

# Effects of Anticoagulant Therapy and Frailty in the Elderly Patients with Atrial Fibrillation

Jiancao Ding<sup>1</sup>, Ying Sun<sup>2</sup>, Kan Zhang<sup>2</sup>, Wei Huang<sup>2</sup>, Mei Tang<sup>2</sup>, Dai Zhang<sup>2</sup>, Yunli Xing<sup>2</sup>

<sup>1</sup>Department of Geriatrics, First People's Hospital of Zigong, Sichuan, People's Republic of China; <sup>2</sup>Department of Geriatrics, Beijing Friendship Hospital, Capital Medical University, Beijing, People's Republic of China

Correspondence: Yunli Xing, Department of Geriatrics, Beijing Friendship Hospital, Capital Medical University, No. 95, Yong'an Road, Xicheng District, Beijing, 100050, People's Republic of China, Tel +86 13121181469, Fax +86 10 6313 8040, Email xingyunli1976@126.com

**Objective:** This study explored whether anticoagulation is safe for frail and non-frail elderly patients who have nonvalvular atrial fibrillation (NVAF).

**Methods:** At hospital discharge, the anticoagulant regimen and frailty status were recorded for 361 elderly patients (aged  $\geq 75$  y) with NVAF. The patients were followed for 12 months. The endpoints included occurrence of thrombosis; bleeding; all-cause death; and cardiovascular events.

**Results:** At hospital discharge, frailty affected 50.42% of the population and the anticoagulation rate was 44.04%. At discharge, age (OR 0.948,  $P = 0.006$ ), paroxysmal NVAF (OR 0.384,  $P < 0.001$ ), and bleeding history (OR 0.396,  $P = 0.001$ ) were associated with a decrease in rate of receiving anticoagulation, while thrombotic events during hospitalization (OR 2.281,  $P = 0.021$ ) were associated with an increase. Relative to non-frail patients, those with frailty showed a higher rate of ischemic stroke (5.33% cf. 3.01%), bleeding ( $P = 0.006$ ) events, and all-cause mortality ( $P = 0.001$ ). Relative to the group without anticoagulation, in those with anticoagulation the rate of thrombotic events was lower (6.99 cf. 10.98%) and bleeding events were higher (20.98 cf. 12.72%), but the risk of major bleeding was comparable.

**Conclusion:** In the elderly patients with NVAF, the decision toward anticoagulation therapy at hospital discharge was influenced by age, bleeding history, paroxysmal atrial fibrillation diagnosis, and absence of thrombosis. Frail patients were at greater risk of bleeding and all-cause mortality. Anticoagulation tended to reduce the risk of thrombotic events.

**Keywords:** elderly, non-valvular atrial fibrillation, frailty, anticoagulation

## Introduction

Atrial fibrillation (AF) is a common arrhythmia in the elderly population, affecting up to 12% of people aged 80 years and older<sup>1</sup> and can raise the risk of stroke by five-fold.<sup>2</sup> AF and related stroke in the elderly seriously affect their quality of life and greatly increase the burden on the healthcare industry.

Frailty is also a common geriatric syndrome that has been associated with adverse events such as disability, hospital-acquired infection, and mortality.<sup>3</sup> Frail elderly patients with AF especially may have a higher risk of stroke and bleeding, and are often complicated with sarcopenia, malnutrition, and multiple comorbidities. Additionally, they are more susceptible to drug side effects. However, the presence of frailty is rarely included as a factor in clinical studies of anticoagulation therapy, and this lack of data confounds management decisions.

Although anticoagulation is cost-effective in reducing stroke risk in AF,<sup>4</sup> it is sometimes not applied to the elderly, despite indications, especially in those with frailty.<sup>5</sup> Relevant studies have shown that elderly patients with AF may need timely anticoagulation, yet there is no unified opinion about whether this therapy will improve prognosis.<sup>4,6</sup> More research evidence is needed.

This study explored whether anticoagulation is safe for elderly patients with AF, and the influence of frailty on medical decisions. We conducted an overall evaluation of elderly patients with nonvalvular atrial fibrillation (NVAF), aged 75 years and older, aided by a comprehensive geriatric assessment.

## Methods

This study was approved by the Ethics Committee of Beijing Friendship Hospital, Capital Medical University (Research Ethics number 2018-P2-037-02). This study was in compliance with the Declaration of Helsinki.

## Participants

The study enrollment comprised elderly patients with NVAF who were hospitalized in the geriatric and cardiovascular departments of Beijing Friendship Hospital from May 2017 to March 2022. All the subjects were aged 75 years or older, and with AF as verified by ECG (electrocardiogram) or 24-hour ECG with onset  $\geq 30$  s. AF types included both paroxysmal (terminating within 7 days, with or without intervention) and persistent (lasting more than 7 days). Patients with any of the following were excluded: AF due to hyperthyroidism; AF combined with mechanical valve or moderate-to-severe mitral stenosis; or failure to sign informed consent or to cooperate with the study.

A comprehensive geriatric assessment was conducted of each enrolled patient, which included polypharmacy (ie, more than 5 kinds of medicines)<sup>7</sup> and measures for frailty, daily living activities, cognitive status, nutritional status, fall risk, burden of comorbidities, AF stroke risk, and bleeding risk. The assessments included the respective components of the FRAIL index (Fatigue, Resistance, Ambulation, Illness and Loss of weight).<sup>8</sup> Each of FRAIL index components was scored with 1 point for presence or 0 (nil) for absence, for a maximum score of 5. Scores of 3 to 5 indicated frailty; patients with scores lower than 3 were characterized as non-frail.

Other scales applied in the present study were: Assessment of Daily Living;<sup>9</sup> Mini-Cognitive Assessment (Mini-Cog);<sup>10</sup> Mini Nutritional Assessment short-form (MNA-SF);<sup>11</sup> Morse Falls Assessment Scale;<sup>12</sup> age-adjusted Charlson Comorbidity Index (aCCI);<sup>13</sup> CHA<sub>2</sub>DS<sub>2</sub>-VASc score;<sup>14</sup> and the HAS-BLED score.<sup>14</sup>

In addition, demographics were recorded and the following clinical data from the medical records: medical history, vital signs, fasting blood; and the estimated glomerular filtration rate (eGFR) calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)<sup>15</sup> equation.

The patients' anticoagulation regimens were recorded at the time of discharge. The patients were followed up at 1, 3, 6, and 12 months via telephone or medical records. The median follow-up period was 12 (11, 12) months. The study deadline was 31 October 2022. The follow-up data included observed events (below) and anticoagulation status, anticoagulation/antiplatelet regimens, compliance, and whether anticoagulation was used before and after bleeding/thrombosis. Observed events were thromboembolism, bleeding, all-cause death, and cardiovascular events. Thromboembolism included systemic circulation (transient ischemic attack, stroke, peripheral) and pulmonary embolism. Bleeding events were either minor or major, the latter including intracranial, spinal, or retroperitoneal bleeding with direct fatal or surgical treatment required; red blood cell transfusion of 2 or more units; a decrease in hemoglobin concentration of 50 g/L or more; and hemorrhagic shock. Cardiovascular events were acute heart failure and acute coronary syndrome.

## Statistical Analysis

All data were analyzed with SPSS 25.0, and patient characteristics are shown as the mean  $\pm$  standard deviation ( $x \pm SD$ ), median (interquartile range) [M (Q1, Q3)], or percentage (%). Logistic regression was used to analyze factors influencing anticoagulation and compliance. Some variables that may be potential confounders were selected for the univariate analysis; items with  $P < 0.05$  in the results were included in the multivariate analysis, and the 95% confidence intervals (CIs) were calculated. Cox proportional hazards analyses were performed to examine, respectively, the associations between frailty and anticoagulation on bleeding, thrombosis, all-cause death, and cardiovascular events. A pooled hazard ratio (HR) was calculated for each factor; a  $P$  value  $< 0.05$  was considered significant.

## Results

The study population comprised 361 patients with NVAF (234 men) with a median age of 85 (81, 90) years. Of these, 231 (63.99%) and 130 (36.01%) were with paroxysmal and persistent AF, respectively. The most common diseases were hypertension (83.10%,  $n = 300$ ), ischemic stroke (52.91%,  $n = 191$ ), and diabetes (40.72%,  $n = 147$ ). The overall prevalence of frailty was 50.42% ( $n = 182$ ). The anticoagulation rate was significantly higher at discharge than at

admission (44.04% cf. 22.71%,  $P < 0.001$ ). In addition, 36.8% received antiplatelets ( $n = 133$ ). The rate of new oral anticoagulants (NOACs) was 69.51% at admission ( $n = 57$ ) and 73.58% at discharge ( $n = 117$ ). Only 29 patients received the standard doses (ie, rivaroxaban 20 mg, edoxaban 60 mg, dabigatran 220 mg).

## Influencing Factors of Anticoagulation

At hospital discharge, 159 of the 361 subjects were given anticoagulation regimens (Tables 1 and 2). Relative to those without anticoagulation regimens, those with anticoagulation were significantly more likely to be: younger and female; with paroxysmal AF (cf. persistent AF); frailty; and bleeding history. They also had significantly higher body mass index (BMI); rate of thrombosis during hospitalization; Assessment of Daily Living, MNA-SF, and Mini-cog scores; and hemoglobin and albumin levels.

**Table 1** Patients with or Without Anticoagulation at Hospital Discharge<sup>a</sup>

	Anticoagulation	No anticoagulation	P
Subjects, n	159	202	—
Age, median (Q <sub>1</sub> , Q <sub>3</sub> )	83 (79, 90)	87 (82, 91)	<0.001 <sup>b</sup>
Male	93 (58.49)	141 (69.80)	0.025 <sup>c</sup>
Paroxysmal AF	82 (51.57)	149 (73.76)	<0.001 <sup>b</sup>
Hypertension	134 (37.12)	166 (82.18)	0.597
Chronic myocardial infarction	30 (18.87)	48 (23.76)	0.262
Chronic heart failure	49 (30.81)	54 (26.73)	0.394
Diabetes	66 (41.51)	81 (40.10)	0.787
Bleeding history	30 (18.87)	70 (34.65)	0.001 <sup>c</sup>
Ischemic stroke history	78 (49.06)	113 (55.94)	0.193
Thrombosis history	20 (12.58)	24 (11.88)	0.841
Thrombosis during hospitalization	31 (19.50)	22 (10.89)	0.022 <sup>c</sup>
Bleeding during hospitalization	25 (15.72)	38 (18.81)	0.443
Hemoglobin, median (Q <sub>1</sub> , Q <sub>3</sub> ), mg/dl	126 (108.25, 136.75)	121 (104, 136)	0.019 <sup>c</sup>
Albumin, median (Q <sub>1</sub> , Q <sub>3</sub> )	35.75 (33.8, 38.2)	34.7 (31.5, 37.4)	0.001 <sup>c</sup>
eGFR, median (Q <sub>1</sub> , Q <sub>3</sub> )	65.64 (52.51, 80.03)	65.34 (44.30, 78.14)	0.508
PT, median (Q <sub>1</sub> , Q <sub>3</sub> )	13.4 (12.65, 14.88)	13.6 (12.5, 14.6)	0.651
PT activity, median (Q <sub>1</sub> , Q <sub>3</sub> )	84.1 (73.20, 95.00)	88.00 (75.45, 97.50)	0.400
Activated PTT, median (Q <sub>1</sub> , Q <sub>3</sub> )	37.35 (28.45, 42.80)	37.90 (29.35, 43.85)	0.203
D-dimer, median (Q <sub>1</sub> , Q <sub>3</sub> )	0.90 (0.40, 2.05)	0.80 (0.48, 1.49)	0.861

**Notes:** <sup>a</sup>Reported as n (%), unless shown as otherwise; <sup>b</sup> $P < 0.001$ ; <sup>c</sup> $P < 0.05$ .

**Abbreviations:** PT, prothrombin time; PTT, partial thromboplastin time.

**Table 2** CGA Items of Patients with or Without Anticoagulation at Hospital Discharge<sup>a</sup>

	Anticoagulation	No Anticoagulation	P
Subjects, n	159	202	—
BMI, $\bar{x} \pm SD$	24.69 $\pm$ 4.17	23.71 $\pm$ 4.16	0.028 <sup>b</sup>
Frailty, n (%)	70 (44.03)	112 (55.45)	0.031 <sup>b</sup>
ADL	90 (65, 95)	75 (50, 95)	0.011 <sup>b</sup>
Risk of falls	45 (45, 60)	50 (45, 70)	0.162
MNA-SF	13 (10, 14)	12 (9, 14)	0.047 <sup>b</sup>
Mini-cog	3 (1, 4)	3 (0, 4)	0.035 <sup>b</sup>
Polypharmacy, n (%)	123 (77.36)	153 (75.74)	0.719
aCCI	6 (4, 8.75)	7 (5, 9)	0.079

**Notes:** <sup>a</sup>Reported as median (Q<sub>1</sub>, Q<sub>3</sub>), unless indicated otherwise; <sup>b</sup> $P < 0.05$ .

The following were found likely factors for anticoagulation at discharge (Tables 1 and 2): age (OR 0.948, 95% CI 0.913–0.985,  $P = 0.006$ ); paroxysmal AF (OR 0.384, 95% CI 0.233–0.635,  $P < 0.001$ ); bleeding history (OR 0.396, 95% CI 0.226–0.694,  $P = 0.001$ ); and thrombosis during hospitalization (OR 2.281, 95% CI 1.130–4.607,  $P = 0.021$ ).

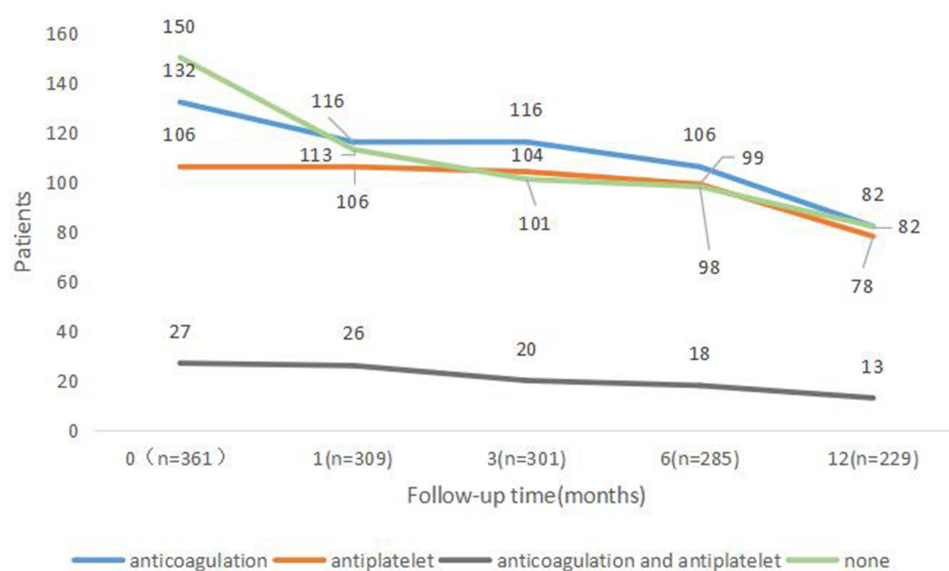
## Influence of Anticoagulation on Prognosis

After removing 33 patients from the present analysis who died in hospital and 11 patients who were lost to follow-up, 316 patients were followed (203 men and 113 women), and changes in anticoagulation during the follow-up were noted (Figure 1).

In all, 52 bleeding events were observed. Of these, 4 patients had major bleeding, including 1 patient with gastrointestinal bleeding (from carcinoma of the esophagus) who did not take anticoagulants. Three patients experienced intracranial hemorrhage, one of whom (with no anticoagulant/antiplatelet regimen) suffered from cerebral trauma; another 1 patient suffered from fall, and took aspirin and clopidogrel. One patient took warfarin (2.25 mg/d), and there were cerebral microbleeds in the right temporal lobe and the left cerebellar dentate nucleus. In this last patient, anticoagulation was not stopped after bleeding and major bleeding did not occur again. Furthermore, 29 thromboembolic events were observed, including 13 strokes (8 patients with frailty). There were 51 cardiovascular events and 56 all-cause deaths. Forty-nine patients withdrew from the medication of their own volition.

Differences were analyzed between the patients with and without anticoagulation (Table 3). The patients with anticoagulation had fewer thrombotic events (6.99% cf. 10.98%) and all-cause deaths (17.48% cf. 17.92%), but more bleeding events (20.98% cf. 12.72%). In addition, patients with anticoagulation had poor compliance.

The Cox regression analysis (which was adjusted for age, sex, daily activity, fall risk, cognition, nutrition, comorbidities, stroke, and bleeding risk) showed that anticoagulation tended to increase the bleeding risk (HR 0.584, 95% CI 0.337–1.013,  $P = 0.056$ ). Anticoagulation was not associated with thromboembolic events (HR 1.618, 95% CI 0.752–3.479,  $P = 0.218$ ), or all-cause death (HR 1.091, 95% CI 0.639–1.863,  $P = 0.750$ ; Table 4). The analysis also showed that frailty (after adjusting for age, sex, type of AF, presence of anticoagulation, comorbidities, ability to perform daily living activities, risk of fall, polypharmacy, and cognitive and nutritional status) was associated with an increased risk of bleeding (HR 2.294, 95% CI 1.264–4.160,  $P = 0.006$ ) and all-cause death (HR 4.947, 95% CI 1.999–12.242,  $P = 0.001$ ), but fatal bleeding did not increase. The frail group experienced a higher rate of cardiovascular events, but not significantly, and frailty was not associated with thrombosis.



**Figure 1** Drug compliance of anticoagulation and antiplatelet during follow-up.

**Table 3** Observed Events in Patients with or Without Anticoagulation or Frailty<sup>a</sup>

	Anticoagulation Regime			Frailty		
	Yes	No	P	Yes	No	P
Subjects, n	143	173	–	150	166	–
Thromboembolic events	10 (6.99)	19 (10.98)	0.221	14 (9.33)	15 (9.04)	0.927
Bleeding events	30 (20.98)	22 (12.72)	0.049 <sup>b</sup>	31 (20.67)	21 (12.65)	0.055
All-cause deaths	25 (17.48)	31 (17.92)	0.919	50 (33.33)	6 (3.61)	0.000 <sup>c</sup>
Drug compliance	30 (20.98)	19 (10.98)	0.015 <sup>b</sup>	21 (14.00)	28 (16.87)	0.482
Cardiovascular events	26 (18.18)	25 (14.45)	0.370	32 (21.33)	19 (11.45)	0.017 <sup>b</sup>

Notes: <sup>a</sup>Reported as n (%); <sup>b</sup>P < 0.05; <sup>c</sup>P < 0.001.

**Table 4** Cox Regression Analysis of the Effects of Anticoagulation and Frailty on Clinical Events

	Anticoagulation		Frailty	
	P	HR (95% CI)	P	HR (95% CI)
Thromboembolic events	0.218	0.618 (0.287–1.330)	0.729	0.826 (0.281–2.430)
Bleeding vents	0.056	1.712 (0.987–2.967)	0.006	2.294 (1.264–4.160)
All-cause death events	0.908	0.969 (0.572–1.642)	0.001	4.947 (1.999–12.242)
Cardiovascular events	0.391	1.271 (0.734–2.202)	0.053	1.899 (0.991–3.641)

## Discussion

Evidence for anticoagulation in elderly patients with AF is relatively insufficient, which leads to caution of administration by physicians.<sup>16</sup> The present study followed elderly patients with NVAf after hospital discharge, with particular attention given to the presence of frailty and anticoagulation regimen. It was determined that assignment of an anticoagulation regimen at hospital discharge for our elderly patients with NVAf was negatively influenced by the patient's age, paroxysmal AF (rather than persistent AF), history of bleeding, and absence of thromboembolism during hospitalization. Yet the anticoagulation rate at discharge (44%) was higher than at admission (23%), suggesting the effectiveness of medical intervention. The prevalence of frailty in the overall population was 50.4%, and frailty significantly increased the risk of bleeding and all-cause death. Ischemic stroke and cardiovascular events were also higher in the frail group, relative to the non-frail. Overall, there was no fatal bleeding caused by anticoagulation. We encourage elderly patients with NVAf, even those who are frail, to try anticoagulation, with close monitoring to ensure safety. However, longer prospective studies of such patients are wanted.

Both the prevalence of AF and frailty increase with age, and they often occur simultaneously. In our study about half of the patients were adjudged frail. This is similar to a previous meta-analysis.<sup>17</sup> Frailty affects both the management and the prognosis of AF in the geriatric population. In the present study, frailty not only increased the incidence of all-cause death, but also significantly increased the risk of bleeding (OR 1.64, 95% CI 1.11–2.41). Therefore, an assessment of geriatric frailty should be considered when planning individualized management of AF in older patients.<sup>14,18</sup>

Paroxysmal AF is often believed, mistakenly, to carry a lower risk of thrombotic events compared with persistent AF.<sup>19</sup> Regarding the history of bleeding as a factor for choosing anticoagulation, guidelines have emphasized that anticoagulation should be considered only after correction of the factors that increase the risk of bleeding. But even in patients with AF who have suffered intracerebral hemorrhage, resuming anticoagulation can significantly reduce the risk of death/ischemic stroke/peripheral vascular embolism, while not increasing the recurrence rate of intracerebral hemorrhage.<sup>20</sup>

Furthermore, it is undeniable that elderly patients with NVAf without anticoagulation have concomitant vulnerabilities, including lower BMI, higher prevalence of frailty, worse daily activities, poorer nutritional and cognitive status, and greater polypharmacy, which all increase the health burden of the elderly population. For example, a study from Spain that included 4724 patients with AF aged 80 years and older found that 43% of the patients were malnourished.<sup>21</sup> Malnutrition was not only an independent risk factor for morbidity and mortality, but also was associated with risk of ischemic stroke and major bleeding.

For patients with multiple medications, each additional drug was associated with a 4% increased risk of all-cause death (HR 1.04, 95% CI 1.00–1.08), and a 5% increased risk of cardiovascular death (HR 1.05, 95% CI 1.00–1.10).<sup>22</sup> We conclude that clinical treatment of elderly patients with NVAf should be guided by a prompt comprehensive geriatric assessment.

NOACs are the most widely used anticoagulant drug, perhaps because they are more effective than warfarin in reducing adverse events such as bleeding and thrombotic events.<sup>23</sup> However, in the present study the dose of NOACs generally was lower than the standard dose recommended by guidelines. A previous study of elderly patients with AF who were at high risk of thrombosis showed that the standard dose of anticoagulant drugs did not increase the risk of bleeding, but a reduced dose of NOAC was not effective in lowering the stroke rate.<sup>24</sup> In addition, the proportion of antiplatelet therapy in the present study was not low (36.8%), but its effect on stroke prevention was limited.

The patients in this study demonstrated poor compliance with anticoagulation, and those with better cognitive status were more likely to self-withdraw. As they gained information from outer sources, many patients stopped taking anticoagulants for fear of side effects such as bleeding, although they had not experienced bleeding events. This reflects that our study population did not know enough about anticoagulation in AF, and that our health education and monitoring during treatment was insufficient. Patients became focused on the possible harms, but not the benefits of stroke prevention offered by the recommended medical interventions.

Anticoagulation did not increase the risk of adverse outcomes. This study found that anticoagulation was appropriate and beneficial for elderly patients with NVAf. Although the difference in the occurrence of observed events was not statistical between the patients with and without anticoagulation, for the former the incidence of thrombosis was lower while the rate of major bleeding was similar. Patients who took anticoagulants before bleeding and continued anticoagulation also did not suffer a higher rate of major bleeding compared to those who did not.

Several other studies have focused on the effect of anticoagulation on the prognosis of very elderly patients with NVAf. Kim et al<sup>4</sup> observed the effects of oral anticoagulants and different regimens on patients' prognosis, and determined that oral anticoagulants were associated with a lower risk of ischemic stroke (HR 0.91, 95% CI 0.86–0.97) and cardiovascular death (HR 0.52, 95% CI 0.99–0.55), with no difference in major bleeding events (HR 1.02, 95% CI 0.95–1.10). However, a large European cohort study regarding AF (n = 10,177 patients) found a significant reduction in all-cause mortality in patients treated with oral anticoagulants when the frailty index was between 0.05 and 0.36; there was no difference in patients with a higher frailty index.<sup>5</sup> The ABC (Atrial fibrillation Better Care) pathway could be helpful in reducing the risk of major outcomes, with a clear trend towards greater benefit for those with high complexity cluster.<sup>25,26</sup>

## Study Limitations

Our analysis has some limitations. Firstly, a short follow-up period may have lowered the rate of long-term adverse events; only hospitalized patients in a single center were included, and the results may not apply to the broader population. Secondly, changes in patients' frailty may have occurred during the follow-up, but this was not reevaluated. Finally, unlike in a previous study, we did not find that anticoagulation was associated with thromboembolic events. This may be due to definitively unknown confounding factors, leading to indication bias. For example, patients who were at higher risk of bleeding may not have initially received anticoagulants.

## Conclusion

Because the effects of anticoagulation in the very elderly with AF are little known, especially in the context of frailty, this study followed patients with NVAf, aged at least 75 years, for 12 months after hospital discharge. It was found that the factors that lowered the rate of anticoagulation administration at discharge were higher age, paroxysmal AF (as opposed to persistent AF), and history of bleeding. Patients were more likely given anticoagulation if they had suffered thrombotic events during hospitalization. Frail patients, compared with the non-frail, showed an increased risk of bleeding, and all-cause death. A geriatric assessment of frailty for older patients with AF is important. Patients given anticoagulant therapy experienced fewer thromboembolic events, and there was no increase in fatal bleeding. It is also worth mentioning that most of the anticoagulant drugs in this study were NOACs, but compliance with anticoagulation was poor. The ABC (Atrial fibrillation Better Care) pathway might be helpful to reduce the risk of major outcomes.



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## Disclosure

The authors report no conflicts of interest in this work.

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