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【 REVIEW ARTICLE 】

Anticoagulant Therapy for Frail Patients with Atrial Fibrillation

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Abstract:
The prevalence of atrial fibrillation (AF) increases with age, as does the proportion of patients with frailty. AF patients with frailty have a higher risk of stroke than those without frailty, and progressive frailty caused by stroke is also associated with a worse prognosis. Despite this, anticoagulant therapy tends to not be used in frail patients because of the risk of falls and bleeding complications. However, some studies have shown that anticoagulant therapy improves the prognosis in patients with frailty. An accurate assessment of the "net-clinical-benefits" is needed in patients with frailty, with the aim of improving the prognoses of patients with frailty by selecting those who will benefit from anticoagulant therapy and actively reducing the risk of bleeding. A comprehensive intervention that includes a team of doctors and social resources is required. We herein review the effectiveness and bleeding risk associated with anticoagulant therapy in frail patients investigated in clinical studies.

Key words: atrial fibrillation, frailty, anticoagulant therapy, risk of falls, net-clinical-benefits

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Atrial Fibrillation and Frailty

Frailty and cardiovascular events

Frailty refers to a "state of reduced ability to recover from stress due to age-related loss of reserve capacity." It refers not only to physical vulnerability but also to a state of a high risk of suffering numerous issues, such as mental and psychological vulnerabilities and social vulnerability, and an inability to live independently, in addition to the onset of health issues.

The proportion of individuals who are frail increases with age, accounting for 34.9% of those ≥80 years old (Fig. 1A, B) (1). In particular, the presence of cardiovascular disease (CVD) is associated with a 4.1-fold increased risk of developing frailty. A decrease in walking speed suggestive of frailty conversely increases the risk of CVD by 1.6-fold [adjusted hazard ratio (HR) 1.61, 95% confidence interval (CI) 1.05-2.45] (2). The rate of frailty in patients with atrial fibrillation (AF) is high, at 39% (95% CI 36-42%) (3). In a retrospective study at a single site, the combination of frailty and prefrailty assessed using the Robinson Frailty Score in patients with AF was as high as 86% (Fig. 1C) (4).

Atrial fibrillation and frailty

Age and CVD link the relationship observed between AF and frailty. In the Fushimi AF registry study, 51.4% of subjects were ≥75 years old and 14.5% were ≥85 years old, clearly indicating that AF is more common in the elderly than in younger individuals (5). CVD is the second-most common cause of elderly patients requiring long-term nursing care (6), and cardiogenic cerebral embolism caused by AF in particular is associated with particularly severe cases.

In the Fushimi AF registry study, the risks of stroke and death were significantly higher in patients with AF and low body weight, which is considered a key marker of frailty, even after adjusting for various factors, such as whether or not anticoagulant therapy was administered (7).

Thus, the prevalence of AF and frailty increases with age, resulting in a vicious cycle in which the risk of cerebral infarction increases and frailty worsens. Therefore, in patients with AF, being frail also leads to worsening of various other clinical outcomes, such as the following, and active thera-

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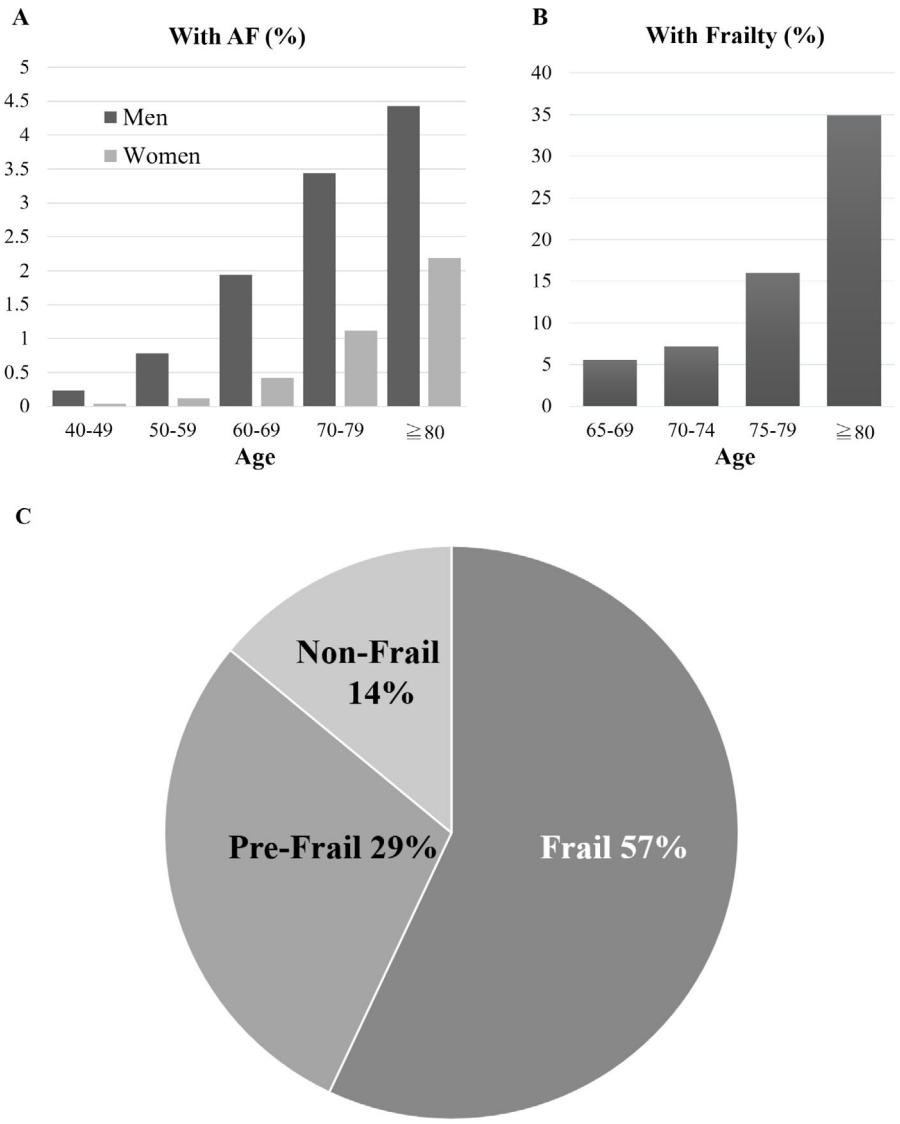

Figure 1. **A, B: Prevalence of AF and Frailty by age. AF: atrial fibrillation. C: 403 patients with AF. The Robinson Frailty Score, 0-1=Non-Frail, 2-3=Re-Frail, ≥4 Frail**

peutic intervention is needed for these pathological conditions:

• *In a systematic review of 20 observational studies, the presence of frailty in patients with AF was associated with stroke, overall mortality, and an increased duration of hospitalization (8).*

• *In a prospective cohort study of 615 hospitalized patients ≥75 years old (mean, 85 years old) with nonvalvular atrial fibrillation (NVAF), the mortality at 1 year was higher in frail patients than in non-frail patients (HR 1.99, 95% CI 1.43-2.76) (9).*

• *In a prospective study of 302 AF patients ≥65 years old (mean, 84.7 years), frailty was associated with an increased risk of death (HR 2.33, 95% CI 1.31-4.14; p=0.004), and the association with risk of death was stronger for frailty than for $CHADS_2$ or HAS-BLED scores (10).*

Risk of Anticoagulant Therapy in Frail Patients (Bleeding and Falls)

The risks of falls and major bleeding should be considered during anticoagulant therapy in frail patients with AF.

Falls are a factor contributing to frailty and to the exacerbation of frailty. Fractures and falls are the fourth-most common cause of requiring nursing care in Japan (12.5%), and the rate of falls increases sharply after 60 years old (6, 11).

Frail patients are at a high risk for falls, and many have a history of falls; thus, these patients can be considered at a high risk for traumatic complications.

• *The ENGAGE AF-TIMI 48 data showed that patients with an increased risk of falls had increased rates of major bleeding (adjusted HR 1.30, 95% CI 1.04-1.64; p=0.023) and fatal bleeding (adjusted HR 1.67, 95% CI 1.11-2.50; p=0.013) (12).*

• *In a post-hoc analysis of the ARISTOTLE trial, patients with a history of falls had an increased risk of intracranial hemorrhaging (adjusted HR 1.87; 95% CI, 1.02-3.43; p= 0.044) and a high risk of death (adjusted HR 1.70, 95% CI 1.36-2.14; p<0.0001) (13).*

Furthermore, falls in patients being administered oral anticoagulant (OAC) therapy have been reported to increase the risk of traumatic complications and death (14).

• *In retrospective cohorts of patients with acute traumatic subdural hematoma attributable to falls, the risk of death was higher in elderly than in young adult patients, and coagulopathy was associated with an increased risk of death (OR 4.0, 95% CI 1.47-11.05; p=0.007) (15).*

• *Patients with severe functional impairment have a 2.7-fold increased risk of traumatic intracranial hemorrhaging with the use of oral anticoagulants (16).*

• *Patients ≥65 years old who were hospitalized for a fall, those taking oral anticoagulants had a higher mortality rate due to bleeding complications from injuries at readmission than those not taking oral anticoagulants (21.5% vs. 6.9%, p<0.01) (17).*

Thus, as anticoagulant therapy in frail elderly patients who are at high risk for falls may increase the risk of traumatic complications and death, physicians may be reluctant to prescribe this therapy.

Frail Patients with AF are Less Likely to be Prescribed OACs than Patients who are not Frail.

Frail patients with AF are thought to be at a higher risk for cerebral infarction and progression of frailty and death than patients who are not frail, making preventive interventions important. However, numerous observational studies have revealed a tendency for physicians to be reluctant to administer anticoagulant therapy to frail patients (Table 1) (9).

• *A meta-analysis of 6 studies in 2019 found that presenting with frailty was associated with a reduced rate of OAC prescription at admission [pooled adjusted odds ratio (OR) 0.45, 95% CI 0.22-0.93 in 3 studies] (8).*

Guidelines recommend the use of risk scores, such as CHA_2DS_2-VASc and HAS-BLED scores, to determine indications for anticoagulant therapy (18). However, frailty has a greater influence on physicians' choices regarding prescribing anticoagulant therapy than these scores.

• *In a retrospective observational study of 419 hospitalized patients with AF who were ≥75 years old, being frail (Clinical Frailty Scale score ≥5) was associated with not being prescribed OAC (OR 0.77, 95% CI 0.70-0.85; p<0.001), and the presence of frailty influenced the prescription of anticoagulant therapy more heavily than CHA_2DS_2-VASc and HAS-BLED scores (19). The median* CHA_2DS_2-VASc *score of patients not prescribed anticoagulant therapy was 4 (IQR 2).*

• *In a cross-sectional study of 86 AF patients in nursing homes, those who were frail [Clinical Frailty Scale score ≥5 (median 7±0)] had a low rate of anticoagulant prescription, at 17%. The decision on whether or not to prescribe anticoagulant therapy was not based on the CHA_2 DS_2-VASc or HAS-BLED scores (20).*

What degree of frailty prompts physicians to withhold anticoagulant therapy? Clinical Frailty Scale scores (Fig. 2) (21) of 6 to 7 may be used as a guide.

• *In an observational study of hospitalized AF patients ≥ 75 years old, Clinical Frailty Scale scores were high in patients not receiving anticoagulant therapy (7±1.95 vs. 5.57± 2.05; p=0.006) (22).*

• *In a cross-sectional study of 682 hospitalized patients with AF ≥80 years old, anticoagulant therapy was used in patients with Clinical Frailty Scale scores <7 (OR 3.41, 95% CI 1.84-6.33) (23).*

Many patients with a Clinical Frailty Scale score of 6 require gait assistance and are at high risk of falling, and many patients with a score of 7 or higher cannot walk. That is, we tend not to prescribe anticoagulants to patients who have a low ability to walk independently. In other words, we may decide whether to prescribe anticoagulants based on an "ability to walk safely".

As shown in Table 1, anticoagulants were less likely to be prescribed to patients with a "fall risk" or "history of falls" (HR 1.53, 95% CI 1.08-2.17) (24), and "recent falls" were particularly strongly associated with discontinuation of anticoagulant therapy (OR 1.9, 95% CI 1.66-2.20) (25).

In frail patients with an impaired walking ability, a history of falls and visual loss prompts physicians to be more aware of the possible complications of falls. Therefore, physicians avoid starting or continuing anticoagulant therapy for such patients.

Anticoagulant Therapy is Effective Even when the Risk of Bleeding is Present

Is it reasonable not to prescribe anticoagulants due to the increased risk of fatal bleeding in frail patients or in those at risk for falls? The results of multiple clinical studies can be used to refute this argument.

(1) Is anticoagulant therapy really related to traumatic hemorrhagic complications in the elderly?

The results of post hoc analyses of prospective cohorts of patients with AF and observational studies of elderly patients experiencing falls are presented in Table 2. These studies do not show that the presence or absence of the risk of falls (12) or anticoagulant therapy (32, 33, 35) increases the rate of major bleeding, such as intracranial hemorrhaging.

Regarding whether or not differences in results are affected by differences in the number of falls and the degree of risks for falls, the findings of several studies rule out a relationship between the risk of traumatic head complica-

Table 1. Factors Affecting Anticoagulant Therapy.

Factor	Impact on Anticoagulant Therapy	Study
Frailty	Adjusted OR (95% CI) 0.29 (0.16–0.54)	23
	Adjusted OR (95% CI) 0.77 (0.70–0.85)	19
	Adjusted OR (95% CI) 0.34 (0.17–0.68)	26
Age	OR (95% CI) 1.1 (1.01–1.17) Odds ratio for un-prescribed anticoagulants	27
	OR (95% CI) 0.98 (0.97–0.98)	19
Severe dependency	OR (95% CI) 0.44 (0.23–0.82)	9
Fall	Recurrent fall OR (95% CI) 4.9 (2.4–9.9) Odds ratio for unprescribed anticoagulants	27
	Previous fall HR (95% CI) 1.53 (1.08–2.17) Hazard ratio for un-prescribed anticoagulants	24
	Recent fall OR (95% CI) 1.91 (1.66–2.20) Odds ratio for un-prescribed anticoagulants	25
Bleeding	Past history of bleeding OR (95% CI) 3.62 (1.54–8.51) Odds ratio for un-prescribed anticoagulants	27
	Bleeding risk OR (95% CI) 0.85 (0.74–0.97)	19
	HAS-BLED score ≥ 3 OR (95% CI) 0.33 (0.12–0.86)	23
CHA_2DS_2–VASc	Lower CHA_2DS_2-VASc scores [median 4, (IQR 2) vs 5 (IQR 2), p=0.01]	19
Others	Short life expectancy Chronic kidney disease HR (95% CI) 1.12 (1.04–1.21) Hazard ratio for un-prescribed anticoagulants	28 24
	Dementia Anticoagulants tended not to be prescribed in patients with dementia	28 27 29

OR: Odds Ratio, HR: Hazard Ratio, CI: Confidence Interval

tions and increased risk of falls or number of falls, as follows:

• *In a prospective cohort study of 515 patients who were taking OAC at discharge, the time to the occurrence of major bleeding in the first year after discharge was compared between the high- and low-fall-risk groups, and no relationship was found between an increased risk of falls and major bleeding (HR 1.09, 95% CI 0.54-2.21) (36).*

• *In analyses using statistical models for fall risks and corresponding outcomes, as many as 295 falls per year were required for the risk of falls to outweigh the benefits of preventing cerebral infarctions (37).*

(2) Frailty itself poses a risk.

Clinical studies have shown that the presence and degree of frailty was more closely associated with stroke and mortality than whether or not they had been administered anticoagulant therapy.

• *In a retrospective observational study of 173 patients ≥ 80 years old in a level 1 trauma center, the presence or absence of anticoagulant use was not found to affect mortality. Instead, Rockwood Frailty Scores were the strongest predictor of the 6-month and overall mortality (p<0.01) (38).*

• *In AF patients with a low weight suggestive of frailty, the risk of stroke or death was significantly higher than in other patients, even after adjusting for various factors, such as the presence or absence of anticoagulant therapy (7).*

(3) Not administering anticoagulant therapy poses a risk.

The decision to refrain from administering anticoagulant therapy due to excessive fear of the risk of bleeding may increase the risk of a decline in the physical function.

• *In an observational study of hospitalized frail patients*

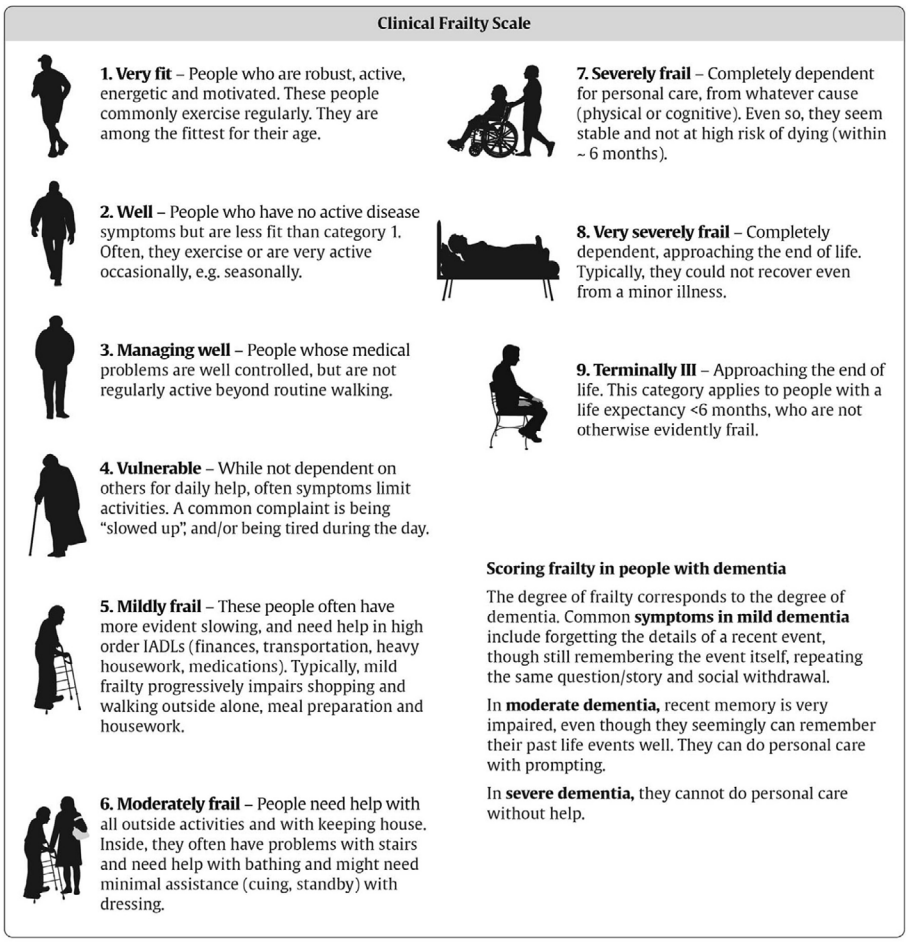

Figure 2. **Clinical frailty scale. Cited from reference (21) with permission from Elsevier, Inc**

≥75 years old, 190 AF patients were evaluated, and not being prescribed OAC at discharge was associated with increased rates of cerebral infarction and bleeding 1 year later (HR 4.54, 95% CI 1.83-11.25; p=0.001) (39).

• In a prospective observational study of hospitalized patients with NVAF ≥75 years old, death 1 year later was more common in patients with sarcopenia, frailty, and cognitive decline than in others, and being prescribed OAC at discharge was associated with a reduced mortality in multivariate analyses (HR 0.415, 95% CI 0.307-0.560) (34).

• In a prospective registry of 400 AF patients who were admitted for acute stroke, 370 had ischemic stroke, and 274 were prescribed anticoagulants at discharge. Death or physical dependency and recurrent stroke occurred in 19.8% and 9.9% of patients treated with anticoagulants and in 33.5% and 27.2% of patients not treated with anticoagulants, respectively (both p<0.001) (31).

Several reports have shown the utility of OAC administration to patients with not only physical frailty but also dementia. OAC administration to patients with cognitive impairment was associated with reduced cerebral infarction and overall mortality (40). AF is also associated with cognitive decline, and the use of OAC is reported to be associated with a reduced risk of cognitive impairment (41, 42).

These results suggest that, in AF patients not receiving anticoagulant therapy, the risk of a decline in the physical function and a worsened prognosis is increased, even if they present with frailty or dementia, and that other alternative treatments are needed.

(4) Age and net clinical benefit

We have observed cases of bleeding associated with anticoagulant therapy. Thus, studies such as those mentioned above that warn of the risk of bleeding with anticoagulant therapy should not be ignored, nor should the risk be underestimated. However, excessive anxiety about bleeding risk may result in overlooking the increased risk of infarct complications due to factors such as frailty and age, which is higher than the risk of the bleeding complications associated with anticoagulant therapy. Both the benefits of anticoagulant therapy and the risks of bleeding need to be assessed correctly and balanced. We should thus consider the "net clinical benefit."

Regarding the effect of age, old age is cited as one reason for withholding anticoagulant therapy (Table 1). While age is also a common risk factor for both bleeding and infarction, studies have shown that the increase in the benefit of anticoagulant therapy with increasing age outweighs the risk of bleeding.

• Fewer ischemic strokes were observed in warfarin users

Table 2. Anticoagulant Therapy, Falls and Clinical Outcomes.

Study	Study design	Patient	Risk factor/Back ground	Intervention/com-parison	Outcome
(30)	Prospective cohort	AF N=76 Mean age (SD) 82.9 (8.9)	Prior History of Falls (with OAC) CHA_2DS_2-VASc, Mean (SD) 4.4 (1.6) HAS-BLED, Mean (SD) 2.07 (1.03)	Prior History of Falls (with OAC) vs. No prior history of fall (with OAC)	Hemorrhagic Stroke HR 4.36 (95% CI:0.60–31.83)
(29)	Prospective cohort	AF with cognitive impairment or dementia N=293 Age 82.0 (76.0–87.0) AF with frailty N=575 Age 83.0 (77.0–88.0)	Patient with cognitive impairment or dementia CHA_2DS_2VASc Risk Score 5.0 (4.0–6.0) HAS-BLED Score 2 (2-3) Patient with frailty CHA_2DS_2VASc Risk Score 5.0 (4.0–6.0) HAS-BLED Score 2(2-3)	OAC vs. No OAC	Major Bleed No difference in patient with cognitive impairment, patient with frailty. Survival No difference in patient with cognitive impairment, patient with frailty.
(31)	Prospective cohort	AF hospitalized with stroke (TIA 8.8% Ischemic stroke 83.8%) N=400 (370 brain infarctions 30 brain hemorrhages) Age, mean (SD) 78.7 (11.0)	Congestive heart failure 13.3% Hypertension 79.3% Diabetes 21.8%	OAC (274) vs. No OAC (95)	Major bleeding 13.5% (with OAC) 20% (No OAC) (p=0.13) death or dependency HR 1.65 (95% CI:1.05-2.61; p=0.032) stroke HR 2.46 (95% CI:1.36-4.44; p=0.003).
(32)	Retrospective cohort	N=2,567 Mean age 82 Low-energy falls	Anticoagulation 20.6% Antiplatelet 31.1% Both 2.7	Anticoagulation or antiplatelet vs. No antithrombotic drug	Traumatic intracranial hemorrhage (tICH) 6.9% OR 1.05 (95% CI: 0.76-1.47; p=0.76) In-hospital mortality OR 1.42 (95% CI:0.75-2.82; p=0.29) Head-specific Injury Severity Scale incident rate ratio1.08 (95% CI: 0.97-1.19; p=0.15)
(33)	Prospective cohort	N=1,753 median age 82 y ED visit following a fall Fall from standing Inside 59% Outside18%	Anticoagulant 25% Hypertension 76% Liver disease 3% CKD 11% Stroke/TIA 19% Heart failure 15% Diabetes 29% Prior major bleeding 11%	OAC vs. No OAC	Intracranial bleeds 5% OR 0.87 (95% CI: 0.48-1.59)
(34)	Prospective cohort	NVAF Hospitalized patient N=596 mean age of 84.9 (SD: 5.2) Sarcopenia 49.5% Frailty 51.2% cognitive impairment 42.1%	CHA_2DS_2-Vasc 5.3 HAS-BLED 2.7	OAC at discharge vs. No OAC at discharge	Mortality HR 0.415 (95% CI: 0.307-0.560)
(35)	Observational study	AF at high risk for falls Mean age 80 N=1,245	Bleeding risk factors* (mean number 2.5)	Warfarin vs. No warfarin	Intracranial Hemorrhage HR 1.0 (95% CI 0.8–1.4)

AF: atrial fibrillation, NVAF: non-valvular atrial fibrillation, OAC: oral anticoagulant, CKD: chronic kidney disease, ED: emergency department, y: years old, OR: Odds Ratio, HR: Hazard Ratio, CI: Confidence Interval

*Anemia, thrombocytopenia or bleeding disorder, Chronic renal disease, Aspirin use, Uncontrolled Hypertension, Malignancy, Alcohol abuse, Rebleeding risk (i.e., prior bleed), Increased age (>75), Neuropsychiatric Impairment, Stroke/TIA history

than in nonusers among patients ≥90 years old [3.83% vs. 5.75%/year (HR 0.69, 95% CI 0.49-0.96)], whereas there was no marked difference between users and nonusers in the rate of intracranial hemorrhaging (HR 1.26, 95% CI 0.70-

Event	Age < 85 y		Age > 85 y		Age > 90 y	
	No OAC (N = 616)	OAC (N = 3975)	No OAC (N = 96)	OAC (N = 371)	No OAC (N = 26)	AOC (N = 58)
Thromboembolic event	2.8%	2.3%	6.3%	4.3%	11.5%	6.9%
Major bleeding	3.4%	2.9%	4.2%	4.0%	7.7%	8.6%
Net clinical benefit	Overall population -2.19% (95% CI −4.23〜 −0.15%)					

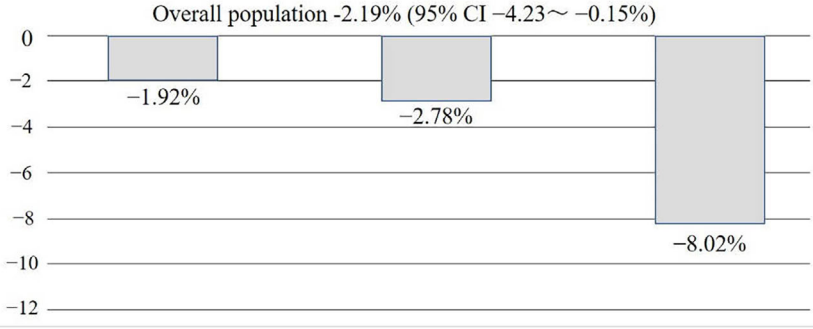

Figure 3. **Age and net clinical benefit (44). y: years old, OAC: oral anticoagulant**

2.25) (43).

• When patients were grouped by age (<85, 85-89, and ≥90 years old), the benefits of anticoagulant therapy were greater than the bleeding disadvantages in elderly patients (Fig. 3) (44).

• Meta-analyses of direct oral anticoagulants (DOACs) have shown that DOACs are associated with a lower incidence of stroke and systemic embolism than warfarin, particularly in the elderly (≥75 years old). Coupled with the decreased risk of bleeding with DOACs, a great net clinical benefit can be expected with the use of DOACs than with warfarin (45).

In other words, even among frail or elderly patients, careful case selection can facilitate the identification of patients likely to significantly benefit from anticoagulant therapy.

However, it should be noted that most of these results were from observational studies or post-hoc analyses of interventional studies. In observational studies in particular, many unadjustable confounding factors affect a physician's decision to administer anticoagulant therapy. For example, a patient who is deemed to be at a high risk for bleeding by the attending physician may not be placed on anticoagulant therapy. There are multiple biases that may exist, including similar selection biases, and high-quality studies are lacking. Therefore, verification by large-scale randomized controlled trials is necessary.

Strategies for Administering Anticoagulant Therapy to Frail Patients

Withholding anticoagulant therapy in frail elderly patients with AF solely because of their age or because of an increased risk of falls is not reasonable. The risk of bleeding can be reduced through aggressive intervention.

We will now discuss in which patients it is better not to prescribe anticoagulant therapy and what is needed to safely prescribe these medications (Fig. 4).

Patients in whom refraining from prescribing OAC is reasonable

There are four scenarios to consider: if the risk of bleeding is high, if the risk of infarction is low, if the prognosis is unfavorable, and if the patient suffers repeated falls despite adequate preventive strategies or if there is significant bleeding (46, 47).

(1) If the risk of bleeding is high

HAS-BLED scores may be used to estimate potential bleeding risks during anticoagulant therapy (48). Scores of ≥3 points are associated with a 3.74% annual risk of bleeding, which is considered a high risk (49). As a history of bleeding was found to be the greatest risk factor (HR 3.52, 95% CI 1.22-10.17) (50), caution is required for such cases.

We should also be aware of the risk factors for bleeding in the elderly that are not included in the HAS-BLED score. In a retrospective cohort of 31,951 veterans ≥75 years old, the risk factors for traumatic intracranial bleeding were dementia (HR 1.76, 95% CI 1.26-2.46), anemia (HR 1.23, 95% CI 1.00-1.52), depression (HR 1.30, 95% CI 1.05-1.61), and the use of anticonvulsants (HR 1.35, 95% CI 1.04-1.75) (51). It has been pointed out that the risk of bleeding may be increased because of noncompliance with medication by elderly patients with dementia who cannot be adequately monitored by caregivers (46). Thus, frail elderly patients who have more than one of these factors may need to be considered to be at a higher risk for bleeding than is suggested by HAS-BLED scores alone.

While a high risk of bleeding makes physicians reluctant to prescribe OAC, attention should be paid to what existing risks can be controlled. Age, dementia, and hepatic dysfunction are factors that cannot be controlled, whereas the use of concomitant drugs, hypertension, and management of the international normalized ratio (INR) are controllable factors. Refraining from prescribing OAC due to the risk of bleeding is reasonable when the risk is elevated to an uncontrollable

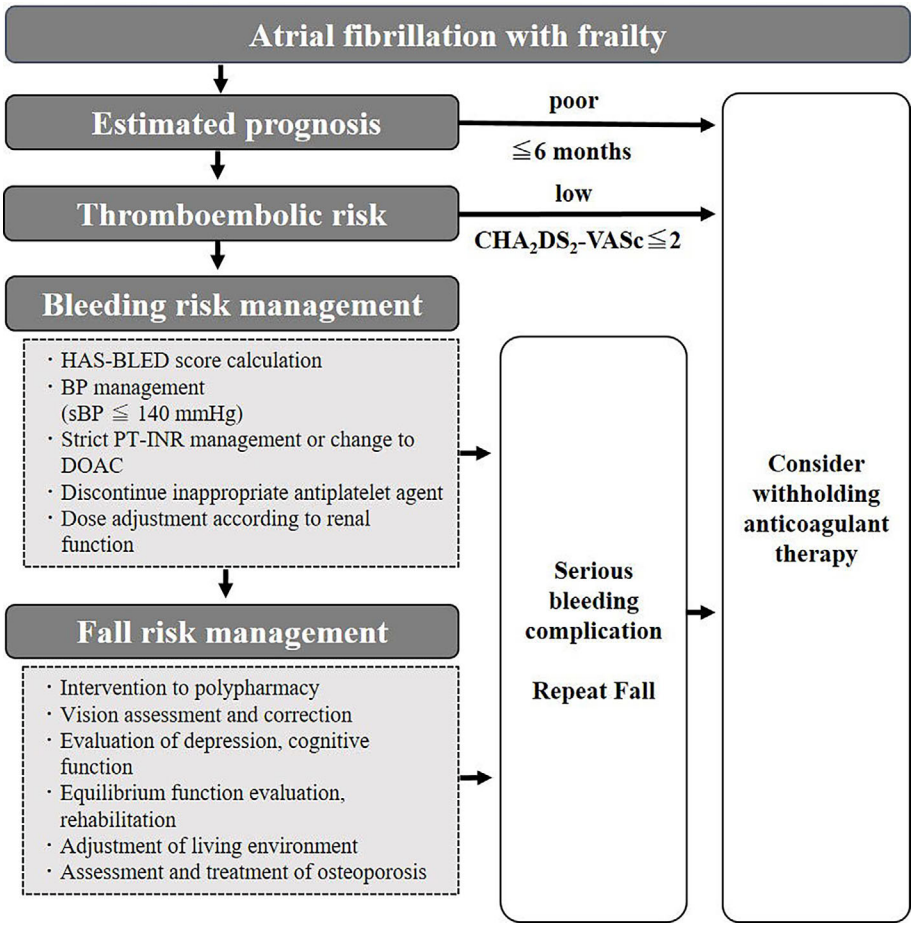

Figure 4. **Correspondence algorithm for AF patients with frailty (Targeting ambulatory patients).**
BP: blood pressure, DOAC: direct oral anticoagulant

level despite taking adequate measures against controllable factors. For example, anticoagulant therapy is not recommended in dialysis patients. Intervention with controllable factors can reduce the risk of bleeding and will be discussed in later sections.

(2) If the risk of cerebral infarction is low

The disadvantage of an elevated risk of bleeding may be outweighed in patients with low CHADs/CHA_2DS_2-VASc scores, as suggested in one study from California. In a retrospective study of 42,913 elderly patients (mean age, 82.4 years old) with AF/flutter, the use of anticoagulants in patients at high risk for falls was found to be associated with an increased mortality, with CHA_2DS_2-VASc scores of ≤2 associated with outcomes that outweighed the risk. In that study, Asian ethnicity was cited as a risk factor for head injury-related death, and the administration of medication to the group who were at low-risk for infarction but at risk for falling was considered to be inappropriate for Japanese patients in particular (52).

(3) If the prognosis is unfavorable

Frail elderly patients generally have poor prognoses. If the survival period is expected to be short (e.g., six months or less), the benefit of anticoagulant therapy is uncertain. In such instances, refraining from prescribing OAC is considered a valid approach (46).

(4) If falls repeatedly occur, particularly in cases with major complications

It is important to perform a fall risk assessment for each patient. An "actual history of falls" is associated with major bleeding and death, particularly in patients on anticoagulants (30), and is of particular importance in the assessment of the fall risk. A history of falls in the past year is a key factor in the assessment of the fall risk (53).

In particular, a "history of two or more falls in the past year" is a risk factor for further falls and should be noted.

• *Among 18 201 patients who participated in the ARISTOTLE trial, a higher rate of intracranial hemorrhaging (adjusted HR 1.87, 95% CI 1.02-3.43; p=0.044) and a higher risk of death (adjusted HR 1.70, 95% CI 1.36-2.14; p<0.0001) were observed in those with a history of falls (13).*

No consensus has been reached regarding whether or not anticoagulants should be discontinued due to a history of one fall. However, if a fall has resulted in a hemorrhagic complication or has required hospitalization (17, 50), withholding anticoagulant therapy is reasonable.

If falls, including minor ones, occur repeatedly despite appropriate preventive measures, the risks must be fully explained when prescribing or resuming OAC, and the option to not receive an OAC should also be provided.

Proposal for administration of anticoagulant therapy

We should be able to provide the full benefits of anticoagulant therapy by focusing on the risks that can be mitigated. Factors affecting bleeding risks that can be reduced include blood pressure and the renal function, polypharmacy, anticoagulant type, and fall prevention.

(1) Blood pressure and the renal function

Not only are blood pressure and renal dysfunction factors affecting the risk of bleeding, they are also risk factors for infarction. In the Fushimi AF registry, the rates of stroke/systemic embolic events (HR 1.74, 95% CI 1.08-2.72) and major bleeding (HR 2.01, 95% CI 1.21-3.23) were increased in cases with a systolic blood pressure of ≥150 mmHg, and managing blood pressure is expected to reduce the risk of infarction and bleeding (54). However, physicians also need to be aware that severe hypotension that causes orthostatic dysregulation may be a risk factor for falls.

The ROCKET-AF and ATRIA studies showed that renal impairment increases the risk of thromboembolism in patients with AF, particularly in patients positive for urinary protein (55, 56). The risk of hemorrhaging also increases with a reduction in the renal function. In particular, advanced chronic kidney disease [estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2] was associated with cerebral hemorrhaging in patients experiencing falls [OR 5.37, 95% CI (1.26-22.9); p = 0.023] (14).

Furthermore, the benefits of anticoagulant therapy are uncertain at an eGFR of <15 mL/min/1.73 m^2 (stage 4 chronic kidney disease). Warfarin use in hemodialysis patients was associated with an increased risk of stroke, and in assessments based on the type of stroke, the risks of not only cerebral hemorrhaging (HR 2.22, 95% CI 1.01-4.91) but also cerebral infarction (HR 1.81, 95% CI 1.12-2.92) were shown to be increased (57, 58). Therefore, anticoagulant therapy is not recommended in patients with advanced renal impairment or dialysis patients.

The renal function often fluctuates. When anticoagulants are used, there is a need to tailor the dosage of the medication to the renal function while carefully monitoring the renal function. In patients with chronic kidney disease, concomitant measures to prevent a decline in the renal function may also be necessary to continue receiving the benefits of anticoagulant therapy.

(2) Polypharmacy

Polypharmacy is a risk factor for which we can quickly implement interventions to administer anticoagulant therapy safely. A combination of drugs destabilizes anticoagulant therapy with warfarin. Furthermore, being treated with at least five types of medication is reported to be associated with an increased risk of falls (59). Polypharmacy is also associated with fall-related traumatic brain injury in the elderly (60). Thus, the number of medications being administered to a patient needs to be minimized.

The concomitant use of antiplatelet drugs is another factor that can increase the risk of bleeding in patients on anticoagulant therapy (50). Some studies have shown that antiplatelet use is the greatest risk factor for not prescribing OAC to AF patients (OR 15.0, 95% CI 14.1-15.8) (61). A randomized clinical trial found that aspirin for the primary prevention of cardiovascular events in elderly Japanese patients was not effective. This clearly indicates that the administration of antiplatelet drugs for the purpose of primary prevention is not appropriate. When aspirin is used for this purpose in patients with AF, it should be discontinued, and anticoagulant therapy should be added (62).

(3) Anticoagulant type (selecting DOACs rather than vitamin K antagonists)

Unstable INR in warfarin increases the risk of traumatic intracranial hemorrhaging (HR 1.34, 95% CI 1.04-1.72) (51). However, DOACs are thought to be effective in reducing the risk of bleeding, and some studies suggest that these agents may be particularly useful in frail patients.

• *In the ARISTOLE study, patients with more complications (high morbidity) were older, took more medications, and had higher CHA_2DS_2-VASc scores than those with fewer complications; however, the efficacy and safety of apixaban were maintained in this group (63).*

• *ENGAGE AF-TIMI 48 data showed that edoxaban reduced the absolute risk of major bleeding and overall mortality compared with warfarin in studies evaluating patients at increased risk for falls (12).*

• *In frail patients, rivaroxaban significantly reduced the incidence of stroke and systemic embolism without increasing the rate of serious bleeding compared with warfarin (64).*

• *A few studies have reported that oral factor Xa inhibitors reduced the risk of intracranial bleeding in AF patients at high risk for falls (65, 66).*

Thus, DOACs rather than warfarin should be selected for such patients.

(4) Fall prevention

Among patients ≥65 years old, 30-40% had a history of falls within a 1-year-period (67, 68). Falls contributed to a reduction in activities of daily living (ADL) by resulting in traumatic intracranial hemorrhaging complications and fractures in 5-10% of cases.

Regarding what is needed to reduce the risk of falls, the gait status should be checked during the medical examination. The presence of staggering as well as a decreased walking speed and the presence of walking disorders (OR for risk of falls 2.06, 95% CI 1.82-2.33) and equilibration disturbance (OR 1.98, 95% CI 1.60-2.46) (69) should be checked, and safe training/rehabilitation and balance function training should be introduced.

The patient's eyesight should also be checked. Decreased visual acuity increases the risk of falls (OR 1.35, 95% CI 1.18-1.54) (69), so interventions, such as glasses and cataract treatment, can be implemented in patients who need these measures.

There is also a need to develop environments that are tailored to reduce impediments to ADL, as such impediments,

as well as associated household and living environment issues, can increase the risk of falls (instrumental disability; OR 1.46, 95% CI 1.20-1.77, household hazards; OR 1.15, 95% CI 0.97-1.36) (69). While measures such as adding handrails and reducing stairs are necessary, long-term nursing care insurance also plays a major role in Japan. An awareness of the risk of falls can trigger the introduction of public resources.

Cognitive impairment (OR 1.32, 95% CI 1.18-1.49) and depression (OR 1.49, 95% CI 1.24-1.79) also increase the risk of falls. These disorders complicate the selection of treatment for AF patients. In patients with cognitive impairment, adherence and decision-making abilities are reduced, and there is a need to ensure safety through the cooperation of family members and home-visit nurses, as well as to implement public resources, such as incorporating home visits and employing pharmacists (40, 46, 47).

In addition to depression, the use of antidepressants also increases the risk of falls. A careful assessment is therefore needed, and consultations with specialist departments and ongoing assessments are critical (69).

As previously mentioned, a reassessment of medications may also be effective in preventing falls. In particular, benzodiazepines, antipsychotics, and loop diuretics are associated with the risk of falls. Discontinuing medications that cause orthostatic hypotension should be considered (69). Osteoporosis should be assessed, and efforts should be made to reduce the risk of fractures.

There are many aspects that physicians cannot understand by merely conducting examinations in the consultation room. There is a need for intervention involving nurses, pharmacists, and physiotherapists. A team- and community-based approach needs to be adopted to resolve pressing issues along with family members by introducing public resources in addition to rehabilitation and medication adjustment.

Future Issues

There have been few high-quality interventional studies on the safety of anticoagulant therapy in elderly people with frailty. The studies cited in this review are post-hoc analyses of interventional studies as well as observational studies, and several biases cannot be ruled out.

Each elderly patient with frailty is unique. Patients should therefore be evaluated individually based on the physical activity they can perform. While some patients are ambulatory, others cannot walk at all; the fall risk therefore does not need to be considered when determining the need for anticoagulant therapy in patients who are unable to walk. However, the merits of administering such therapy are also unclear. Therefore, large-scale randomized controlled trials are necessary to stratify patients according to the extent of frailty and fall risk and to identify groups that can benefit from anticoagulant therapy.

Conclusion

In patients with AF, factors such as being “elderly” or “frail” alone are not crucial for determining the need for anticoagulant therapy. To prevent the further progression of frailty, active interventions to reduce modifiable risk factors for bleeding are important in order to provide the full benefits of anticoagulant therapy. There are many factors that need to be assessed and mediated. In particular, a history of falls is a risk factor associated with important complications, and fall prevention is very important. When treating frail patients, a comprehensive social approach should be followed by including not only physicians but also other health professionals and the use of public resources.

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