Drugs & Aging (2018) 35:897–905
https://doi.org/10.1007/s40266-018-0587-6

SHORT COMMUNICATION

Frailty Status Affects the Decision for Long-Term Anticoagulation Therapy in Elderly Patients with Atrial Fibrillation

Panteleimon E. Papakonstantinou[1] · Natalia I. Asimakopoulou[1] · John A. Papadakis[1] · Dimitrios Leventis[1] · Michail Panousieris[1] · George Mentzantonakis[1] · Ermis Hoda[1] · Simeon Panagiotakis[1] · Achilleas Gikas[1]

Published online: 11 September 2018

Abstract

Background Elderly patients are underrepresented in the studies concerning anticoagulation therapy (AT) in atrial fibrillation (AF), while patients' frailty status is lacking in most of the studies.

Objective Our objective was to evaluate AT in AF elderly patients and study the effect of patients' frailty status on their long-term AT.

Methods We conducted an observational prospective study that enrolled consecutive AF patients (≥ 75 years) who were hospitalized in the Department of Internal Medicine of the University Hospital of Heraklion, Crete, Greece from 1 June 2015 to 1 June 2016. We recorded the AT on admission and at discharge, all-cause mortality, and hospital readmission in a follow-up period of 1 year after hospital discharge. Frailty status was assessed by pre-established scores.

Results One hundred and four consecutive patients (49% male; median age 87 years) were enrolled, 78 (78.8%) of whom received AT at discharge. Patients who did not receive AT at discharge had a higher $HEMORR_2HAGES$ (Hepatic or renal disease, Ethanol abuse, Malignancy, Older age, Reduced platelet count or function, Re-bleeding, Hypertension, Anemia, Genetic factors, Excessive fall risk and Stroke) score (5.5 ± 1.15 vs. 4.79 ± 1.68; $p = 0.032$), a lower Katz score (2.48 ± 2.23 vs. 4.08 ± 2.25; $p = 0.006$), and a higher Clinical Frailty Scale score (7 ± 1.95 vs. 5.57 ± 2.05; $p = 0.006$). Sixty-five patients (62.5%) were readmitted to a hospital during the follow-up period. In-hospital death occurred in five patients (4.8%) and 57 patients (57.6%) died within the follow-up period.

Conclusion A high percentage of the elderly AF patients did not receive AT, even at discharge. Patients who did not receive AT at discharge had higher bleeding and frailty scores. In the 1-year follow-up period after hospital discharge, high all-cause mortality and a high number of hospital readmissions were recorded.

Key Points

Elderly hospitalized patients with atrial fibrillation (AF) presented a high frailty status along with high 1-year all-cause mortality.

Most of the AF patients were treated with reduced dosages of non-vitamin K antagonist oral anticoagulants (NOACs) at discharge.

Frailty status affects the treating physician's decision regarding long-term anticoagulation therapy (AT) in AF. A high percentage of elderly patients with AF did not receive AT, even at hospital discharge. Age remains one of the major reasons leading physicians to withhold AT from AF patients.

✉ Panteleimon E. Papakonstantinou
pantelispapakon@gmail.com

[1] Department of Internal Medicine, University Hospital of Heraklion "PAGNI", School of Medicine, University of Crete, Voutes, 71110 Heraklion, Crete, Greece

1 Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia with greater prevalence in elderly patients [1, 2]. AF patients present deterioration in quality of life along with high rates of hospitalizations [3], with up to 40% being hospitalized every year [4]. Age is one of the strongest predictors for AF-related ischemic stroke [5] and is independently associated with increased thromboembolic and bleeding risk [4, 6]. Anticoagulation therapy (AT) is the cornerstone of AF treatment for the prevention of ischemic strokes and/or systematic thromboembolism [4]. However, AT is not without adverse effects, especially in elderly patients [2, 4, 6, 7]. The presence of concomitant physical and medical problems and the use of other drugs increase the risk of medication interactions and bleeding, requiring an assessment of the overall risk:benefit ratio [2, 8].

According to the current European Society of Cardiology (ESC) guidelines (2016) for AF [4], AT is indicated in all patients aged over 75 years as their CHA_2DS_2-VASc (Congestive Heart failure, hypertension, Age ≥ 75 [doubled], Diabetes, Stroke [doubled]–Vascular disease, Age 65–74, and Sex [female]) [4] score is at least 2. Until recently, Vitamin K antagonists (VKAs) were the only available oral anticoagulants (OACs). Nowadays, non-VKA OACs (NOACs) offer a better safety profile along with a more predictable effect with rapid onset and offset of their action [2, 4].

Is AT in AF feasible for all elderly patients in the era of NOACs? AF is mainly a geriatric disease [9], affecting up to 2% of the general population but up to 13% of AF patients aged > 75 years [10]. However, data regarding AT management in older AF patients are sparse in the literature [2]. In fact, these patients are underrepresented in most of the studies, even in the main studies of the NOACs—RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) [11], ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) [12], ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) [13], and ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48) [14]—with only 31–43% of enrolled patients in these studies ≥ 75 years old [2]. This can be explained by the fact that concern regarding bleeding in elderly patients leads to underutilization of OACs in daily clinical practice. Interestingly, with respect to the safety and efficiency of NOACs, there has been no randomized controlled trial that enrolled only elderly AF patients [2, 15]. Hence, even in the era of NOACs, AT for AF in geriatric patients still requires more research [16]. Recent studies have shown that the risk of stroke outweighed the risk of bleeding [7], even in very elderly patients (> 85 years) with AF receiving AT [6, 16]. Nevertheless, most studies [6] selected elderly AF patients from cardiology departments for enrollment and did not provide specific evidence regarding the functional (activities of daily living activities, performance status, etc.) and mental status of the patients, which are crucial factors in their geriatric evaluation.

In the present 'real-world' prospective observational study, we aimed to evaluate the current anticoagulation management in hospitalized elderly AF patients in order to study the effect of bleeding risk, thromboembolic risk, and patients' frailty status on their long-term AT, and to record patients' all-cause mortality and hospital readmissions in a 1-year follow-up period after hospital discharge.

2 Methods

We conducted a single-center, observational prospective study, which included consecutive patients aged ≥ 75 years with a known history of AF. Patients who were hospitalized in the Department of Internal Medicine of the University Hospital of Heraklion, Crete, Greece from 1 June 2015 to 1 June 2016 were enrolled. We recorded the AT the patient had been taking on admission and the AT taken during the hospitalization; finally, we recorded the AT at discharge. The international normalized ratio (INR) treatment goal value for AF patients taking a VKA (acenocoumarol) was 2–3. The patient's medical history of past ischemic strokes before and after initiation of the AT as well as past major bleeding before and after the initiation of the AT was obtained by analyzing the patient's regular files and electronic medical records from the hospital. We followed up the patients for a 1-year period after hospital discharge.

Types of AF were defined according to the latest ESC guidelines (2016) [4]. Stroke risk was assessed using the CHA_2DS_2-VASc score [4], the Katz score [17] was used to estimate the patients' activities of daily living, and the Charlson score [18] was used as the co-morbidity index in our study. In order to assess the patient's frailty status, we used the Clinical Frailty Scale (CFS) [19], which provides an estimation of frailty on a scale ranging from 1 to 9 based on the patient's functional autonomy status, mobility, and need for assistance with activities of daily living [6, 19]. CFS is a simple tool and time efficient as it can be completed based on routine clinical admission and there is no need for extra equipment. CFS can predict mortality [20, 21] and functional decline in hospitalized elderly patients [21], while no specific training of non-geriatricians, even of junior doctors,

is required [21]. Consequently, there are minimal barriers to CFS implementation. The bleeding risk was assessed using the HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly, Drugs/alcohol) score [4, 22] and the $HEMORR_2HAGES$ (Hepatic or renal disease, Ethanol abuse, Malignancy, Older age, Reduced platelet count or function, Re-bleeding, Hypertension, Anemia, Genetic factors, Excessive fall risk and Stroke) score [22].

The presence of anemia was defined as hemoglobin (Hb) < 13 g/dL in men and Hb < 12 g/dL in women. The anemia definition and categorization as mild, moderate, and severe was made according to Hb levels as per the World Health Organization (WHO) recommendations [23]. Mild anemia was defined as Hb > 11 to < 13 g/dL in men and Hb > 11 to < 12 g/dL in women. Moderate and severe anemia was defined as Hb > 8 to < 11 and < 8 g/dL, respectively, in both men and women.

Major bleeding was defined according to the recommendations of the International Society on Thrombosis and Haemostasis [24] as (1) fatal bleeding; and/or (2) bleeding into a critical organ (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome); and/or (3) clinically relevant bleeding with a fall in Hb of ≥ 2 g/dL, or leading to transfusion of two or more units of whole blood or red cells.

We recorded the all-cause mortality and hospital readmission in a follow-up period of 1 year after hospital discharge. The follow-up was performed using telephone communications and the electronic 'real-time' system of our hospital.

Patients who were hospitalized for < 48 h were excluded from our analysis based on the rationale that the treating physicians would not change the AT during short-term hospitalization in elderly patients. Furthermore, we wanted to exclude patients who were hospitalized for investigation of chronic diseases. Newly diagnosed AF patients, defined as patients without a known history of AF (AF was recorded on admission), were excluded as the purpose of the study was to observe and record AT in elderly patients with known AF admitted to the hospital (on admission and at discharge). We also excluded patients with prosthetic heart valves and/or a glomerular filtration rate (GFR) < 30 mL/min according to the Cockroft–Gault formula [25].

The study was designed according to ethical considerations, as described in the Declaration of Helsinki for human medical studies, and the protocol was approved by the institutional medical ethics committee. Informed consent was obtained from all individual participants included in the study.

2.1 Statistics

Values are expressed as mean ± standard deviation for continuous variables and number (frequency [%]) for categorical values. All p values are two-tailed. Between-group results were assessed by independent samples t tests. Frequency analysis was by Chi-square (χ^2) test, with Yates' correction. Correlation was assessed by Pearson's correlation (r).

3 Results

One hundred and four consecutive patients (51 [49%] male; median age 87 [range: 75–97] years) were enrolled. The patients' baseline demographic and clinical characteristics are shown in Table 1. The vast majority of patients had permanent AF (78%). The most common cause of admission and hospitalization was infectious diseases (48%), followed by anemia (21.15%) and acute heart failure (HF) (20.2%) (Table 2). Seventy-four patients (71.2%) received AT on admission (Table 3). Fifty-nine patients (56.7%) were treated with OACs (24 patients [23.1%] with NOACs), while 15 patients (14.4%) were admitted with low molecular weight heparin (LMWH). AT with a VKA was recorded in 35 patients (33.7%), of whom only six had an INR in the therapeutic range on admission (INR: 2–3), while 15 patients (42.8%) had an INR < 2 and 14 patients (40%) had an INR > 3.

Seventy-eight patients (78.8%) received AT at discharge. All patients who were discharged from the hospital having been prescribed AT with NOACs were treated with a reduced NOAC dose (dabigatran 110 mg twice daily, rivaroxaban 15 mg once daily, apixaban 2.5 mg twice daily) (Table 3).

Nineteen patients (18.2%) had a medical history of ischemic stroke or transient ischemic attack prior to the initiation of antithrombotic therapy (nine patients treated with VKA, four patients with single antiplatelet therapy, two patients with LMWH, one patient with a NOAC, and three patients with no AT), while four patients (3.8%) presented an ischemic stroke after initiation of the antithrombotic therapy (two patients treated with VKA, one patient with a NOAC, and one patient with single antiplatelet therapy).

3.1 Rehospitalizations and All-Cause Mortality

Data regarding hospital readmissions were available for 97 patients (93.3%); 65 patients (62.5%) were readmitted to a hospital in our region during the follow-up period. There was no statistical significant difference between readmissions and the AT (NOACs, VKA, LMWH, no AT) at discharge ($p = 0.76$) (Table 3).

Table 1 Baseline demographic and clinical characteristics of patients

Patients' characteristics	Mean ± SD or *n* (%), *n* = 104 (100%)
Men	51 (49)
Age	84.9 ± 5
Hypertension	54 (51.9)
Smokers	53 (50.96)
Active smokers	14 (13.46)
Ex-smokers	39 (37.5)
Dyslipidemia	36 (34.6)
Diabetes mellitus	34 (32.7)
Coronary artery disease or PAD	47 (45.19)
Heart failure	68 (65.38)
AF type	
Paroxysmal AF	23 (22.1)
Permanent AF	81 (77.9)
Chronic kidney disease (GFR < 60 mL/min)	75 (72.11)
GFR	41.62 ± 22.26
COPD	35 (33.65)
Dementia	34 (32.7)
CHA_2DS_2-VASc score	4.23 ± 1.27
HAS-BLED score	3.3 ± 1.24
$HEMORR_2HAGES$ score	4.92 ± 1.57
Charlson score	6.9 ± 2.37
Katz score	3.68 ± 2.32
Clinical Frailty Scale (CFS) score	5.9 ± 2.08
Medications	
Drugs for heart rate control	59 (56.7)
β-Blockers	43 (41.3)
Diltiazem	7 (6.7)
Digoxin	9 (8.7)
Drugs for heart rhythm control	10 (9.6)
Propafenone	5 (4.8)
Amiodarone	5 (4.8)
Other cardiac medications	
ACEI/ARB	43 (41.3)
Calcium channel blockers (dihydropyridine)	15 (14.4)
Diuretics	62 (59.6)
Spirinolactone/eplerenone	18 (17.3)
Statins	30 (28.8)
Other medications	
Proton pump inhibitors	57 (54.8)
Ranitidine	5 (4.8)
Allopurinol	22 (21.15)

ACEI angiotensin-converting enzyme inhibitor, *AF* atrial fibrillation, *ARB* angiotensin receptor blocker, *CHA_2DS_2-VASc* Congestive Heart failure, hypertension, Age ≥ 75 (doubled), Diabetes, Stroke (doubled)–Vascular disease, Age 65–74, and Sex (female), *COPD* chronic obstructive pulmonary disease, *GFR* glomerular filtration rate, *HAS-BLED* Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly, Drugs/alcohol, *$HEMORR_2HAGES$* Hepatic or renal disease, Ethanol abuse, Malignancy, Older age, Reduced platelet count or function, Re-bleeding, Hypertension, Anemia, Genetic factors, Excessive fall risk and Stroke, *PAD* peripheral artery disease, *SD* standard deviation

Table 2 Causes of hospital admissions

Cause of admission	Patients (*n* = 104; 100%) [*n* (%)]
Infectious diseases	50 (48.05)
Lower respiratory tract infection	30 (28.85)
Urinary tract infection	8 (7.7)
Abdominal infection	8 (7.7)
Soft tissue infection	2 (1.9)
Osteomyelitis	1 (0.95)
Infective endocarditis	1 (0.95)
Acute heart failure	21 (20.2)
Acute renal failure	2 (1.9)
Anemia	22 (21.15)
Anemia without active bleeding	16 (15.4)
Anemia with active bleeding	6 (5.75)
Lower gastrointestinal bleeding	3 (2.9)
Upper gastrointestinal bleeding	2 (1.9)
Hematuria	1 (0.9)
Soft tissue hematoma	3 (2.9)
Syncope	2 (1.9)
Thyroid gland disease	1 (0.95)
Thrombophlebitis	1 (0.95)
Pericardial effusion	1 (0.95)
Ascites	1 (0.95)

In-hospital death occurred in five patients (4.8%). Ninety-nine patients (95.2%) were followed up for a period of 1 year after hospital discharge (Table 3); 57 patients (57.6%) died within the follow-up period. Linear regression analysis revealed that AT status ($p < 0.0001$) and CHA_2DS_2-VASc ($p = 0.02$) were independent factors for the outcome.

Significant higher all-cause mortality was observed in patients discharged with no AT (95.2% vs. 47.4%; $p < 0.001$). No difference was observed between the type of AT at discharge (NOACs, VKA, LMWH) and all-cause mortality. Patients who did not receive AT at discharge had a higher $HEMORR_2HAGES$ score (5.5 ± 1.15 vs. 4.79 ± 1.68; $p = 0.032$), a lower Katz score (2.48 ± 2.23 vs. 4.08 ± 2.25; $p = 0.006$), and a higher CFS score (7 ± 1.95 vs. 5.57 ± 2.05; $p = 0.006$). No significant difference in HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly, Drugs/alcohol) score (3.5 ± 1.05 vs. 3.32 ± 1.324; $p = 0.52$), Charlson score (7.3 ± 2.36 vs. 6.79 ± 2.43; $p = 0.4$), and CHA_2DS_2-VASc score (4.35 ± 1.18 vs. 4.21 ± 1.34; $p = 0.64$) between patients with or without AT at discharge was observed. Linear regression analysis revealed that only the Katz score was an independent factor for the decision regarding AT in our patients at discharge ($p = 0.007$).

Table 3 Antithrombotic therapy on admission and at discharge, readmissions, and deaths during the 1-year follow-up period after the hospital discharge

Anticoagulant	Anticoagulation therapy on admission ($n=104$; 100%) [n (%)]	Anticoagulation therapy at discharge ($n=99$; 100%) [n (%)]	Readmission ($n=36$; 100%) [n (%)]	Death ($n=57$; 100%) [n (%)]
VKA	35 (33.7)	21 (21.2)	6 (16.7)	10 (17.5)
NOAC	24 (23.1)	37 (37.4)	15 (41.7)	16 (28)
Dabigatran 110 mg	6 (5.8)	7 (7.1)		
Rivaroxaban 15 mg	12 (11.5)	5 (5)		
Apixaban 2.5 mg	6 (5.8)	25 (25.3)		
LMWH	15 (14.4)	20 (20.2)	6 (16.7)	11 (19.3)
No anticoagulant	30 (28.8)	21 (21.2)	9 (25)	20 (35.1)
Single antiplatelet agent[a]	16 (15.4)	12 (12.1)		
No antithrombotic therapy	14 (13.4)	9 (9.1)		

LMWH low molecular weight heparin, *NOAC* non-vitamin K antagonist oral anticoagulant, *VKA* vitamin K antagonist

[a]Aspirin 100 mg/day or clopidogrel 75 mg/day

3.2 Bleeding Episodes and Anemia

Nine patients (8.6%) had a medical history of a major bleeding episode after the initiation of AT; however, no significant correlation was observed between the type of AT and the history of a bleeding episode. Patients with a history of a major bleeding after the initiation of AT had a higher HAS-BLED score (3.68 ± 1.15 vs. 2.79 ± 1.09; $p=0.01$) and HEMORR$_2$HAGES score (5.21 ± 1.57 vs. 4.5 ± 1.51; $p=0.051$), while no significant difference in the CHA$_2$DS$_2$-VASc score (4.29 ± 1.3 vs. 4.32 ± 1.23; $p=0.9$), Katz score (4.04 ± 2.38 vs. 3.79 ± 2.49; $p=0.66$), CFS score (5.46 ± 2.15 vs. 5.81 ± 2.32; $p=0.5$), and Charlson score (6.79 ± 2.67 vs. 7.09 ± 2.28; $p=0.59$) was observed.

Seventy-six patients (73%) presented with anemia on admission (Table 4). Twenty-three patients (22.1%) were admitted to the hospital with severe anemia (Hb < 8 g/dL); six patients (5.75%) had anemia with active bleeding. In patients presenting with severe anemia, there was a change in their AT in about half (12/23 patients; 52.2%), while one patient died during the hospitalization. More specifically, seven patients who received VKA on admission were discharged with low-dose apixaban (five patients), LMWH (one patient), and no AT (one patient). Moreover, four patients were on AT with rivaroxaban, all of whom switched to low-dose apixaban. Three patients with severe anemia recorded on admission did not receive therapeutic AT; two of them were discharged without AT, while in one patient AT with a prophylactic dose of LMWH was initiated (enoxaparin 40 mg once daily). No statistically significant differences were recorded between the type of antithrombotic therapy and the severity of the anemia. The severity of anemia was significantly correlated only with the HEMORR$_2$HAGES score ($p<0.001$). There was no correlation between the presence of anemia and its severity with the use of proton pump inhibitors (Table 1).

Table 4 Anemia and antithrombotic therapy on admission

Antithrombotic drug	Anticoagulation therapy on admission ($n=104$; 100%) [n (%)]	Mild anemia ($n=104$; 100%) [n (%)]	Moderate anemia ($n=104$; 100%) [n (%)]	Severe anemia ($n=104$; 100%) [n (%)]
VKA	35 (33.7)	5 (4.8)	12 (11.5)	8 (7.7)
NOAC	24 (23.1)	4 (3.8)	7 (6.7)	8 (7.7)
LMWH	15 (14.4)	2 (1.9)	5 (4.8)	2 (1.9)
Single antiplatelet agent[a]	16 (15.4)	5 (4.8)	6 (5.7)	2 (1.9)
No antithrombotic agent therapy	14 (13.4)	1 (1)	6 (5.7)	3 (2.9)
Total	104 (100)	17 (16.3)	36 (34.6)	23 (22.1)

LMWH low molecular weight heparin, *NOAC* non-vitamin K antagonist oral anticoagulant, *VKA* vitamin K antagonist

[a]Aspirin 100 mg/day or clopidogrel 75 mg/day

4 Discussion

In our study, we observed that hospitalized AF patients aged ≥ 75 years present high thromboembolic risk, bleeding risk, and frailty scores. Acenocoumarol was the most common anticoagulation agent on admission, while most patients received NOACs at discharge, with apixaban being the most prescribed agent. Moderate to severe anemia was observed on admission in 56.7% of patients. A high percentage of elderly patients with AF did not receive AT, even at discharge (21.2%). Patients who did not receive AT at discharge had a higher $HEMORR_2HAGES$ score, a lower Katz score, and a higher CFS score. In the 1-year follow-up period after hospital discharge, high all-cause mortality and a high number of hospital readmissions were recorded.

To our knowledge, this is the first prospective study in the 'real world' that included unselected elderly patients with AF, and which aimed to evaluate AT in the era of NOACs in association with the frailty status and record the rehospitalizations and all-cause mortality during a 1-year follow-up period after discharge.

Age remains one of the major reasons causing physicians to withhold AT from AF patients and/or to administer antiplatelet agents instead of AT. However, this clinical practice is not evidence based. An overestimation of bleeding risk in elderly populations along with an underestimation of thromboembolic risk has been reported [26]. Most studies showed great benefit in elderly patients receiving AT, while AT presented almost the same bleeding risk as antiplatelet therapy [27, 28]. The BAFTA (Birmingham Atrial Fibrillation Treatment of the Aged Study) study [27] showed that in AF patients aged ≥ 75 years, the use of VKA was associated with a significant reduction of thromboembolic events compared with aspirin. In accordance with the BAFTA study, a subgroup analysis [28] from the AVERROES (Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) trial indicated that elderly patients with AF ≥ 75 years, or even those ≥ 85 years who received apixaban, had greater benefit in stroke prevention than did younger patients, while the administration of aspirin instead of AT (apixaban) presented a greater thromboembolic risk with almost the same bleeding risk. Furthermore, the data from a recent subanalysis of PREFER in AF (PREvention oF Thromboembolic Events-European Registry in Atrial Fibrillation) study in 'real-world' data from very elderly patients (≥ 85 years) [6] recorded that, despite the high bleeding risk in these patients, the absolute benefit of AT outweighs the risk of bleeding. In a recently published nationwide study of very elderly (age ≥ 90 years) AF patients in Taiwan [16], in which antithrombotic therapy for stroke prevention was investigated, the use of warfarin was associated with a lower risk of ischemic stroke and positive net clinical benefit, while NOACs were associated with a lower risk of intracranial hemorrhage than warfarin. In our study, we observed a significant percentage of patients who were receiving no AT on admission (28.8%) and, more importantly, a significant percentage of patients (21.2%) who were also not receiving AT at discharge. Interestingly, most of these patients did not present an absolute contraindication to receiving AT.

Elderly patients present a high thromboembolic risk with a concomitant high bleeding risk [6]. The studies already discussed indicate that the benefit from AT is great, even in elderly patients. However, the weak point of those studies was the absence of the patients' geriatric evaluation. Although aging is a heterogeneous process, data on the functional, mental, and frailty status of the elderly patients is lacking in the vast majority of studies. This has led clinicians to adopt a more personalized approach, taking into account the frailty status of geriatric patients as far as AT management in AF is concerned. In an effort to study the association between the frailty status and the decision to administer OACs or not, the FRAIL-AF (Frailty, Stroke Risk and Bleeding Risk on Anticoagulation in the Elderly with Atrial Fibrillation) [29] study investigated the effect of thromboembolic risk, bleeding risk, and frailty status on the administration of AT in hospitalized AF elderly patients ≥ 80 years. A higher thromboembolic risk was associated with a higher probability of OAC prescription, while higher bleeding risk and severe frailty status were associated with lower probability of receiving AT. However, in this study some severely frail patients who died during hospitalization and patients admitted to a palliative care unit were excluded. Previous smaller studies [26, 30] have also demonstrated the association between frailty status and the administration of AT in elderly patients. In line with these observations, in our study we recorded that patients discharged without AT had a significantly higher $HEMORR_2HAGES$ score, a significant lower Katz score, and a significant higher CFS score, while only the Katz score was an independent factor in the decision regarding prescribing AT in our patients at discharge ($p = 0.007$). Consequently, both high frailty scores and high bleeding scores have a negative impact on the physicians' decision regarding long-term AT administration in elderly patients with AF.

Another intriguing issue is how beneficial AT is in elderly, frail AF patients. Indeed, there is broad interest in the best anticoagulation management for elderly AF patients [6, 9, 26, 29], while the data in the literature are mainly based on small observational studies [9]. For the first time, in the current ESC guidelines for AF [4] frail and elderly

patients are considered as a specific group of patients regarding AF management. Frail elderly patients usually present many co-morbidities, with a few hospitalizations and a high mortality rate [4, 6, 18, 26, 31]. It is also known that AF is independently associated with high morbidity and mortality [4, 6, 31], especially in elderly patients. In our study, a significant percentage of patients (22%) had severe anemia on admission and/or a history of severe bleeding after the initiation of AT (8.6%); six patients (5.75%) were admitted to hospital due to severe anemia with active bleeding. Moreover, patients presented a high percentage of readmissions, while 57.6% of the patients died within the 1-year follow-up period. AT status ($p < 0.0001$) and CHA_2DS_2-VASc score ($p = 0.02$) were independent factors regarding the outcome. It is of clinical significance that the vast majority of patients (20/21; 95.2%) who were discharged without AT died during the 1-year follow-up period. This can be attributed to the fact that this group of patients was very frail elderly AF patients, some of whom suffered from severe chronic diseases. However, it is unknown whether there was a direct correlation between AF, AT, and mortality in these patients. Undoubtedly, these observations raise a few questions about the administration of OACs in frail elderly patients, making the treating physician's final decision challenging.

In our study, most of the patients were treated with VKAs on admission. However, only a minority of patients (6/35 patients; 17.1%) treated with VKAs had an INR within the therapeutic range. This observation can be explained by two reasons. Firstly, almost half of the patients were admitted to the hospital due to infectious diseases, which could affect maintenance of the INR in the therapeutic range. Secondly, a number of patients lived in remote and rural areas on the island of Crete, Greece, and consequently they did not have a follow-up adjustment of the VKA dosages with regular (monthly) INR measurements. In a significant percentage of patients, there was a change in the AT from a VKA to a NOAC. Although there is no randomized controlled head-to-head trial to compare and contrast the four available NOACs [2, 4], in our study the most commonly prescribed NOAC was apixaban, prescribed at the reduced dosage, while acenocoumarol was the only VKA recorded. The clinicians' preference for apixaban and lower NOACs dosages can be explained by the fact that renal function is reduced at high age, as in our study population (72% with moderate to severe renal failure), and the particular concern of the physicians regarding any drug with predominant renal excretion. According to the OAC-FORTA (Oral Anticoagulant–Fit-fOR-The-Aged) 2016 [9] expert meeting procedure which evaluated the data on OACs in elderly AF patients, dabigatran, edoxaban, rivaroxaban, and warfarin were rated FORTA-B (beneficial), while apixaban was assigned FORTA-A (highly beneficial). Interestingly, other VKAs except for warfarin (FORTA-B [beneficial]), such as acenocoumarol, were rated FORTA-C (questionable) due to a lack of clinical data, making their efficacy and safety unknown in AF elderly patients.

Finally, it is known that there is a synergy between AF and HF [32], which are morbid conditions that frequently coexist and share common risk factors. An interesting observation is that despite the high prevalence of HF (65.38%) in our population, the use of angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers and β-blockers was relatively low (41.3%). Although this is an important finding that showed that some frail elderly patients may not have received optimal medical treatment for HF, it cannot be explained by the present study and requires further investigation and research in the future.

5 Limitations

Our study was a relatively small prospective, observational single-center study that included frail elderly patients hospitalized at our internal medicine department, the first such study in the literature. Given the small number of patients enrolled, our results should be interpreted with caution. We enrolled only consecutive unselected elderly patients with known AF, while newly diagnosed AF patients were excluded from our analysis. The population of the study was hospital based, and although AF is associated with an increased rate of hospitalizations [3, 4], it is unknown if our results are representative of non-hospitalized patients. The 1-year mortality rate and the hospital readmissions cannot be directly attributed to AF, as a high percentage of patients were severely frail and AF should be interpreted mainly as a co-morbidity in those patients, which may have affected the final outcome. We excluded patients with prosthetic valves and a GFR < 30 mL/min in order to study the current trend of AT in the era of NOACs in patients who were suitable for both VKAs and NOACs. In addition, baseline echocardiography parameters were not available for the vast majority of patients. Furthermore, as the study was non-interventional, we did not perform a computed tomography brain scan at the time of the enrollment in order to identify possible silent strokes. Additionally, edoxaban was not commercially available in our country (Greece) during the study period.

6 Conclusion

Our study attempted to evaluate AT management in elderly hospitalized AF patients and its association with geriatric syndromes. Elderly hospitalized patients with AF presented a high frailty status which affected the physicians' decision regarding long-term AT. Frailty status is a crucial factor in the evaluation of elderly patients and should be taken

into account at the initiation of any pharmaceutical therapy. Given the limited available literature concerning AT in frail elderly patients with AF, randomized controlled trials should be performed to study the safety/efficiency of OACs in these patients, even in the era of NOACs. Until then, AT in daily clinical practice in frail elderly patients may be personalized, based partly on the treating physician's discretion.

Compliance with Ethical Standards

Funding No external funding was used in the preparation of this manuscript.

Conflict of interest Panteleimon E. Papakonstantinou, Natalia I. Asimakopoulou, John A. Papadakis, Dimitrios Leventis, Michail Panousieris, George Mentzantonakis, Ermis Hoda, Simeon Panagiotakis, and Achilleas Gikas declare that they had no conflict of interest related to this article.

References

1. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. Circulation. 2014;129(8):837–47.
2. Karamichalakis N, Georgopoulos S, Vlachos K, Liatakis I, Efremidis M, Sideris A, et al. Efficacy and safety of novel anticoagulants in the elderly. J Geriatr Cardiol. 2016;13(8):718–23.
3. Friberg J, Buch P, Scharling H, Gadsbphioll N, Jensen GB. Rising rates of hospital admissions for atrial fibrillation. Epidemiology. 2003;14(6):666–72.
4. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016;37(38):2893–962.
5. Hijazi Z, Lindback J, Alexander JH, Hanna M, Held C, Hylek EM, et al. The ABC (age, biomarkers, clinical history) stroke risk score: a biomarker-based risk score for predicting stroke in atrial fibrillation. Eur Heart J. 2016;37(20):1582–90.
6. Patti G, Lucerna M, Pecen L, Siller-Matula JM, Cavallari I, Kirchhof P, et al. Thromboembolic risk, bleeding outcomes and effect of different antithrombotic strategies in very elderly patients with atrial fibrillation: a sub-analysis from the PREFER in AF (PREvention oF Thromboembolic Events-European Registry in Atrial Fibrillation). J Am Heart Assoc. 2017;6(7):e005657.
7. Lip GY, Clementy N, Pericart L, Banerjee A, Fauchier L. Stroke and major bleeding risk in elderly patients aged ≥ 75 years with atrial fibrillation: the Loire Valley atrial fibrillation project. Stroke. 2015;46(1):143–50.
8. Gage BF, Fihn SD, White RH. Warfarin therapy for an octogenarian who has atrial fibrillation. Ann Intern Med. 2001;134(6):465–74.
9. Wehling M, Collins R, Gil VM, Hanon O, Hardt R, Hoffmeister M, et al. Appropriateness of oral anticoagulants for the long-term treatment of atrial fibrillation in older people: results of an evidence-based review and international consensus validation process (OAC-FORTA 2016). Drugs Aging. 2017;34(7):499–507.
10. Wilke T, Groth A, Mueller S, Pfannkuche M, Verheyen F, Linder R, et al. Incidence and prevalence of atrial fibrillation: an analysis based on 8.3 million patients. Europace. 2013;15(4):486–93.
11. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361(12):1139–51.
12. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365(10):883–91.
13. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365(11):981–92.
14. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013;369(22):2093–104.
15. Sharma M, Cornelius VR, Patel JP, Davies JG, Molokhia M. Efficacy and harms of direct oral anticoagulants in the elderly for stroke prevention in atrial fibrillation and secondary prevention of venous thromboembolism: systematic review and meta-analysis. Circulation. 2015;132(3):194–204.
16. Chao TF, Liu CJ, Lin YJ, Chang SL, Lo LW, Hu YF, et al. Oral anticoagulation in very elderly patients with atrial fibrillation—a nationwide cohort study. Circulation. 2018;138(1):37–47.
17. Hartigan I. A comparative review of the Katz ADL and the Barthel Index in assessing the activities of daily living of older people. Int J Older People Nurs. 2007;2(3):204–12.
18. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373–83.
19. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ. 2005;173(5):489–95.
20. Wallis SJ, Wall J, Biram RW, Romero-Ortuno R. Association of the clinical frailty scale with hospital outcomes. QJM. 2015;108(12):943–9.
21. Gregorevic KJ, Hubbard RE, Lim WK, Katz B. The clinical frailty scale predicts functional decline and mortality when used by junior medical staff: a prospective cohort study. BMC Geriatr. 2016;2(16):117.
22. Fauchier L, Chaize G, Gaudin AF, Vainchtock A, Rushton-Smith SK, Cotte FE. Predictive ability of HAS-BLED, $HEMORR_2HAGES$, and ATRIA bleeding risk scores in patients with atrial fibrillation. A French nationwide cross-sectional study. Int J Cardiol. 2016;15(217):85–91.
23. WHO. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Vitamin and Mineral Nutrition Information System (WHO/NMH/NHD/MNM/11.1). Geneva: World Health Organization; 2011.
24. Schulman S, Kearon C. Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost. 2005;3(4):692–4.
25. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31–41.
26. Sanchez-Barba B, Navarrete-Reyes AP, Avila-Funes JA. Are geriatric syndromes associated with reluctance to initiate oral anticoagulation therapy in elderly adults with nonvalvular atrial fibrillation? J Am Geriatr Soc. 2013;61(12):2236–7.
27. Mant J, Hobbs FD, Fletcher K, Roalfe A, Fitzmaurice D, Lip GY, et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. Lancet. 2007;370(9586):493–503.
28. Ng KH, Shestakovska O, Connolly SJ, Eikelboom JW, Avezum A, Diaz R, et al. Efficacy and safety of apixaban compared with aspirin in the elderly: a subgroup analysis from the AVERROES trial. Age Ageing. 2016;45(1):77–83.

29. Lefebvre MC, St-Onge M, Glazer-Cavanagh M, Bell L, Kha Nguyen JN, Viet-Quoc Nguyen P, et al. The effect of bleeding risk and frailty status on anticoagulation patterns in octogenarians with atrial fibrillation: the FRAIL-AF study. Can J Cardiol. 2016;32(2):169–76.
30. Perera V, Bajorek BV, Matthews S, Hilmer SN. The impact of frailty on the utilisation of antithrombotic therapy in older patients with atrial fibrillation. Age Ageing. 2009;38(2):156–62.
31. Heckman GA, Braceland B. Integrating frailty assessment into cardiovascular decision making. Can J Cardiol. 2016;32(2):139–41.
32. Byrne M, Kaye DM, Power J. The synergism between atrial fibrillation and heart failure. J Card Fail. 2008;14(4):320–6.