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Stroke prevention and guideline adherent antithrombotic treatment in elderly patients with atrial fibrillation

A real-world experience

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Abstract

Patients aged ≥75 years with the diagnosis of atrial fibrillation (AF) are at a higher risk of stroke and, according to recent recommendations, should receive oral anticoagulant (OAC) therapy. This study aimed to assess the recommended prophylactic antithrombotic therapy among patients with AF aged ≥75 years and its compliance with current guidelines. We also aimed to identify predisposing factors associated with the administration of non-vitamin K antagonist oral anticoagulants (NOACs) in elderly patients with AF.

This was a retrospective, single-center observational study. Patients with AF aged ≥75 years hospitalized at a reference cardiology center from 2014 to 2017 were included in the analysis.

Among the 1236 eligible patients (43.4% male; mean age, 82 years), OACs were recommended in 90.1% of cases. Of these, 59.8% of patients used NOACs and 40.2% used vitamin K antagonists. Additionally, 3.3% of patients received antiplatelet (AP) therapy and 2.5% were administered low molecular weight heparin. Only 4.5% of patients did not receive any anticoagulant treatment. The majority (89.9%) of patients received relevant prophylactic antithrombotic therapy according to current guidelines; only 1.4% were overtreated and 8.7% were undertreated. The significant predictors of NOAC therapy among patients treated with anticoagulants were non-permanent AF (odds ratio [OR] = 1.68, 95% confidence interval [CI] = 1.30–2.18, $P = .0001$), age-by 5 years (OR = 1.33, 95% CI = 1.16–1.52, $P = .0001$), and glomerular filtration rate-by 5 units (OR = 1.06, 95% CI = 1.02–1.10, $P = .0066$).

A high percentage of AF patients aged ≥75 years receive OACs, mainly NOACs. Most patients are treated according to the current guidelines; under treatment is primarily observed in patients receiving AP therapy. Non-permanent AF, age, and preservation of renal function are significant predictors of NOAC use.

Abbreviations: ACS = acute coronary syndrome, AF = atrial fibrillation, ANAFIE = All Nippon AF in the Elderly, AP = antiplatelet, ATRIA = AnTicoagulation and Risk factors In AF, CI = confidence interval, GFR = glomerular filtration rate, HGB = hemoglobin, LMWH = low molecular weight heparin, MDRD = Modification of Diet in Renal Disease, NOACs = non-vitamin K antagonist oral anticoagulants, OAC = oral anticoagulant, OCTOFA = Atrial Fibrillation in Octogenarians, OR = odds ratio, ORBIT-AF = Outcomes Registry for Better Informed Treatment of Atrial Fibrillation, PCI = percutaneous coronary intervention, PLT = platelet count, PREFER = PREvention oF thromboembolic events-European Registry, RE-LY = Randomized Evaluation of Long-term anticoagulant therapY, ROCKET = Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial, SD = standard deviation, VKAs = vitamin K antagonists.

Keywords: adherence, antithrombotic therapy, atrial fibrillation, contraindications, observational

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1. Introduction

Atrial fibrillation (AF) is the most common supraventricular arrhythmia, whose prevalence significantly increases with age.[1–4] Data from the AnTicoagulation and Risk factors In AF (ATRIA) and Val-FAAP studies (for the characterization and evaluation of AF patients treated in primary care) have shown 9% and 17.6% of patients aged ≥80 years, respectively, have AF.[5,6] In addition, 37% of patients with AF in the Global Anticoagulant Registry in the FIELD-AF (GARFIELD-AF) study were 75 years old and older.[7] Furthermore, the PREvention oF thromboembolic events-European Registry (PREFER) showed a higher percentage of patients with AF (45%) who were aged ≥75 years.[8] Therefore, the elderly represent a major proportion of the patient population with AF worldwide.

Elderly AF patients are also at a higher risk of stroke and are therefore more likely to benefit from anticoagulation therapy than younger patients. For example, a subanalysis of a Fushimi AF Registry demonstrated patients with AF aged ≥85 years had a higher incidence of stroke compared with a younger population with AF, although the risk of major bleeding was similar.[9] Indeed, current guidelines for the management of AF have doubled the score of the age factor for patients aged ≥75 years in the CHA_2DS_2-VASc calculation for estimating AF stroke risk, and recommend initiating anticoagulant therapy for all patients aged ≥75 years, excluding those with contraindications to oral anticoagulants (OACs).[10] As further evidence, a subanalysis of the PREFER in AF study showed the absolute benefit of OAC therapy was higher in patients with AF aged ≥85 years than in those aged <85 years.[11] Unfortunately, despite the proven efficacy of OACs, numerous patients qualifying for treatment AF aged ≥75 years currently do not receive recommended prophylactic antithrombotic therapy.[8]

This study aimed to assess the prophylactic antithrombotic therapies recommended to AF patients aged ≥75 years and their compliance with the current guidelines.[10,12] We also determined the predisposing factors associated with the administration of non-vitamin K antagonist oral anticoagulants (NOACs) in elderly patients with AF.

2. Methods

2.1. Study design and participants

This was a retrospective, single-center, observational study. Patients with AF hospitalized at a reference cardiology center from 2014 until 2017 were included in this analysis. The following inclusion criteria were applied: diagnosis of AF at discharge from hospital and hospitalization not resulting in death. Patients with valvular AF (mechanical valve prosthesis or severe mitral stenosis) were excluded from the study.

The study was approved by the ethics committee of the regional Chamber of Physicians and meets all requirements of The Declaration of Helsinki. According to the ethics committee decision, signed informed consent was not required.

2.2. Data analysis

All clinical, laboratory, and echocardiographic data were retrospectively obtained from patients medical records. Thrombocytopenia was defined as a platelet count (PLT) below 150,000/μl based on results during hospitalization. Anemia was defined as a hemoglobin (HGB) level below 12 g/dl (in females) or below 13 g/dl (in males) based on results during hospitalization. The glomerular filtration rate (GFR) was calculated using the Modification of Diet in Renal Disease (MDRD) Study equation.[13]

2.3. Thromboembolic risk and guideline adherence in stroke prevention

We assessed thromboembolic risk among patients using the CHA_2DS_2-VASc score.[10] As all included patients were aged ≥75 years, the minimal CHA_2DS_2-VASc score was 2 points in males and 3 points in females. All patients in our study had a high thromboembolic risk based on their CHA_2DS_2-VASc scores. We also assessed patients $CHADS_2$ scores as a stratification tool.[10]

Anticoagulation treatment was evaluated at the time of discharge from the hospital. To assess guideline adherence in stroke prevention, we referred to the 2012 and 2016 ESC guidelines for AF management,[10,12] as patients were hospitalized from 2014 to 2017. We then categorized stroke prevention adherence in the included AF patients with high thromboembolic risk as follows:

- guideline adherent:
  - OAC therapy, or
  - no OAC therapy in patients with reported contraindications to anticoagulation therapy, or
  - combination therapy of OAC plus antiplatelet (AP) therapy in patients with acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI), or
  - low molecular weight heparin (LMWH) in patients with active cancer;
- undertreated:
  - no OAC therapy in patients without reported contraindications to OAC (but AP therapy or no therapy), or
  - no combination therapy (OAC plus AP therapy) in patients with ACS/PCI;
- overtreated:
  - OAC therapy in patients with reported contraindications to anticoagulation therapy, or
  - combination therapy (OAC plus AP therapy) in patients with no evidence of ACS/PCI.

Contraindications for OAC treatment were as follows:

- prior intracranial hemorrhage or diseases predisposing to intracranial hemorrhage,
- active gastrointestinal bleeding or diseases predisposing to gastrointestinal bleeding (such as active ulcer), or inflammation of the gastrointestinal tract,
- anemia defined as HGB level <8 mg/dl,
- thrombocytopenia defined as PLT < 50,000/μl,
- end-stage liver disease,
- allergy.

2.4. Statistical analysis

Continuous variables are presented as the mean and standard deviation (SD) and compared using the Student *t* test. Categorical data are summarized by their frequencies and percentages, and compared using the Chi-square test or Fisher exact test. Uni- and multivariate models for prescriptions of NOACs were created using logistic regression analysis, in which the odds ratios (OR) and 95% confidence intervals (CI) were calculated. Multivariate

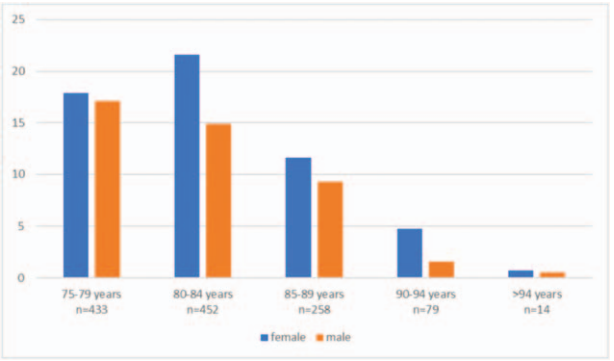

Figure 1. Percentages of males and females in the various age groups included in the study.

logistic regression models included variables that were statistically significant in univariate analysis and available in the majority of patients.

A two-tailed *P* value <.05 was considered statistically significant. All statistical analyses were performed using R (version 3.1.2; The R Foundation for Statistical Computing, Vienna, Austria) and Statistica (TIBCO Software Inc. (2017). Statistica (data analysis software system), version 13 (http://statistica.io).

3. Results

3.1. Characteristics of the study group

The study population comprised 1236 patients (43.4% male) aged ≥75 years with a diagnosis of non-valvular AF (mean age, 82 years). The reasons for hospital admission included: congestive heart failure (35%), implantation or reimplantation of a pacemaker or cardioverter-defibrillator (19.1%), ACS or planned coronary revascularization (12%), scheduled electrical cardioversion (4.2%), and others (29.6%). Most patients (36.7%) were aged 80 to 84 years (Fig. 1).

AF was classified as paroxysmal in 48.2% of patients, persistent in 7.1%, and permanent in 44.7%. The most frequent comorbidities in the patients were hypertension, heart failure, and coronary artery disease. The clinical characteristics of the study group are presented in Table 1.

3.2. Stroke prophylaxis in the study group

In the study group, 90.1% of patients were administered an OAC either as a monotherapy or in combination with AP therapy. AP therapy was used in 3.3% of patients and LMWH was used in 2.5%. A total of 4.5% of patients did not receive any prophylactic antithrombotic therapy.

In the group of patients receiving OACs, 59.8% used NOACs and 40.2% used vitamin K antagonists (VKAs). OAC in combination with an AP therapy was administrated to 9.8% of patients. Among those using combination therapy, 12.9% were treated with VKAs and 9.7% were treated with NOACs (*P*=.005). In patients treated with NOACs, 50% were treated with dabigatran, 36.5% with rivaroxaban, and 13.5% with apixaban. A reduced dose was used in 75.8% of patients treated with NOACs (Table 2).

Table 1

Clinical characteristics of the study group of patients aged ≥75 years with atrial fibrillation.

Variable	All patients N=1,236
Comorbidity, n (%)	
Hypertension	1002 (81.1)
Heart failure	903 (73.1)
Coronary artery disease	730 (59.1)
Previous myocardial infarction	342 (27.7)
Previous stroke	157 (12.7)
Previous transient ischemic attack	31 (2.5)
Previous peripheral embolism	27 (2.2)
Diabetes mellitus	385 (31.1)
Chronic obstructive pulmonary disease	97 (7.8)
Cancer	78 (6.3)
Thromboembolism and bleeding stratification, mean ± SD	
$CHADS_2$ score	3.2 ± 2.1
CHA_2DS_2-VASc score	5.3 ± 2.1
HAS-BLED score	2.5 ± 0.7
Laboratory and echocardiographic findings, mean ± SD	
GFR, ml/min/1.73m^2	51.8 ± 9.7
EF, %	46 ± 1.4
LA, mm	46.5 ± 7.2

EF = ejection fraction, GFR = glomerular filtration rate, LA = left atrial, SD = standard deviation.

3.3. Guideline adherence in stroke prevention

Contraindications to the use of OACs were found in 4% of patients, including active cancer (28.6%), anemia (26.5%), an extreme form of liver disease (20.4%), recent bleeding other than intracranial (24.5%), thrombocytopenia (8.2%), and intracranial hemorrhage (8.2%).

In total, 89.9% of individuals were given relevant prophylactic antithrombotic therapy according to current guidelines, while 1.4% of patients were overtreated and 8.7% were undertreated.

Table 2

Comparison of oral anticoagulants schemes in elderly patients with atrial fibrillation.

Variable	Apixaban (n=89)	Dabigatran (n=333)	Rivaroxaban (n=243)	*P* value (apixaban vs. dabigatran)	*P* value (apixaban vs. rivaroxaban)	*P* value (dabigatran vs. rivaroxaban)
Monotherapy, n (%)	74 (83)	316 (94.9)	224 (92.2)	**.0005**	**.0278**	.248
NOAC + ASA, n (%)	0 (0)	0 (0)	1 (0.4)	1	1	.422
NOAC + klopidogrel, n (%)	10 (11.2)	9 (2.7)	3 (1.2)	**.0019**	**.00017**	.356
NOAC + ASA + klopidogrel, n (%)	5 (5.6)	8 (2.4)	15 (6.2)	.159	1	**.0387**
Reduced dose, n (%)	72 (80.1)	269 (80.8)	164 (67.5)	1	**.024**	**.0004**

ASA = acetylsalicylic acid, NOAC = non-vitamin K antagonist oral anticoagulant.

Table 3

Compliance with current guidelines for the management of stroke prevention in elderly patients with atrial fibrillation.

	All patients (n = 1,236)	Patients treated with OAC + AP (n = 1,113)	Patients treated with AP (n = 41)	Patients treated with LMWH (n = 31)	Patients without prophylactic treatment (n = 51)
Guideline adherent, n (%)	1,111 (89.9)	1,081 (97.1)	0	16 (51.6)	14 (27.5)
Undertreated, n (%)	107 (8.7)	18 (1.6)	37 (90.2)	15 (48.4)	37 (72.5)
Overtreated, n (%)	18 (1.4)	14 (1.3)	4 (9.8)	0	0

AP = antiplatelet, LMWH = low molecular weight heparin, OAC = oral anticoagulant.

The highest percentage of patients treated in accordance with the guidelines was found among those receiving OACs. The compliance of prophylactic antithrombotic therapy among patients with AF with respect to the current guidelines is shown in Table 3.

3.4. Comparison of patients treated with VKAs and NOACs

Patients treated with NOACs were older and more often had the non-paroxysmal type of AF than those treated with VKAs. Meanwhile, patients treated with VKAs were more likely to have heart failure, coronary artery disease, and thrombocytopenia than those treated with NOACs. Additionally, individuals with lower left ventricular ejection fraction and increased left atrial size in echocardiography were more likely to receive VKAs than NOACs.

Patients treated with VKAs had similar $CHADS_2$ and CHA_2DS_2-VASc scores to those treated with NOACs; however, those treated with VKAs had a higher risk of bleeding complications based on their HAS-BLED scores. Table 4 shows the comparison of patients treated with NOACs and VKAs.

3.5. Factors predisposing to NOACs treatment

The univariate logistic regression analysis of predictors of NOAC use in patients with AF aged ≥75 years treated with OACs is presented in Table 5. Neither the $CHADS_2$ score nor the CHA_2DS_2-VASc score were predictors of the use of NOACs. Multivariate analysis showed non-permanent AF, age, and GFR were independent predictors of NOAC use in patients treated with OACs (Fig. 2). However, other factors may potentially reduce the chance of using NOACs, such as the presence of coronary heart disease, thrombocytopenia, and combining AP therapy with OACs (Table 5).

4. Discussion

Overall, 90% of individuals diagnosed with non-valvular AF aged 75 years or older were treated with OACs, primarily NOACs. Dabigatran was the most commonly used NOACs, although rivaroxaban was more frequently used at a full dose compared to the other NOACs. We found a high percentage of elderly patients with AF receiving NOACs were properly treated according to current guidelines. We also found the risk of thromboembolic events and bleeding (as assessed by available scales) were not predictive of the use of NOACs in AF patients aged 75 years or older.

Our findings that 90% of elderly AF patients were treated with OACs are similar to the All Nippon AF in the Elderly (ANAFIE) Registry, in which 92% of the 32,726 patients aged ≥75 years included in the study received OACs.[14] Similarly, the OCTOFA (Atrial Fibrillation in Octogenarians) study found that 92% of 738 patients aged ≥80 years received OACs.[15] Despite this, several studies indicate OACs may be underused in elderly patients with AF. For example, in a study of 1170 patients aged ≥80 years, OACs were only used in 63% of patients,[16] and a recent study including Fushimi AF Registry data found only half of the patients aged 73.7 ± 10.9 years were on anticoagulant therapy.[9] Likewise, only 41.1% of elderly patients aged ≥65 years were treated with OACs (41.10%) in a retrospective study conducted in China.[17] Therefore, OAC use does appear to vary according to age and geographical location.

NOACs were recently found to be as effective as VKAs in preventing thromboembolic complications in patients with AF, yet they rarely cause hemorrhagic complications.[18] As such, the percentage of patients on anticoagulant therapy who were treated with NOACs increased from 34% to 62% over the 3 years of the GARFIELD-AF study.[7] While the efficacy and safety of NOAC use in the elderly has not yet been studied in detail, a subanalysis of the ROCKET (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial) in AF showed elderly patients had higher rates of stroke and major bleeding events than younger patients.[19] Despite this, the study showed the efficacy and safety of rivaroxaban relative to warfarin did not differ with age, supporting rivaroxaban as an alternative for the elderly.[19] In addition, a subanalysis of the Randomized Evaluation of Long-term anticoagulant therapY (RE-LY) trial showed dabigatran had lower risks of intracranial and extracranial bleeding than warfarin in AF patients aged <75 years; however, in those aged ≥75 years, the risk of extracranial bleeding was similar or higher when treated with dabigatran.[20] Therefore, long-term NOAC use in the elderly may be preferential to treatment with VKAs.

In the ANAFIE Registry, 72% of elderly AF patients receiving anticoagulant treatment were treated with NOACs.[14] Meanwhile, we found NOACs were used in only 60% of elderly AF patients receiving anticoagulant treatment. We also found that most patients in our study group were treated with a reduced dose of NOAC, except for rivaroxaban, which was commonly used at its full dose. This reduction in NOAC dose is likely due to limitations of renal function that occurs with increasing age.

We also assessed compliance with the current guidelines for the use of anticoagulation prophylactic therapy in elderly AF patients. The guidelines recommend that all patients with AF aged ≥75 years should use OAC therapy, except for those with certain contraindications.[10,12] Older adults with AF rarely have absolute contraindications to OAC therapy, and indeed, only 4% of patients in our study had such contraindications (primarily, active cancer and anemia). However, reported OAC contra-

Table 4

Comparison of the clinical characteristics of patients with atrial fibrillation aged ≥75 years treated with either a vitamin K antagonist (VKA) or a non-vitamin K antagonist oral anticoagulant (NOAC).

Variable	OAC group (n = 1,113)	VKA group (n = 448)	NOAC group (n = 665)	*P* value
Age, years				
Mean ± SD	81.8 ± 4.8	81.3 ± 4.3	82.2 ± 5.1	**.018**
Median (Q1–Q3)	82 (78–85)	81 (78–84)	82 (78–86)	
Min–Max	75–98	75–98	75–98	
Age, years, n (%)				
Age 75–79	402 (36.1)	165 (36.9)	237 (35.6)	**.0005**
Age 80–84	404 (36.3)	181 (40.4)	223 (33.5)	
Age 85–89	228 (20.5)	87 (19.4)	141 (21.2)	
Age 90–94	67 (6.0)	13 (2.9)	54 (8.1)	
Age ≥95	12 (1.1)	2 (0.4)	10 (1.6)	
Female, n (%)	628 (56.4)	241 (53.9)	387 (58.1)	.164
Form of atrial fibrillation, n (%)				
Paroxysmal	473 (42.5)	159 (35.5)	314 (47.2)	**.0002**
Persistent	80 (7.2)	30 (6.7)	50 (7.5)	
Permanent	560 (50.3)	259 (57.8)	301 (45.3)	
Non-permanent	553 (49.7)	189 (41.2)	364 (54.7)	**<.001**
Medical history, n (%)				
Hypertension	910 (81.8)	376 (83.9)	534 (80.3)	.106
Heart failure	800 (71.9)	340 (75.9)	460 (69.2)	**.012**
Diabetes mellitus	344 (30.9)	141 (31.5)	203 (30.5)	.788
Previous stroke	143 (12.8)	56 (12.5)	87 (13.1)	.847
Previous transient ischemic attack	29 (2.6)	12 (2.7)	17 (2.6)	1.00
Previous peripheral embolism	26 (2.3)	7 (1.6)	19 (2.9)	.230
Previous any embolism	195 (17.5)	74 (16.5)	121 (18.2)	.521
Coronary artery disease	361 (32.4)	168 (37.5)	193 (29)	**.004**
Myocardial infarction	294 (26.4)	125 (27.9)	169 (25.4)	.321
Percutaneous coronary intervention	185 (16.6)	88 (19.6)	97 (14.6)	**.032**
Coronary artery bypass grafting	71 (6.4)	31 (6.9)	40 (6)	.631
Chronic obstructive pulmonary disease	90 (8.1)	43 (9.6)	47 (7.1)	.160
Hyperthyroidism	70 (6.3)	31 (6.9)	39 (5.9)	.559
Hypothyroidism	123 (11.1)	55 (12.3)	68 (10.2)	.331
Thrombocytopenia	215 (19.3)	111 (24.8)	104 (15.6)	**.0002**
Anemia	394 (35.4)	161 (35.9)	233 (35)	.807
Active cancer	61 (5.5)	22 (4.9)	39 (5.9)	.581
Thromboembolism and bleeding risk				
$CHADS_2$ score				
Mean ± SD	3.2 ± 1.1	3.2 ± 1.1	3.2 ± 1.1	.15
Median (Q1–Q3)	3 (2–4)	3 (3–4)	3 (2–4)	
Min–Max	1–6	1–6	1–6	
$CHADS_2$ = 1 point, n (%)	31 (2.8)	8 (1.8)	23 (3.5)	.134
$CHADS_2$ = 2 points, n (%)	261 (23.5)	98 (21.9)	163 (24.5)	
$CHADS_2$ ≥3 points, n (%)	821 (73.7)	342 (76.3)	479 (72)	
CHA_2DS_2-VASc score				
Mean ± SD	5.3 ± 1.4	5.3 ± 1.4	5.3 ± 1.4	.862
Median (Q1–Q3)	5 (4–6)	5 (4–6)	5 (4–6)	
Min–Max	2–9	2–9	2–9	
CHA_2DS_2VASc = 2 points, n (%)	10 (0.9)	2 (0.4)	8 (1.2)	.748
CHA_2DS_2VASc ≥ 3 points, n (%)	1003 (91.1)	446 (99.6)	657 (98.8)	
HAS-BLED score				
Mean ± SD	2.7 ± 0.8	2.8 ± 0.8	2.7 ± 0.8	**.021**
Median (Q1–Q3)	3 (2–3)	3 (2–3)	3 (2–3)	
Min–Max	1–6	1–5	1–6	
HAS-BLED ≥3, n (%)	674 (60.6)	282 (62.9)	392 (58.9)	.202
Echocardiography parameters				
EF, %	n = 904	n = 354	n = 550	**.037**
Mean ± SD	48.3 ± 12.3	47.3 ± 12.7	49 ± 12	
Median (Q1–Q3)	50 (40–58)	50 (40–55)	50 (42–60)	
Min–Max	10–75	15–75	10–72	
EF, n (%)				
EF >50%	394 (43.6)	137 (38.7)	257 (46.7)	**.013**
EF 50–30%	430 (47.6)	176 (49.7)	254 (46.2)	

(*continued*)

Table 4

(continued).

Variable	OAC group (n = 1,113)	VKA group (n = 448)	NOAC group (n = 665)	*P* value
EF <30%	80 (8.8)	41 (11.6)	39 (7.1)	
LA, mm	n = 894	n = 353	n = 541	**<.0001**
Mean ± SD	46.6 ± 7.3	47.9 ± 7.3	45.8 ± 7.1	
Median (Q1–Q3)	46 (42–51)	47 (43–52)	45 (4–50)	
Min–Max	23–77	27–77	23–77	
LA > 40 mm, n (%)	728 (81.4)	308 (87.3)	420 (77.6)	**.0004**
Laboratory tests				
HGB, g/dl				
Mean ± SD	12.9 ± 1.6	12.8 ± 1.6	12.9 ± 1.6	.870
Median (Q1–Q3)	12.9 (11.8–13.9)	12.9 (12.0–13.9)	12.9 (11.8–14.0)	
Min–Max	3.8–17.5	3.8–16.6	8.0–17.5	
PLT, $10^3/\mu l$				
Mean ± SD	199.6 ± 69.6	189.3 ± 65.2	206.5 ± 71.6	**<.0001**
Median (Q1–Q3)	187 (159–227)	178 (150–217)	195 (164–233)	
Min–Max	66–793	69–793	66–742	
GFR, ml/min				
Mean ± SD	52.8 ± 15.3	51.5 ± 15.4	53.6 ± 15.3	.053
Median (Q1–Q3)	52.5 (42.5–62.5)	51.5 (41.5–61.7)	53.1 (43.0–63.2)	
Min–Max	10.08–107.84	10.08–99.98	12.86–107.84	
GFR, n (%)				
GFR ≥60 ml/min	370 (30.1)	142 (28.3)	228 (34.3)	.069
GFR 59–46 ml/min	364 (35.8)	141 (34.6)	223 (33.5)	
GFR 45–30 ml/min	308 (27.7)	125 (28.1)	183 (27.5)	
GFR 29–15 ml/min	66 (5.9)	37 (8.3)	29 (4.4)	
GFR <15 ml/min	5 (0.5)	3 (0.7)	2 (0.3)	

EF = ejection fraction, GFR = glomerular filtration rate, HGB = hemoglobin, LA = left atrial, PLT = platelet count, SD = standard deviation.

indications rates do vary, ranging from less than 20% to more than 50%,[21–23] which may be due to the subjective identification of contraindications to OAC therapy and significant local practice variation. For example, Steinberg et al[24] reported only 2% of 86,671 elderly patients with AF were ineligible for OAC therapy because of an absolute contraindication (most frequently, a history of intracranial hemorrhage), whereas 13% of the 10,130 patients enrolled in the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) had contraindications to OACs.[25] In addition, a previous study showed AF patients aged ≥75 years are more likely to have prior bleed, frequent falls/frailty, and high bleeding risk reported as reasons for non-treatment compared with younger patients, who are more likely to list contraindications related to patient refusal.[25] Paroxysmal AF is not a contraindication to OAC application due to the lack of univocal proof of AF being connected with thromboembolic risk. On the other hand, recurrence of arrhythmia, sometimes the asymptomatic one, in elderly people is more frequent than in younger people due to advanced, multilevelled remodeling of the left atrium.[26–28]

Table 5

Univariate analysis of the predictors of non-vitamin K antagonist anticoagulant prescription in elderly patients with atrial fibrillation.

Factor	Univariate analysis		
	OR	95% CI	*P* value
AF non-permanent	1.66	1.3–2.11	<.0001
Age (by 5 years)	1.21	1.06–1.37	.0036
GFR (by 5 units)	1.05	1.01–1.09	.0253
Heart failure	0.7	0.53–0.92	.01
Coronary artery disease	0.68	0.53–0.88	.0031
Thrombocytopenia	0.56	0.42–0.76	.0002
Combination therapy with antiplatelet drugs	0.56	0.38–0.83	.004

AF = atrial fibrillation, CI = confidence intervals, GFR = glomerular filtration rate, OR = odds ratio.

The majority (89.9%) of individuals in our study received proper anticoagulant prophylactic therapy according to the current guidelines. The lowest rates of compliance with management according to the guidelines was observed in patients not receiving any antithrombotic prophylactic therapy. Indeed, almost 75% of elderly AF patients who were not receiving anticoagulant prophylactic therapy were classified as undertreated. Meanwhile, 1.4% of elderly AF patients in this study were overtreated, primarily those who were receiving AP therapy alone or in combination with an OAC. The anticoagulant prophylactic therapy in elderly patients with AF is especially difficult when the contraindications for anticoagulant treatment are associated with a high thromboembolic risk, and consequently, patients receive AP therapy for thromboembolic prevention.

Averlant et al[29] reported the underuse of OAC is associated with the prescription of AP therapy in elderly patients with AF, regardless of the presence or absence of known atheromatous disease. Indeed, our findings also suggest AP therapy is often inappropriately prescribed instead of OAC. Furthermore, it was previously shown that 30.3% of patients with reported contraindications enrolled in ORBIT-AF still received warfarin or dabigatran,[25] suggesting the perceived benefit of OACs outweighs the potential harm posed by the relative contraindication. However, we found some patients with AF and a high risk of thromboembolic complications did not receive anticoagulation prophylactic therapy, despite the absence of contraindications. It

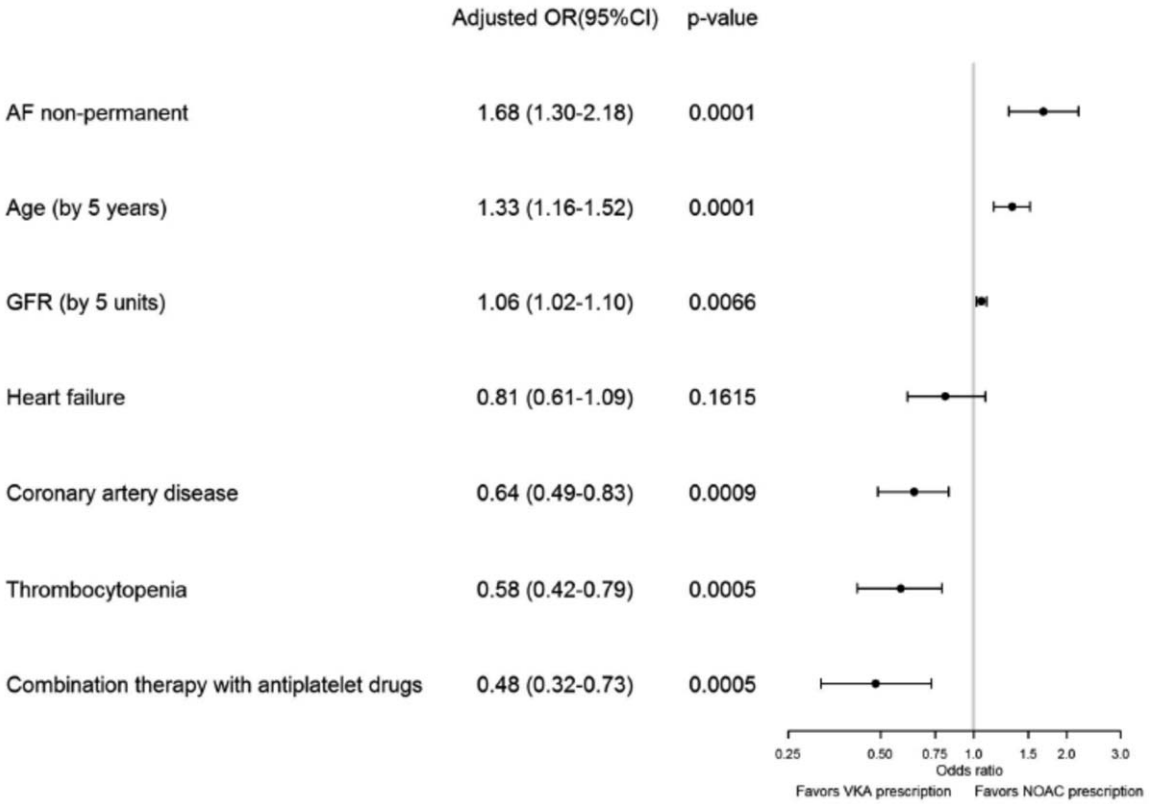

Figure 2. Adjusted odds ratios (ORs) for non-vitamin K antagonist oral anticoagulant (NOAC) prescriptions among OAC recipients.

is possible that a clear definition of the contraindications for OAC therapy (incorporating factors such as frailty syndrome, dementia, and the use of NOACs) would facilitate the decision to use or withdraw from OAC therapy in patients with AF.[29,30]

Next, we examined whether there are any predictors of NOAC use among elderly patients receiving oral anticoagulants. The indications and eligibility of patients for NOACs and VKAs are well codified by prescribing information, clinical guidelines, expert opinion, and a wealth of published data.[31–34] However, it remains difficult to implement some of these recommendations regarding the choice between NOACs and VKAs in clinical practice.

In the present study, the predisposing factors for the use of NOACs among elderly AF patients were non-permanent AF, age, and estimated GFR, while the predisposing factors for VKAs use were thrombocytopenia, coronary artery disease, and the necessity of combining AP therapy with OAC. In the GARFIELD-AF study, NOAC recommendation seemed to be favored in lower-risk groups (including patients with paroxysmal AF, normotensive patients, and those with moderate alcohol consumption), but was also commonly used in elderly patients and those with ACS.[35] Meanwhile, VKAs were preferentially used in patients with permanent AF, moderate to severe kidney disease, heart failure, vascular disease, and diabetes, as well as with concomitant AP therapy.[35] At present, guidelines for the management of AF recommend NOAC therapy for patients who are beginning anticoagulant treatment,[10] which likely explains the increased percentage of patients with non-permanent AF who were treated with NOACs. Age may be a predisposing factor for NOAC use, as there are fewer potential drug interactions with NOACs than VKAs in elderly patients. The risk of thromboembolic complications assessed by the CHA_2DS_2-VASc scale was not a predisposing factor for the use of NOACs, in contrast to previous studies using the national Danish registry[36] and the GARFIELD-AF registry.[35] There are some reports confirming that short, asymptomatic attacks of AF in patients with diabetes significantly increase the risk of ischemic stroke in spite of the low risk in CHA_2DS_2-VASc score.[36–38] VKAs are the treatment of choice in cases of severe renal failure,[39] and we found a higher GFR was a predictor of NOAC use. Notably, in patients with coronary artery disease requiring combined OAC plus AP therapy, VKAs were more commonly used. It is worth mentioning, however, that our analysis was based on patients hospitalized from 2014 to 2017, and was created prior to the publication of studies that confirmed the efficacy of NOACs in patients with ACS requiring combined OAC plus AP therapy.[40–42]

This study has its limitations. First, it is limited by the observational nature of the data collected and the lack of follow-up data. For that reason, the effect of anticoagulation on outcomes could not be evaluated. In addition, comorbidities and the incidence of fragility syndrome and dementia, which are relevant factors limiting the use of OACs, have not been assessed. Finally, the impact of drug costs and levels of reimbursement could not be quantified accurately; however, this is likely to be the main driver limiting the access to NOACs for a broad cross-section of eligible patients.

In conclusion, this study representing the real-world clinical status of AF anticoagulant treatment among elderly patients showed a high percentage of patients were receiving OACs.

Patients treated with OACs mostly received NOACs, mainly at reduced doses. We found AP therapy is often incorrectly prescribed instead of OAC. We also showed the risk of thromboembolic events and the risk of bleeding assessed by available scales were not predictors of the use of NOACs in elderly patients with AF. Our results indicate that non-permanent AF, age, and preservation of renal function predispose elderly patients with AF to NOAC use.

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