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Choice of new oral anticoagulant agents versus vitamin K antagonists in atrial fibrillation: FANTASIIA study

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Abstract

Introduction: Atrial fibrillation (AF) is associated with an increased risk of thromboembolic events. Many patients with AF receive chronic anticoagulation, either with vitamin K antagonists (VKAs) or with non-VKA oral anticoagulants (NOACs). We sought to analyze variables associated with prescription of NOAC.

Methods: Patients with AF under anticoagulation treatment were prospectively recruited in this observational registry. The sample comprised 1290 patients under chronic anticoagulation for AF, 994 received VKA (77.1%) and 296 NOAC (22.9%). Univariate and multivariate analyses were performed to identify variables associated with use of NOAC.

Results: Mean age was 73.8 ± 9.4 years, and 42.5% of the patients were women. The CHA_2DS_2-VASc score was 0 in 4.9% of the population, 1 in 24.1%, and ≥2 in 71% (median = 4, interquartile range = 2). Variables associated with NOAC treatment were major bleeding (odds ratio [OR] = 3.36; confidence interval [CI] 95%: 1.73-6.51; $P < .001$), hemorrhagic stroke (OR = 3.19; CI 95% 1.00-10.15, $P = .049$), university education (OR = 2.44; CI 95%: 1.55-3.84; $P < .001$), high diastolic blood pressure (OR = 1.02; CI 95%: 1.00-1.03; $P = .006$), and higher glomerular filtration rate (OR 1.01, CI 95% 1.00-1.01; $P = .01$). And variables associated with VKA use were history of cancer (OR = 0.46; CI 95%: 0.25-0.85; $P = .013$) and bradyarrhythmia (OR = 0.40; CI 95% 0.19-0.85; $P = .020$).

Conclusion: Medical and social variables were associated with prescription of NOAC. Major bleeding, hemorrhagic stroke, university education, and higher glomerular filtration rate were more frequent among patients under NOAC. On the contrary, patients with history of cancer or bradyarrhythmias more frequently received VKA.

Key words

Atrial fibrillation; Anticoagulant treatment; Vitamin K antagonists; Nonvitamin K antagonist oral anticoagulants

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and the main indication for chronic oral anticoagulation worldwide.[1] Atrial fibrillation is associated with an increased risk of thromboembolic events.[2] Vitamin K antagonists (VKAs) have been the mainstay of oral anticoagulation for decades, but they have many limitations including narrow therapeutic window, variability in dose response, slow onset and offset of action, and drug and food interactions. Recently, 3 oral anticoagulants have proven to be equal or superior to VKA in the prevention of thromboembolic events in patients with AF: dabigatran, rivaroxaban, and apixaban (NOAC, standing initially for new oral anticoagulants and now for non-VKA oral anticoagulants).[3⇓⇓–6] Current guidelines recommend preferential use of NOAC in patients with nonvalvular AF and risk of thromboembolic events.[7] Nevertheless, the use of NOAC has been limited due to both economical and medical reasons. We sought to assess variables associated with NOAC versus VKA prescription in the prevention of thromboembolism in AF.

Methods

Patients

Fibrilación Auricular: influencia del Nivel y Tipo de Anticoagulación Sobre la Incidencia de Ictus y Accidentes hemorrágicos (FANTASIIA) is a multicenter observational study. Cardiologists, general practitioners, and internists participated in the study recruiting 20 consecutive patients with nonvalvular AF receiving uninterrupted anticoagulant treatment for prevention of stroke for more than 6 months. By design, 16 patients had to receive VKA and 4 NOACs. Patients were excluded if they were younger than 18 years old, had history of heart valve disorder (including prosthesis or moderate/severe valve disease), were hospitalized at the moment, or were participating in a clinical trial. Patients unwilling or unable to provide written informed consent were also excluded. The study was conducted in Spain. The research protocol complied with the Declaration of Helsinki and was approved by the local ethics committee.

Data Collection

Demographic data were collected, including labor situation (employed, unemployed, retired, disability, and housework), level of education (cannot read or write, primary school, high school, vocational training, and college), cardiovascular risk factor, such as high blood pressure, hypercholesterolemia, diabetes mellitus, smoking habit, and other comorbidities: chronic obstructive pulmonary disease, chronic kidney disease (glomerular filtration rate <60 mL/min), dialysis, liver dysfunction (persistent elevation of transaminases 3 times above the upper limit of normality), cancer, peripheral artery disease, ictus (ischemic, hemorrhagic, or transient attack), thyroid dysfunction, and alcohol consumption. Major bleeding was defined as hemorrhage in a critical anatomical site (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, intramuscular with compartment syndrome, or pericardial), bleeding that led to a drop ≥2 g/dL in hemoglobin level or bleeding that required transfusion. Cardiac disease such as heart failure, coronary artery disease and other cardiomyopathies, previous tachycardia or bradyarrhythmias, ablation, and pacemaker or implantable cardioverter defibrillator, were also collected. Data related to AF, including year of diagnosis, symptoms, type of AF, and medical treatment were collected. Stroke and hemorrhagic risks were calculated by means of the C = Congestive heart failure, H = Hypertension, A = Age ≥ 75 years, D = Diabetes mellitus, S = stroke or transient ischemic attack, V = Vascular disease, A = Age 65-74 years Sc = Sex category (CHA_2DS_2-VASc)[8] and H = Hypertension, A = Abnormal renal/liver function, S = Stroke, B = Bleeding history or predisposition, L = Labile INR, E = Elderly >65 y D = Drugs/alcohol (HAS-BLED)[9] scores. An electrocardiogram was performed and blood pressure and heart rate were measured after 5 minutes of rest. Weight and height were measured. Laboratory analyses were performed by the laboratory of reference of each patient. Medical treatment data were also collected, including type and dose of oral anticoagulation, antiarrhythmic drugs, and other cardiovascular medication. In patients treated with VKA, the 6 months previous INR controls were collected. A total of 1290 patients were recruited, of those 994 received VKA (77.1%) and 296 NOAC (22.9%).

Statistical Analyses

All continuous variables showed normal distribution and are presented as mean (standard deviation) and compared by Student *t* test. Discrete variables are presented as values (percentages) and compared between patients under VKA or NOAC treatment by chi-square test or Fisher exact test, as appropriate. Logistic regression analyses were employed for multivariate adjustment. Multivariate models were performed including variables with recognized clinical relevance with VKA control and those with a *P* value <.1 in the univariate analysis. Logistic regression was performed by a backward conditional test. Results are presented as odds ratio (OR) and 95% confidence interval (CI). A 2-sided *P* value of <.05 was considered to be significant for all analyses. All statistical analyses were performed using SPSS 13.0.

Results

Mean age of the study population was 73.8 (9.4) years, and 42% of the patients were women, 81% had history of hypertension, 54% dyslipidemia, and 29% diabetes. Only 5% were active smokers. Cardiac disease was present in 48%: 376 (28%) patients had history of heart failure, more than half of them with preserved ejection fraction, and 18% previous coronary artery disease. In all, 16% had history of

cerebrovascular disease, 17% of obstructive chronic pulmonary disease, and 19% chronic kidney disease. Median (interquartile range) C = Congestive heart failure, H = Hypertension, A = Age ≥ 75 years, D = Diabetes mellitus, S = stroke or transient ischemic attack ($CHADS_2$), CHA_2DS_2-VASc, and HAS-BLED were 2 (2), 4 (2), and 2 (2), respectively, and mean (standard deviation) were 2.22 (0.6), 3.64 (0.9), and 1.93 (0.5), respectively. Of the 1318 patients included, 994 (77%) were under VKA treatment, while 296 (23%) were under NOAC. In all, 169 (57%) patients were treated with dabigatran, 113 (38%) with rivaroxaban, and 14 (5%) with apixaban. Most patients were followed by a cardiologist. Patients under VKA treatment were followed by an internist in 7.4% and by primary care in 5.6% and patients treated with NOAC in 6.4% and 5.4%, respectively (no differences were observed). However, 93.86% of patients treated with VKA and 97.64% with NOAC have been studied by a cardiologist (P = .01). Table 1 shows baseline characteristics of the study population stratified by the anticoagulant treatment.

Table 1. Baseline Characteristics of the Population: Univariate Analysis.[a]

Variable	VKA (n = 994)	NOAC (n = 296)	*P* Value
Age, years	74 (9.4)	72.7 (9.2)	.03
Gender (women), %	42	44	.56
University studies, %	6	12	<.001
Physical examination and laboratory analyses			
SBP, mm Hg	132.6 (19.0)	132.5 (18.6)	.93
DBP, mm Hg	75.7 (11.5)	78.0 (11.6)	.002
Heart rate, bpm	72.6 (15.0)	72.4 (15.0)	.89
Weight, kg	78.3 (14.3)	78.9 (14.1)	.55
Height, cm	164.0 (8.9)	165.2 (9.3)	.05
Body mass index, kg/m^2	29.0 (4.9)	28.8 (4.3)	.56
Serum creatinine, mg/dL	1.1 (0.5)	0.98 (0.2)	.02
Glomerular filtration rate, mL/min	65.8 (23.2)	71.5 (22.6)	<.001
Cardiovascular risk factors			
Arterial hypertension, %	80	82	.53
Hyperlipidemia, %	55	50	.13
Diabetes mellitus, %	31	25	.06
Smoking habit, %	61	61	.42
Active smoker	4	4	
Recent former smoker (<1 year)	2	3	
Distant former smoker (>1 year)	31	29	
Comorbidities			
COPD, %	17	17	.93
Kidney disease, %	21	12	<.001
Liver disease, %	1	0.3	.19
Cancer, %	9	4	.01
Peripheral artery disease, %	7	6	.87
Cerebrovascular disease, %	85	80	.06
Ischemic	9	11	
Transient ischemic	4	5	
Hemorrhagic	0.7	2	
Systemic embolism, %	2	3	.26
Major bleeding, %	2	6	<.001
Cardiological history			
Cardiac disease, %	50	40	.004
Heart failure, %	69	78	.01
Preserved ejection fraction (≥45%)	16	12	
Reduced ejection fraction (<45%)	14	9	
Coronary artery disease, %	20	14	.03
Acute coronary syndrome, %	84	89	.05
Non-ST-segment elevation ACS	8	6	
ST-segment elevation ACS	7	4	
Left ventricular hypertrophy, %	17	13	.20
Bradyarrhythmia, %	7	2	.002
Type of AF (vs paroxysmal), %	27	30	.01
Persistent	17	18	
Long-term persistent	3	7	
Permanent	51	43	
Concomitant antiplatelet treatment			
Overall, %	11	8	.40
Aspirin, %	7	7	
P2Y12 inhibitors, %	2	1	
Dual antiplatelet treatment, %	1	0	
Anticoagulant treatment			
TTR Rosendaal	60.3 (24.5)		
TTR <65%, %	54		

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; COPD, chronic obstructive pulmonary disease; ACS, acute coronary syndrome; AF, atrial fibrillation; NOCA, non-VKA oral anticoagulant; VKA, vitamin K antagonist; TTR, therapeutic time in range.

[a]Categorical data presented as percentage. Continuous variable presented as mean (standard deviation). Kidney disease was defined as glomerular filtration rate <60 mL/min. Liver disease was defined as persistent elevation of transaminases three times above the upper limit of normality. Major bleeding was defined as hemorrhage in a critical anatomical site (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, intramuscular with compartment syndrome, or pericardial), bleeding that led to a drop ≥2 g/dL in hemoglobin level or bleeding that required transfusion. Cardiac disease was considered if any of the followings: heart failure, coronary artery disease and other cardiomyopathies, previous tachycardia or bradyarrhythmias, ablation and pacemaker, or implantable cardioverter defibrillator.

Univariate Analysis

Patients under VKA were older and had higher rates of kidney disease, heart failure, coronary artery disease, bradyarrhythmias, and cancer, compared to patients under NOAC treatment. Patients under NOAC had higher diastolic blood pressure and glomerular filtration rate, higher frequency of university degree, hemorrhagic stroke, and major bleeding.

Mean and median $CHADS_2$ score was 2.31 (0.6) and 2 (2) in patients treated with VKA and 2.19 (0.6) and 2 (2) in patients with NOAC (P = .92), but distribution among categories varied significantly. Patients at low risk ($CHADS_2$ = 0-1) were more prone to be treated with NOAC (33.45% were treated with NOAC vs 22.86% treated with VKA) while patients at intermediate or high risk ($CHADS_2 \geq 2$) were treated more frequently with VKA (77.14% vs 66.55% treated with NOAC; P < .001, comparing treatments in patients with $CHADS_2$ score <2 vs $CHADS_2 \geq 2$; Figure 1).

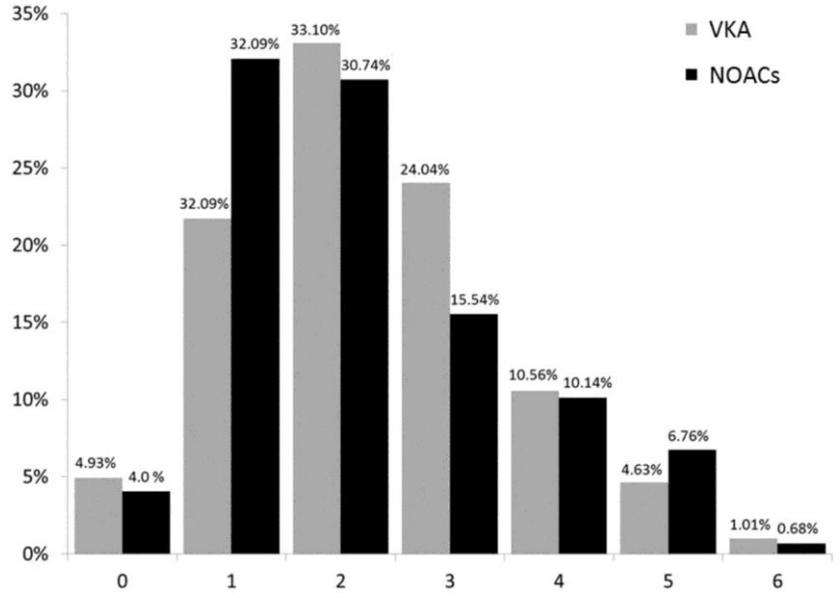

Figure 1. Patients with $CHADS_2$ score <2 were treated more frequently with non-VKA oral anticoagulant (NOAC; 33.4% vs 22.9%) and patients with $CHADS_2$ score ≥2 were treated more frequently with vitamin K antagonist (VKA; 77.1% vs 66.6%; chi-square = 12.97; P < .001, $CHADS_2$ <2 vs $CHADS_2$ ≥2).

Mean and median CHA_2DS_2-VASc score was 3.78 (0.9) and 4 (2) in patients under VKA and 3.6 (0.9) and 4 (2) in patients under NOAC (P = .104). CHA_2DS_2-VASc score was 0 in 1.35% of patients under NOAC and in 1.21% of patients under VKA, was 1 in 6.08% versus 6.24%. A significant higher use of NOAC was found in patients with lower CHA_2DS_2-VASc score. In all, 28.38% of patients treated with NOAC had CHA_2DS_2-VASc score of 0, 1, or 2, and this proportion was 20.30% in patients treated with VKA (P = .003; Figure 2).

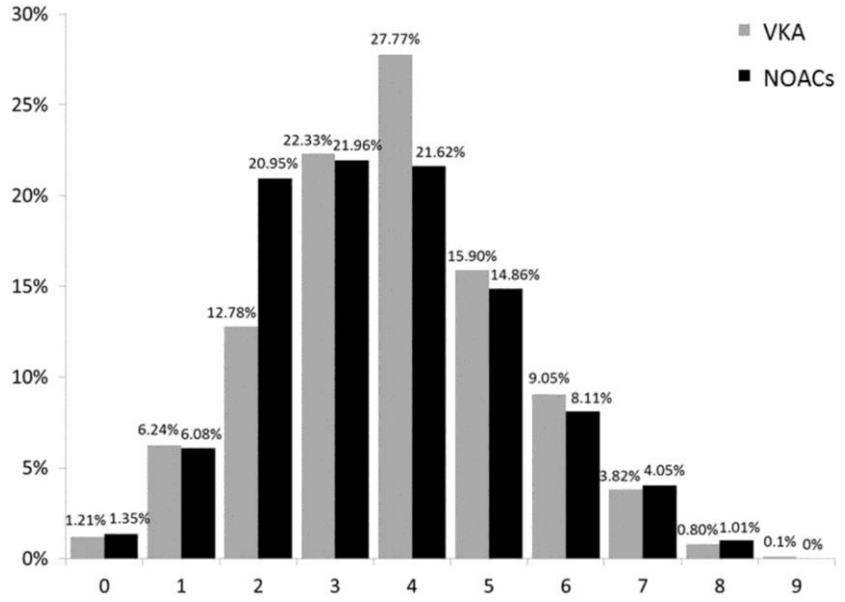

Figure 2. Patients with CHA_2DS_2-VASc score <3 were treated more frequently with NOAC and patients with CHA_2DS_2-VASc score ≥3 were treated more frequently with VKA. Chi-square = 8.82; *P* = .001 when comparing CHA_2DS_2-VASc <3 (28.4% patients were treated with NOAC and 20.3% treated with VKA) and CHA_2DS_2-VASc ≥3 (71.6% and 79.7%, respectively). NOCA, non-VKA oral anticoagulant; VKA, vitamin K antagonist.

Figure 3 shows HAS-BLED score for both anticoagulant treatment strategies. Mean and median HAS-BLED score was 1.92 (0.5) and 2 (2) in patients under NOAC and 1.98 (0.6) and 2 (2) in patients under VKA. Distribution of HAS-BLED score was similar between groups.

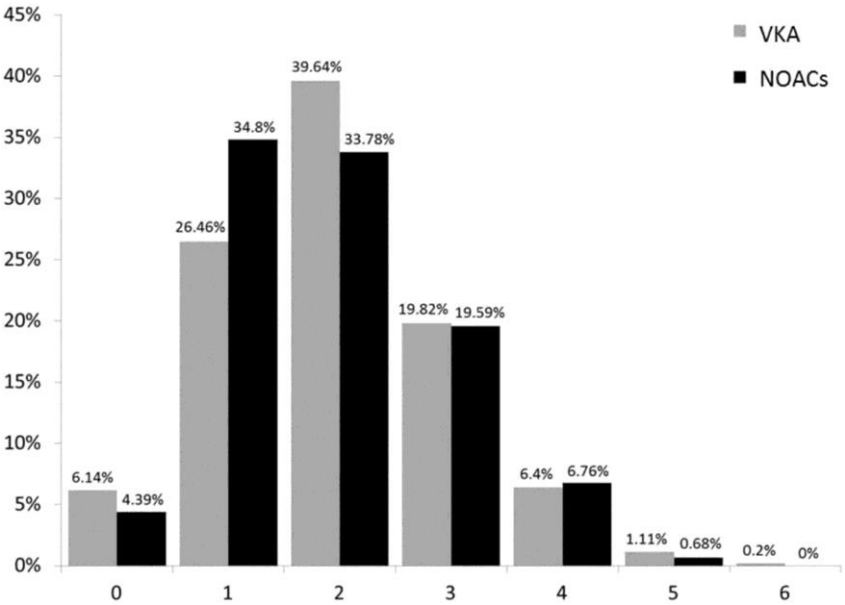

Figure 3. No differences were observed between both the groups.

Multivariate Analysis

The multivariate analysis (Table 2) showed the following variables associated with NOAC prescription: major bleeding (OR = 3.24; CI 95%: 1.68-6.25; $P < .001$), hemorrhagic stroke (OR = 3.19; CI 1.00-10.15; $P = .049$), university degree (OR = 2.37; CI 95%: 1.52-3.71; $P < .001$), high diastolic blood pressure (OR = 1.02 per mm Hg; CI 95%: 1.01-1.03; $P < .001$), and higher glomerular filtration rate (OR 1.01 per mL/min, CI 95% 1.00-1.01; $P = .01$), and a trend toward statistical significance was observed in long-term persistent AF (OR = 1.80; CI 95%: 0.98-3.30; $P = .059$).

Table 2. Variables Associated With the NOAC Prescription: Multivariate Analysis.[a]

Variable	OR	95% CI	*P* Value
University education	2.44	1.55-3.84	<.001
Cancer	0.46	0.25-0.85	.013
Cerebrovascular disease			
Ischemic/transient ischemic	1.37	0.95-1.95	.095
Hemorrhagic	3.14	1.00-10.15	.049
Previous bradyarrhythmia	0.40	0.19-0.87	.02
Major bleeding	3.36	1.73-6.51	<.001
Atrial fibrillation type (paroxismal)			
Persistent	0.90	0.60-1.34	.60
Long-standing persistent	1.83	1.00-3.35	.059
Permanent	0.81	0.59-1.12	.20
Diastolic blood pressure, mm Hg	1.02	1.01-1.03	.006
Glomerular filtration rate, mL/min	1.01	1.00-1.02	.009

Abbreviations: CI, confidence interval; NOCA, nonvitamin K antagonist oral anticoagulant; OR, odds ratio.
[a]Model adjusted by age, heart failure, coronary artery disease, diabetes mellitus, and hemoglobin.

On the contrary, variables associated with VKA treatment were history of cancer (OR = 0.46; CI 95%: 0.25-0.85; $P = .013$) and bradyarrhythmia (OR = 0.39; CI 95% 0.18-0.82; $P = .01$).

Discussion

In the FANTASIIA study, we found the following variables associated with the prescription of NOAC over VKA: previous major bleeding, hemorrhagic stroke, having a university degree, higher diastolic blood pressure, and higher glomerular filtration rate. Patients with history of cancer and bradyarrhythmia were more prone to be treated with VKA.

Incidence of major bleeding and hemorrhagic stroke seems to be higher in patients under VKA. In the HAS-BLED study,[9] performed with patients under VKA, the major bleeding rate was 1.75% per year. In the studies Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY),[3] Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF),[4] and Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE),[5] patients under warfarin presented major bleeding rates of 3.36%, 3.4%, and 3.09% per year, respectively, and of hemorrhagic stroke of 0.74%, 0.70%, and 0.80% per year, respectively. The NOAC showed a significant reduction in hemorrhagic stroke (dabigatran 150 mg 0.3%, dabigatran 110 mg 0.23%, rivaroxaban 0.49%, and apixaban 0.33%) and similar or inferior major bleeding rates (dabigatran 150 mg 3.11%, dabigatran 110 mg 2.71%, rivaroxaban 3.6%, and apixaban 2.13%). Therefore, it is expected to find more NOAC prescription among patients with history of major bleeding or hemorrhagic stroke.

The higher glomerular filtration rate found among patients under NOAC is explained by their restrictions in case of chronic kidney disease. Depending on the specific drug and the level of renal impairment, NOAC may need dose adjustment, special surveillance, or even be contraindicated in case of chronic kidney disease. A recent meta-analysis focused on NOAC and kidney disease showed that patients with NOAC and kidney disease had higher rates of major bleeding and hemorrhagic stroke compared to those without kidney disease and similar to patients treated with warfarin.[10]

Recently, a Danish registry including more than 18 000 patients treated with VKA or NOAC between 2011 and 2013 has been published. Patients under NOAC treatment were elder and had higher prevalence of heart failure, stroke, myocardial infarction, bleeding, hepatic disease, and alcoholism. The main factor associated with VKA treatment was the presence of kidney disease.[11] In our study, patients under NOAC also had higher rates of previous stroke and bleeding, and on the contrary, our analyses revealed that patients treated with NOAC were younger and had lower rate of previous heart failure and coronary artery disease (Table 1).

We found a higher prescription of NOAC over VKA in patients with university degrees (12.84% vs 6.14%, $P = .01$). Platt and collaborators[12] described that patients with an active job and those with higher education presented worst anticoagulant compliance. This finding has been observed by other groups[13] and has been explained as a reflect of mistrust in the medical profession and in the treatment prescribed among patients with higher education[14] and also as a consequence of a reduction in adherence to medication and to controls among patients with more workload. Other possible explanation is that patients with higher educational degree could be more prone to request NOAC prescription.

A recently retrospective observational study comparing factors driving anticoagulant selection (warfarin, dabigatran, or rivaroxaban) included 70 498 patients, 43 865 treated with warfarin, 21 070 patients treated with dabigatran, and 5563 patients treated with rivaroxaban.[15] Patients with higher ischemic stroke risk (CHA_2DS_2-VASc $\geq$ 2) have 25% less probability to receive dabigatran or rivaroxaban, compared with warfarin, and patients at high bleeding risk, defined as a Anticoagulation and Risk Factors in Atrial Fibrillation score >5, were less likely to receive an NOAC. Patients were divided by level of payment into 3 categories, no/poor coverage (patients pay >80% of costs prescription), fair coverage (20%-80%), and good coverage (<20%). Patients with good benefits' generosity were more likely to receive an NOAC. Because in Spain public health coverage is free and universal, the use of NOACS has become a financial challenge for the Spanish government and therefore the Ministry of Health and The Spanish Medicine Agency published a series of recommendations to regulate NOAC prescription.[16] In this sense, the VKA therapy remains the cornerstone of anticoagulant therapy in patients with AF and its use is recommended in patients' naive to oral anticoagulation. The NOACs are recommended in specific clinical scenarios: (1) patients with contraindications to the use of VKA, hypersensitivity, or allergy; (2) patients with a history of intracranial hemorrhage; (3) patients with a history of stroke and high risk of bleeding (HAS-BLED >3 and leukoaraiosis grade III/IV or multiple cortical microbleedings); (4) embolic events in patients with VKA, despite good control of INR; (5) VKA-treated patients who have poor control of INR (time in therapeutic range <65% according to Rosendaal method[17] or < 60% as direct calculation, in the previous 6 months); and (6) patients with inability to access to the controls of INR. In our study, patients with history of major bleeding and intracranial hemorrhage were more frequently treated with NOACS, as recommended. Because of the design of the study, we don't know which patients under treatment of NOCAS were previously treated with VKA and if the control of INR was in range or not, but in our experience, the main reason to switch from VKA to NOAC is a poor INR control. In our registry,[18] patients treated with VKA have a mean therapeutic time in range (TTR) calculated with Rosendaal method of 60.27% ± 24.48% and 63.77% ± 23.80% calculated with direct method, and 54% of patients have a poor anticoagulation control (defined as TTR <65%; Table 1), thus a large proportion of those patients might have indication of switching to NOAC.

Although several cost-effectiveness studies have demonstrated that NOACs are cost effective in high-risk patients, both in patients at high embolic or hemorrhagic risk, and in patients with poor control of VKA,[19⇓–21] in our study patients with low risk of embolic events ($CHADS_2$ < 2) are more frequently treated with NOAC (36.14% vs 26.66% of patients under VKA treatment, $P = .002$). These differences are not observed using CHA_2DS_2-VASc score, but some investigators recommend the use of $CHADS_2$ score for most patients, and use the additional variables of CHA_2DS_2-VASc score in patients with low risk in order to decide the indication of anticoagulation.[22] It is worth remarking that RE-LY, ROCKET-AF, and ARISTOTLE used $CHASD_2$ score.[3⇓–5] Our data suggest that NOAC are not being prescribed to the patients who could benefit most from them.

The main limitation of our study is the nature of the transversal observational study. Each investigator had to recruit the first 16 consecutive patients with VKA and the first 4 with NOAC. This selection process prevents the analysis of proportion of anticoagulation type. Patients are representative of a Spanish population and results might not be extrapolated to other countries. Another peculiarity of our study is that in Spain, the predominant VKA is acenocoumarol as opposed to most Western countries, where warfarin is mainly used.

In conclusion, in the FANTASIIA registry, we found that patients who were prescribed NOAC had more frequently history of major bleeding, university education, and higher glomerular filtration rate. On the contrary, patients with cancer or bradyarrhythmias received more frequently VKA.

Declaration of Conflicting Interests
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Author Contribution
J. Moreno-Arribas contributed to conception and design, analysis and interpretation, drafted the article, critically revised the article, gave final approval, and agrees to be accountable for all aspects of work ensuring integrity and accuracy. V. Bertomeu-Gonzalez contributed to design, interpretation, drafted the article, critically revised the article, and gave final approval. M. Anguita-Sanchez, A. Cequier, J. Castillo, I. Roldan, F. Marin, and V. Bertomeu-Martinez contributed to interpretation, critically revised the article, gave final approval, and agree to be accountable for all aspects of work ensuring integrity and accuracy. J. Muñiz contributed to analysis, critically revised the article, gave final approval, and agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Authors' Note
All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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