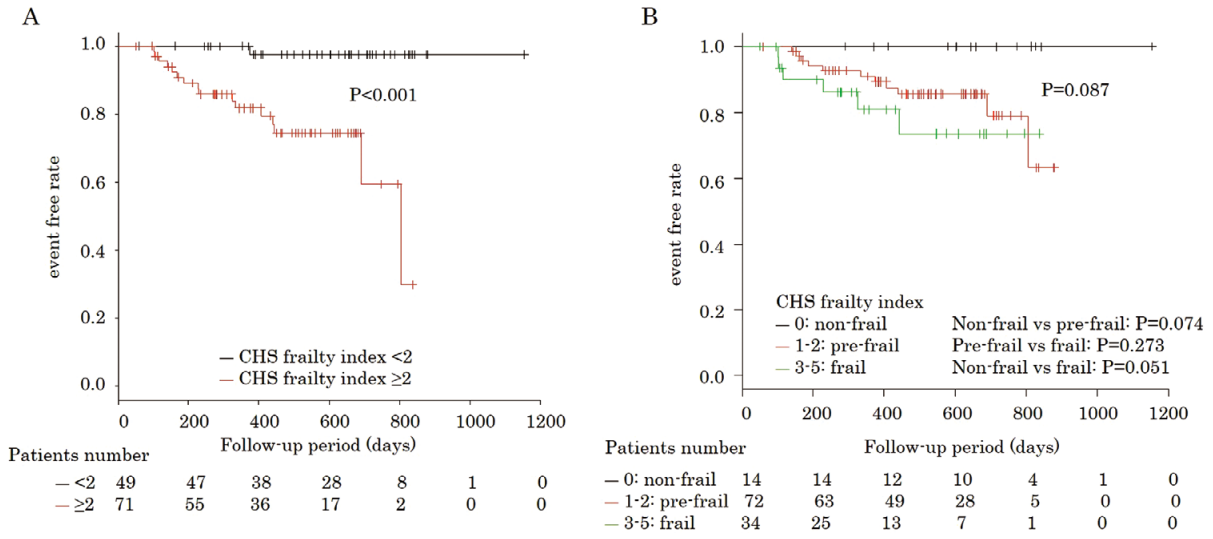

Figure 2. Kaplan-Meier estimates of major bleeding event-free survival in elderly patients with atrial fibrillation stratified by Cardiovascular Health Study (CHS) frailty index (**A**) <2 and ≥2, and (**B**) 0, 1–2, and 3–5.

were not statistically different: 98.0% (95% CI: 86.4–99.7) in patients with CHS frailty index <2 and 96.9% (95% CI: 88.3–99.2) in patients with CHS frailty index ≥2 (P=0.792).

The event-free rates of all-cause death at 2 years were 92.0% (95% CI: 76.9–97.4) in patients with CHS frailty index <2 and 75.7% (95% CI: 50.0–89.5) in patients with CHS frailty index ≥2 (P=0.138).

Discussion

Our findings showed that frailty was a risk factor for bleeding events related to anticoagulant therapy in patients with AF. To our knowledge, this is the first study to demonstrate an association between frailty and bleeding events in AF patients on anticoagulant therapy.

Frailty involves age-dependent deregulation of several biological pathways and systems, encompassing sarcopenia, age-associated hormonal derangements, inflammation, and nutritional or metabolic deficiencies. Frail individuals are at much higher risk of falls, fractures, infections, developing disabilities, hospitalization, institutionalization, and death compared with their age-matched non-frail counterparts.[15] Although frailty is associated with advanced age and increased disability, evidence suggests that neither old age nor disability alone identifies those at highest risk of adverse outcomes.[24] Thus, frailty is thought to reflect an individual's biological age and be a more accurate predictor of morbidity and mortality than chronological age.

There are a number of mechanisms by which frailty could mediate bleeding. Variable pharmacokinetics and inappropriate medication dosing can increase the risk. Epidemiological studies have shown that frail people are more likely to receive polypharmacy than non-frail individuals.[25] Similarly, in our study, patients with CHS frailty index ≥2 received more medications, including antiplatelet agents (**Table 4**). Consequently, frail patients with AF receiving anticoagulants may be taking drugs that alter the absorption, distribution, and metabolism of traditional oral anticoagulants or the direct factor inhibitors and therefore increase the risk of bleeding.[26,27] In addition, falls, which were the cause of the intracranial hemorrhages in this study, are associated with both polypharmacy and frailty.[28,29] Furthermore, kidney function may be overestimated by the serum creatinine levels of frail patients due to their reduced muscle bulk,[30] which might explain the lower weight and BMI in patients with CHS frailty index ≥2 in this study (**Table 4**). This can lead to either overdosing of anticoagulant or inadequate prescription to patients with contraindications, resulting in a higher risk of bleeding.

Reduced perivascular support is another possible mechanism of increased bleeding risk in frail patients. Skin stiffness decreases as less collagen is produced by fibroblasts, elastin fibers start to be degraded, and collagen fibers become more disorganized.[31] These changes result in an increased fragility of blood vessels, leading to tears in superficial vessels caused by only minimal trauma.[31] Similar changes are also observed in the oral mucosa of frail elderly patients.[32] Moreover, capillary fragility may also contribute to bleeding risk. In general, as pressure increases in the proximal arteries during cardiac contraction, distal arterioles will vasoconstrict to limit pressure and blood flow into the microcirculation through a mechanism called myogenic vasoconstriction.[33] However, in the elderly, the regulation of blood flow into structurally fragile capillaries is affected, resulting in higher capillary pressure and rupture of capillaries.[34,35]

Studies have shown that frailty influences a physician's decision not to prescribe anticoagulants.[9,10] In 1 study, patients who did not receive anticoagulant therapy at discharge had higher bleeding and frailty scores, and this was associated with higher rates of both bleeding and stroke.[14] On the other hand, accurate determination of bleeding risk in the elderly is reported to be difficult with existing risk-prediction scores, indicating a clear need for improvement in clinical utility.[36,37] Accurate bleeding prediction models could reduce overtreatment with anti-

Table 4. Comparison of Clinical Characteristics Between CHS Frailty Index <2 and ≥2, Before Follow-up for Major Bleeding Events Over a Median 518 Days

Characteristics	CHS frailty index <2 (n=49)	CHS frailty index ≥2 (n=71)	P value
Age, years, mean (±SD)	72.9 (9.0)	81.1 (8.3)	<0.001
<65, n (%)	7 (14.3)	3 (4.2)	0.001
65–74, n (%)	18 (36.7)	11 (15.5)	
≥75, n (%)	24 (49.0)	57 (80.3)	
Male sex, n (%)	32 (65.3)	40 (56.3)	0.349
Weight, kg, mean (±SD)	63.7 (13.7)	54.8 (11.0)	<0.001
BMI, kg/m^2, mean (±SD)	24.5 (4.6)	22.5 (4.1)	0.013
Length of hospital stay, days, mean (±SD)	17.2 (18.9)	19.1 (12.3)	0.489
Paroxysmal AF, n (%)	24 (49.0)	35 (49.3)	1.000
Hypertension, n (%)	24 (49.0)	49 (69.0)	0.036
Dyslipidemia, n (%)	14 (28.6)	24 (33.8)	0.690
Coronary artery disease, n (%)	8 (16.3)	27 (38.0)	0.014
Diabetes, n (%)	10 (20.4)	18 (25.4)	0.661
Chronic kidney disease, n (%)	30 (61.2)	59 (83.1)	0.010
Dialysis, n (%)	1 (2.0)	2 (2.8)	1.000
Congestive heart failure, n (%)	47 (95.9)	66 (94.3)	1.000
Previous stroke or transient ischemic attack, n (%)	10 (20.4)	19 (26.8)	0.517
Previous major bleeding event, n (%)	5 (10.2)	4 (5.6)	0.484
$CHADS_2$ score, mean (±SD)	1.6 (1.2)	2.3 (1.1)	0.001
CHA_2DS_2-VASc score, mean (±SD)	2.5 (1.3)	3.5 (1.1)	<0.001
NYHA, mean (±SD)	2.1 (0.8)	2.6 (0.9)	<0.001
HAS-BLED score, mean (±SD)	2.7 (1.2)	3.3 (1.0)	0.008
Oral anticoagulant agent, n (%)			
Warfarin	14 (28.6)	35 (49.3)	0.025
Direct oral anticoagulant	35 (71.4)	36 (50.7)	
Underdosing of oral anticoagulant agent, n (%)			
Warfarin	5 (10.2)	10 (14.1)	0.059
Direct oral anticoagulant	11 (22.4)	6 (8.5)	
Coadministration of an antiplatelet agent, n (%)			
Single-antiplatelet therapy	9 (18.4)	29 (40.8)	0.005
Dual-antiplatelet therapy	7 (14.3)	2 (2.8)	
No. of medications, (±SD)	9.4 (3.3)	11.4 (4.1)	0.006
Hb, g/dL, mean (±SD)	12.6 (1.9)	11.7 (1.8)	0.009
Cr, mg/dL, mean (±SD)	1.5 (1.8)	1.3 (0.6)	0.270
CCr, mL/min, mean (±SD)	53.0 (24.4)	38.4 (18.2)	<0.001
BNP, pg/mL, mean (±SD)	597.0 (465.5)	851.4 (835.8)	0.057
LVEF, %, mean (±SD)	42.9 (19.6)	46.7 (17.9)	0.270
E/E', mean (±SD)	14.8 (7.0)	16.5 (7.5)	0.223
LAD, mm, mean (±SD)	49.8 (6.8)	51.5 (16.8)	0.511
LAVI, mL/m^2, mean (±SD)	67.7 (17.8)	77.2 (30.1)	0.049

P values were generated by Student's t-test for continuous variables and Chi-square test for categorical variables. $CHADS_2$=congestive heart failure, 1 point; hypertension, 1 point; ≥75 years old, 2 points; diabetes mellitus, 1 point; previous stroke, transient ischemic attack or thromboembolism, 2 points. CHA_2DS_2-VASc=congestive heart failure, 1 point; hypertension, 1 point; ≥75 years old, 2 points; diabetes mellitus, 1 point; previous stroke, transient ischemic attack or thromboembolism, 2 points; vascular disease, 1 point; 65–74 years old, 1 point; female sex, 1 point. HAS-BLED=hypertension, 1 point; >65 years old, 1 point; abnormal renal function, 1 point; abnormal liver function 1 point; stroke history, 1 point; bleeding history or predisposition, 1 point; labile international normalized ratio, 1 point; ethanol or drug abuse, 1 point; drug predisposing to bleeding, 1 point. Abbreviations as in Tables 1,2.

coagulant therapy.

Awareness of vulnerability may help reduce bleeding events. Delaying and reversing frailty is thought to be possible with optimal nutrition and aerobic exercise.[38] Furthermore, more frequent monitoring of hemoglobin level, changes in renal function, therapy adherence, and modifiable stroke and bleeding risk factors, such as hypertension, alcohol abuse, or unnecessary use of antiplatelet or nonsteroidal anti-inflammatory drugs, is likely to result in safer anticoagulant therapy.[4]

Study Limitations

The main limitation of this study is the enrolled population; the study was conducted in a single center, and all patients had been hospitalized with symptomatic AF or congestive HF. The study had a high prevalence of pre-frail and frail

patients, which might be due to this limited population. Further research in a large, general population, particularly for the establishment of a risk-based anticoagulation strategy using an assessment of frailty, is needed.

Conclusions

Frailty is associated with increased bleeding events related to anticoagulant therapy in patients who have been hospitalized with AF. Greater attention should be paid to patients with a CHS frailty index ≥2.

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Data Availability

The deidentified participant data will not be shared.

Disclosures

All authors declare no conflict of interests.

Research Ethics

This study was approved by the Institutional Ethics Committee of Teine Keijinkai Hospital (reference no. 2-019231-00).

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