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ORIGINAL ARTICLE

Patterns and outcomes of switching direct oral anticoagulants in non-valvular atrial fibrillation: A real-world experience from Spain

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KEYWORDS
Direct oral anticoagulants (DOACs);
Non-valvular atrial fibrillation (NVAF);
Real-world experience;
Outcomes;
Drug use review;
Medication adherence

Abstract
Aims: The aim is to evaluate a management program for direct oral anticoagulants (DOACs) in non-valvular atrial fibrillation (NVAF) patients according to their profiles, appropriateness of dosing, patterns of crossover, effectiveness and safety. This is an observational and longitudinal prospective study in a cohort of patients attended in daily clinical practice in a regional hospital in Spain with 3-year a follow-up plan for patients initiating dabigatran, rivaroxaban or apixaban between JAN/2012-DEC/2016.
Methods: We analyzed 490 episodes of treatment (apixaban 2.5 9.4%, apixaban 5 21.4%, dabigatran 75 0.6%, dabigatran 110 12,4%, dabigatran 150 19.8%, rivaroxaban 15 17.8% and rivaroxaban 20 18.6%) in 445 patients. 13.6% of patients on dabigatran, 9.7% on rivaroxaban, and 3.9% on apixaban switched to other DOACs or changed dosing.
Results: Apixaban was the most frequent DOAC switched to. The most frequent reasons for switching were toxicity (23.8%), bleeding (21.4%) and renal deterioration (16.7%). Inappropriateness of dose was found in 23.8% of episodes. Rates of stroke/transient ischemic attack (TIA) were 1.64/0.54 events/100 patients-years, while rates of major, clinically relevant non-major (CRNM) bleeding and intracranial bleeding were 2.4, 5, and 0.5 events/100 patients-years. Gastrointestinal and genitourinary bleeding were the most common type of bleeding events (BE). On multivariable analysis, prior stroke and age were independent predictors of stroke/TIA. Concurrent platelet inhibitors, male gender and age were independent predictors of BE.

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Conclusion: This study complements the scant data available on the use of DOACs in NVAF patients in Spain, confirming a good safety and effectiveness profile.

PALABRAS CLAVE
Anticoagulantes orales de acción directa (ACODs);
Fibrilación auricular no valvular (FANV);
Experiencia real;
Resultados;
Revisión del uso de fármacos;
Adherencia a la medicación

Prevalencia y fenotipo de la hiperplasia suprarrenal macronodular bilateral primaria con secreción autónoma de cortisol: un estudio de 98 pacientes

Resumen
Objetivo: El objetivo es evaluar el manejo de anticoagulantes orales de acción directa (ACOD) en pacientes con fibrilación auricular no-valvular (FANV) según perfiles de pacientes, idoneidad de dosis, patrones de cruce, eficacia y seguridad. Estudio observacional, longitudinal, prospectivo en una cohorte de pacientes atendidos en consulta clínica diaria en un hospital regional de España seguimiento de hasta 3 años para pacientes tratados con dabigatrán, rivaroxabán o apixabán entre ENE/2012-2012DIC/2016.
Metodología: En 490 episodios (apixabán 2,5 9,4%, apixabán 5 21,4%, dabigatrán 75 0,6%, dabigatrán 110 12,4%, dabigatrán 150 19,8%, rivaroxabán 15 17,8%, rivaroxabán 20 18,6%) de 445 pacientes, el 13,6% de los pacientes con dabigatrán, 9,7% con rivaroxabán y 3,9% con apixabán, cambiaron a otros o dosis.
Resultados: Apixaban fue el ACOD más frecuente. Las causas más frecuentes fueron toxicidad (23,8%), sangrado (21,4%) y deterioro renal (16,7%). Se encontró inadecuación de la dosis en el 23,8% de casos. Las tasas de accidente cerebrovascular/ataque isquémico transitorio fueron de 1,64/0,54 eventos/100 pacientes-año, mientras que las de hemorragia no mayor, clínicamente relevante (NMCR) y hemorragia intracraneal fueron de 2,4, 5 y 0,5 eventos/100 pacientes-año. El sangrado gastrointestinal y genitourinario fue el evento hemorrágico más común. En el análisis multivariable, el ictus previo y la edad fueron predictores independientes de ictus/AIT. Los inhibidores plaquetarios simultáneos, el sexo masculino y la edad fueron predictores independientes de eventos hemorrágicos.
Conclusión: Este estudio complementa los escasos datos disponibles sobre el uso de ACOD en pacientes con FANV en España, confirmando un buen perfil de seguridad y eficacia.

Introduction

Patients with non-valvular atrial fibrillation (NVAF) have an up to fivefold increased risk of stroke.[1] For many years, vitamin K antagonists (VKA) have been the only anticoagulant treatment available. Recently, direct oral anticoagulants (DOACs) have entered the scene, demonstrating a better risk-benefit profile than VKA in randomized controlled trials (RCTs).[2–4] Post-marketing real-world observational studies on the effectiveness and safety of dabigatran,[5,6] rivaroxaban[7] and apixaban[8] vs. warfarin have shown general consistency with the respective RCTs. An important advantage of DOACs with respect to AVK is the predictable pharmacokinetics and no need for periodic laboratory monitoring. Thus, the current guidelines of the European Society of Cardiology (ESC) recommend that DOACs should be preferred to VKAs in patients with NVAF who initiate anticoagulation.[9,10]

Despite its ease of use, DOACs remain high-risk medications which must be handled carefully to avoid bleeding and thrombotic complications. To maximize safety, efficacy, appropriate initial DOAC, dose selection and over time dose adjustments, we must take into consideration patients' characteristics such as age, renal function, weight, comorbidities and concomitant medications. In addition, careful handling of invasive procedures and surgery should be done, as well as appropriate management of bleeding events. Hence, for proper handling of these drugs, training of physicians attending anticoagulated patients–as well as patient education–is essential.

Nevertheless, the usage rates of DOACs in Spain has been lower than in neighboring countries, mainly because of administrative restrictions limiting the indications of DOACs to situations of poor INR control, ineffectiveness of VKA, contraindications to VKA, increased risk of intracranial hemorrhage or inability to access INR facilities. Moreover, studies evaluating effectiveness and safety of DOAC in the Spanish population are very scarce.[11–13] The lack of information about real world practice with DOACs in Spain represents a burden that prevents many patients from getting an adequate treatment of NVAF.

Therefore, we have designed a management program for patients with NVAF initiating DOACs in our health area, in the Hematology Service of the Hospital (in Valencia, Spain). We have included recommendations for indication, dosage, risk factors and influence of renal function, contraindications,

and recommendations for switching, management and treatment of all clinical situations that involve DOACs such as bleeding, surgery, monitoring and bibliography, with special focus on the role of the specialists in this field (supplementary guide). Our goal was to evaluate the effectiveness and safety of DOACs in patients initiating anticoagulation for NVAF between 2012 and 2016, reporting the results of our program.

Subjects and methods

Our center, Hospital Universitario de Sagunto (Valencia, Spain) is a regional hospital that provides care for over 150,000 people and manages over 3500 patients anticoagulated with VKA. In 2012 we designed a management plan for prescription of DOACs patients in patients with NVAF. This study was a longitudinal, prospective observational study in which all patients with NVAF who had signed the informed consent were attending the Hematology Service and they were on treatment with apixaban, rivaroxaban or dabigatran between April, 1st of 2012 and December, 31st of 2016—were included.

According to the management protocol, patients underwent clinical and analytic evaluation before the study began and at three months, one year, two years and three years after initiating DOACs. For each patient, standard clinical data was obtained before the study began, including treatment with platelet aggregation inhibitors. CHA2DS2VASc and HAS-BLED scores.

Following up, we collected analytic data, adverse reactions, thromboembolic events and bleeding events. Clinical effectiveness was assessed according to: the presence or absence of episodes of ischemic stroke, TIA, systemic thromboembolism (TE) and safety—according to major and clinically relevant non-major (NMCR) bleeding (ISTH criteria).[14] Appropriate dosing was defined according to international standards included in the Management Program (Supplementary guide).

The confidentiality of records was respected. The study was classified by the Spanish Agency for Medicines and Health Products (EPA-OD) and it was approved by the Research Ethics Committee of the Hospital. The study was conducted under conditions of routine clinical practice and no additional procedures or interventions were performed. All patients gave their informed consent before the study began.

All patients who had completed at least the 3 months visit were included in the analysis. The statistical analyses were performed using the statistical software R, 3.5.2.[15] For the descriptive analysis, qualitative variables were described as absolute frequencies and percentages, and quantitative variables were described as median and interquartile range. In order to reduce the possibility of false positive inferences due to multiple comparisons between groups, the p-values were adjusted using the Benjamini & Hochberg method.[16] In addition to calculating incidence rates of TE and bleeding events, Kaplan Meier curves were built. The comparison of these curves was performed using the log-rank test. The limit of significance was set at 0.05.

Results

Demographic characteristics of the study population

In total, 490 episodes of treatment in 445 patients were analyzed. Baseline patient characteristics are shown in Table 1. Median age was 76 years (Q1–Q3: 70—80), 53% of patients were male, median CHA2DS2VASc score was 4 (Q1–Q3: 3—5), median HAS-BLED score was 1 (Q1–Q3: 1—2). Overall, median follow-up was 24 months (Q1–Q3: 12—36). It was similar amongst all treatment groups. The distribution of DOACs is also shown in Table 1. In the whole cohort, the standard dose was prescribed in 60% of episodes and the lower presentation in 40%.

Patients taking apixaban 2.5 mg were older, had higher CHA2DS2VASc score and lower creatinine clearance. Patients taking dabigatran 150 mg and rivaroxaban 20 mg were younger and they had lower CHA2DS2VASc and higher creatinine clearance. Subjects on apixaban 2.5 had significantly higher percentage of prior TE than patients on apixaban 5 mg or rivaroxaban 20 mg.

In 445 patients initiating DOACs, 387 (86.9%) were previously receiving VKA and 58 (13.1%) started anticoagulation de novo. The most frequent reasons for substituting AVK for DOAC were poor INR control in 308 patients (79.5%) and TE in 42 patients (10.8%) (Table 2).

During the follow-up period 42 patients switched to a second DOAC, and of these, two patients switched to a third DOAC, and one was prescribed a fourth DOAC (Supplementary Table 1), Fig. 1. Dose adjustments and crossover data from the first switch between DOAC are shown in Supplementary Table 2. Apixaban was the most frequent DOAC switched to. The most frequent reasons for switching were toxicity (23.8%), bleeding (21.4%) and renal deterioration (16.7%) (Table 3). According to the summary of product characteristics, the DOACs dose was inappropriate in 23.8% of episodes (Supplementary Table 3).

Table 4 shows DOACs interruption before completion of the study. Seven patients (1.4%) were lost in the follow-up; forty-two patients (8.6%) died, three in the context of stroke and one in the context of a subarachnoid hemorrhage. The remaining deaths were due to other causes. DOAC treatment was permanently discontinued in 107 episodes (21.8%) for reasons listed also in Table 4. The most common bleeding by 4.3%, worsening of kidney function by 3.3% toxicity by 2.4%, and stroke by 2.2%.

Outcomes

Rates of stroke and transient ischemic attack for the whole series were 1.64 and 0.54 events/100 patients-years, respectively (Supplementary Table 4). In the 3 patients taking dabigatran 75 mg rates were much higher (24.14 events/100 patients-years). Regarding the rest of the series, rates were higher with rivaroxaban 15 mg and dabigatran 110 mg, but the difference did not reach statistical significance ($p = 0.071$ in the log-rank test).

In the multivariate analysis which consisted of analyzing time to occurrence of a TE event, the following variables were initially included: treatment group, age, gender,

Table 1 Baseline patients' characteristics by study group.

Study groups	Apixaban 2.5 mg	Apixaban 5 mg	Dabigatran 110 mg	Dabigatran 150 mg	Rivaroxaban 15 mg	Rivaroxaban 20 mg	*Dabigatran 75 mg*	Total	
Number of episodes	*n* = 46 (9.4%)	*n* = 105 (21.4%)	*n* = 61 (12.4%)	*n* = 97 (19.8%)	*n* = 87 (17.8%)	*n* = 91 (18.6%)	*n = 3 (0.6%)*	**n = 490 (100%)**	
Follow-up (months) median	21.6 (12—3.4)	24	24	24	24	24	*7.7*	**24**	NS
interquartile range		(12—36)	(12—36)	(12—36)	(12—36)	(12—36)	*(6.8—21.8)*	**(12—36)**	
Age — yr									
median	83	74	80	71	79	71	*79*	**76**	<0.001[a]
interquartile range	(80—86)	(69—78)	(78—82)	(64—76)	(77—82)	(66—75)	*(78.5—81.5)*	**(70—80)**	
Female sex — no. (%)	27 (58.7%)	47 (44.8%)	34 (55.7%)	37 (38.1%)	45 (51.7%)	36 (39.6%)	*3 (100%)*	**229 (46.7%)**	NS
Weight — kg median			74						
interquartile range	70 (60—82)	79 (71—90)	(65—85)	80 (73—92)	75 (66—82)	82 (70—95)	– –	**78 (68—88)**	<0.001[f]
creatinine clearance —			65						
ml/min median	42	68	(52—77)	83.5	58	79	47	**68**	<0.001[b]
interquartile range	(33.3—52)	(55—88)		(71–102.3)	(45–70)	(61—107.5)	(41—55.5)	**(53.8—88)**	
CHADsVASc									
median	5.5	4	5	3	5	3	*5*	**4**	<0.001[c]
interquartile range	(4—6)	(3—5)	(4—6)	(2—5)	(4—6)	(2—4)	*(4.5—6)*	**(3—5)**	
Prior stroke, TIA, or systemic embolism — no. (%)	21 (45.7%)	18 (17.1%)	21 (34.4%)	29 (29.9%)	28 (32.2%)	17 (18.7%)	1 (33.3%)	**135 (27. 6%)**	<0.001[d]
HAS-BLED									
median	2	1	1	1	1	1	1	**1**	<0.001[e]
interquartile range	(1—2)	(1—2)	(1—2)	(1—2)	(1—2)	(1—1)	(1—2)	**(1—2)**	
Antiplatelet drugs — no. (%)	0 (0%)	1 (0.95%)	1 (1.6%)	0 (0%)	4 (4.6%)	0 (0%)	0 (0%)	6 (1.2%)	NS

[a] Age: there were significant differences in all comparisons, except D150 versus R20 and D110 versus R15. Patients receiving A2.5 were significantly older than all other groups and those receiving D150 and R20 significantly younger than all other groups (Ax2.5 > D110 y R15 > A × 5 > D150 y R20).

[b] Creatinine clearance: there were significant differences in all comparisons, except D150 versus R20, D110 versus R15, D110 versus A5 and A2.5 versus R15. Patients who received A2.5 had CrCl significantly lower than all other groups and those receiving D150 and R20 significantly higher than all other groups (Ax2.5 < R15, D110, Ax5 < D150 y R20).

[c] CHA2DS2VASc: significant differences in all comparisons, except A2.5 versus D110, A2.5 versus R15, D110 versus R15 and D150 versus R20. Patients who received A2.5 had a significantly higher score than all other patients (except those receiving D110 and R15) and those receiving D150 and R20 significantly lower than all other patients (A2,5 > D110 y R15 > A5 > D150 y R20).

[d] Previous TE: significant differences between A2.5 - AP5 and A2.5 − R20.

[e] HAS-BLED: significant differences between A2.5 versus A5, R20 and D150; between R15 versus R20 and D150; and between D110 versus R20 and D150 (A2,5 > D110 y R15 > A5 > D150 y R20.

[f] Weight: significant differences between A2.5–A5, A2.5–D150, A2.5–R20, A5–R15, D110–D150, D110–R20, D150–R15, and R15–R20.

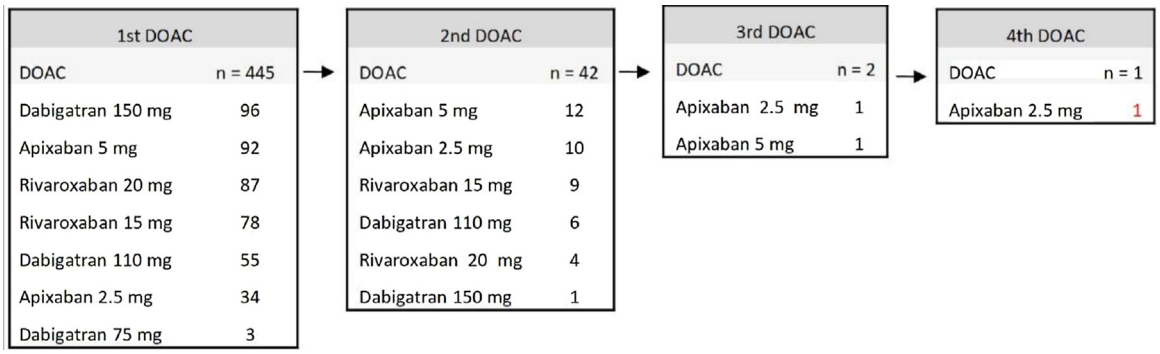

Figure 1 Study Flow diagram.

Table 2 Previous use of VKA and reasons for switching from VKA to DOAC.

No	58 patients (13.1%)	
Yes	387 patients (86.9%)	
	Reasons for switching to DOAC:	
		308
	Poor INR control with good VKA compliance	(79.5%) 42
	Thromboembolic complication	(10.8%) 12
	Previous hemorrhagic stroke or high risk of intracranial bleeding	(3.1%) 7 (1.8%)
	Allergy or intolerance to VKA	5 (1.3%)
	Difficulties with follow-up	13 (3.3%)
	Other	

Patients $n = 445$.

Table 3 Description of the reasons for switching between DOAC.

Reasons for switching	Patients no. (%)
Toxicity[a]	10 (23.8%)
Hemorrhage	9 (21.4%)
Other	9 (21.4%)
Increased creatinine clearance	7 (16.7%)
Stroke	4 (9.5%)
Hemorrhage + increased creatinine clearance	2 (4.8%)
Iron-deficiency anemia without evident bleeding	1 (2.4%)

[a] 9/10 cases of toxicity were related to dabigatran dyspepsia.

weight, creatinine clearance, CHA2DS2VASC, previous TE and previous use of AVK. Previous use of AVK and weight were excluded after applying the automatic backward selection model, CHA2DS2VASC.Prior stroke and age were independently associated with an increased risk of stroke (Table 5).

Rates of major, NMCR and intracranial bleeding were 2.4, 5 and 0.5 events/100 patients-years, respectively (supplementary Table 5). Rates were higher with dabigatran 110 mg, but the difference did not reach statistical significance ($p = 0.54$ in the log-rank test).

In the multivariate analysis, which consisted of analyzing time to occurrence of a major or NMCR bleeding event, the following variables were initially included: treatment group, age, gender, weight, creatinine clearance, HAS-BLED, previous use of AVK and anti-platelet drugs. After applying the automatic backward selection model, HAS-BLED, creatinine clearance, previous use of AVK and weight were excluded. Concomitant platelet aggregation inhibitors, male gender and age were independently associated with an increased risk of bleeding (Table 5). The results were the same in a model according to forward selection.

Discussion

We present the results of a management program for DOACs in a cohort of 445 patients (490 episodes) with NVAF controlled in routine clinical practice with a pre-planned follow-up for up to 3 years, in the Hematology Service at a regional hospital in Spain (Hospital Universitario de Sagunto, Valencia, Spain). There are two main findings in our study, first, despite significant differences in target population between pivotal studies and daily clinical practice, the key messages of the former in terms of the benefit associated with DOACs remain valid. Second, the description of a prevalent pattern of switching between DOACs. In addition, we describe a specific example of implementing international guidelines in form of a consensus program for DOAC management.

The use of DOACs in Spain is markedly lower than in other neighboring countries because reimbursement of prescriptions requires approval by health care authorities. Accordingly, real-world studies evaluating DOACs in the Spanish population are scarce. A few retrospective studies have been published based on databases containing electronic health records[17–21] or prospective registries,[11] but most of these studies have focused exclusively on the distribution of the different DOACs/doses prescribed and patients characteristics [17–21] and only a few have analyzed stroke and bleeding events.[11–13,22] To our knowledge, the study by Cerda et al.,[13] performed in a cohort of 1443 patients from a single center is the only one with a comparable methodology to ours, showing basal characteristics and a follow-up similar to those of our cohort of patients. While in Cerda's study rivaroxaban was the DOAC most commonly prescribed (almost 50% of all the prescriptions), in our study the different DOACs were well balanced.

Table 4 Episodes with interrupted follow-up before study conclusion.

	Apixaban 2.5 mg (*n* = 46)	Apixaban 5 mg (*n* = 105)	Dabigatran 110 mg (*n* = 61)	Dabigatran 110 mg (*n* = 97)	Rivaroxaban 15 mg (*n* = 87)	Rivaroxaban 20 mg (n = 91)	*Dabigatran 75 mg (n = 3)*	Total (*n* = 490)
Total with interrupted follow-up (%)	17 (37%)	28 (26.7%)	25 (41%)	25 (25.8%)	35 (40.2%)	24 (26.4%)	*2 (66.7%)*	156 (31.8%)
Lost in follow-up								
no. (%)	1 (2.2%)	3 (2.9%)	1 (1.6%)	0 (0%)	1 (1.2%)	1 (1.1%)	0 (0%)	7 (1.4%)
months — median (Q1-Q3)	12	13.2 (10.3—3.8)	11.8	–	3	4	–	11.8 (5.7—12.6)
Death from								
stroke-hemorrhage[a]	0 (0%)	1 (0.9%)	1 (1.6%)	0 (0%)	2 (2.3%)	0 (0%)	*0 (0%)*	4 (0.8%)
no. (%)	–	35	10	–	15.5 (13.7—17.4)	–	–	15.5 (11.4—23.1)
months — median (Q1-Q3)								
Death from other causes								
no. (%)	10 (21.7%)	7 (6.7%)	5 (8.2%)	2 (2.1%)	11 (12.6%)	3 (3.3%)	*0 (0%)*	38 (7.8%)
months — median (Q1-Q3)	12.2 (9.3–18)	16.8 (7.7—20.8)	12.3 (12.3—15.6)	16.3 (13.2—19.4)	8.8 (4.9–18.8)	22.9 (12—23.9)	–	12.4 (6—21.4)
DOAC permanent Interruption								
no. (%)	6 (13%)	17 (16.2%)	18 (29.5%)	23 (23.7%)	21 (24.1%)	20 (22%)	*2 (66.7%)*	107 (21.8%)
months — median (Q1-Q3)	11 (9–11.9)	4.7 (3.1–16.9)	7.2 (1.9–20)	4.2 (1.9–7.7)	11.1 (6.2–19.7)	11.9 (3.8–19.3)	*6.8 (6.4–7.3)*	7.7 (3.1—17.7)
Reasons for interruption —no. (%)								
Bleeding	1 (2.2%)	3 (2.9%)	2 (3.3%)	4 (4.1%)	3 (3.4%)	8 (8.8%)	*0 (0%)*	21 (4.3%)
Worsening CrCl	0 (0%)	4 (3.8%)	1 (1.6%)	2 (2.1%)	4 (4.6%)	5 (5.5%)	*0 (0%)*	16 (3.3%)
Toxicity[b]	0 (0%)	1 (0.9%)	4 (6.6%)	7 (7.2%)	0 (0%)	0 (0%)	*0 (0%)*	12 (2.4%)
Stroke	1 (2.2%)	2 (1.9%)	2 (3.3%)	1 (1%)	4 (4.6%)	0 (0%)	*1 (33.3%)*	11 (2.2%)
Anemia without overt bleeding	0 (0%)	0 (0%)	1 (1.6%)	0 (0%)	2 (2.3%)	1 (1.1%)	*0 (0%)*	4 (0.8%)
Bleeding + worsening CrCl	0 (0%)	1 (0.9%)	3 (4.9%)	0 (0%)	0 (0%)	0 (0%)	*0 (0%)*	4 (0.8%)
Other[c]	4 (8.7%)	6 (5.7%)	5 (8.2%)	9 (9.3%)	8 (9.2%)	6 (6.6%)	*1 (33.3%)*	39 (7.9%)
New treatment — no. (%)								
DOAC	3 (50%)	8 (47.1%)	10 (55.5%)	15 (65.2%)	5 (23.8%)	16 (80%)	1 (50%)	58 (54.2%)
VKA	0 (0%)	4 (23.5%)	5 (27.8%)	5 (21.7%)	7 (33.3%)	3 (15%)	0 (0%)	24 (22.4%)
None	3 (50%)	5 (29.4%)	3 (16.7%)	3 (13%)	9 (42.9%)	1 (5%)	1 (50%)	25 (23.4%)

Abbreviations: CrCl: creatinine clearance; VKA: Vitamin K antagonists.
In 29 episodes follow-up was interrupted before 3 months of DOAC treatment initiation.
[a] Subarachnoid hemorrhage: 1 patient on apixaban 5 mg; stroke: 1 patient on dabigatran 110 mg and another on rivaroxaban 15 mg; stroke with hemorrhagic transformation: 1 patient on rivaroxaban 15 mg.
[b] All toxicities were related to dabigatran dyspepsia except for one patient who was on apixaban 5 mg.
[c] Other reason for discontinuation: 11 patients => serious clinical condition; 7 patients => dose adjustments, 2 patients => platelet aggregation inhibitors initiation, etc.

Table 5 Hazard ratios for time to occurrence of a thromboembolic (TE) event, **top panel,** and hazard ratios for time to occurrence of a bleeding event, **bottom panel** (Cox regression model).

Variables	Hazard ratio	95% CI	P-value
Rivaroxaban 15 mg	1	–	–
Apixaban 2,5 mg	0.227	0.026–1.999	0.182
Apixaban 5 mg	1.019	0.287–3.624	0.977
Dabigatran 110 mg	0.414	0.103–1.658	0.213
Dabigatran 150 mg	0.541	0.094–3.116	0.491
Rivaroxaban 20 mg*	–	–	–
Age	**1.196**	**1.052–1.359**	**0.006**
Gender (male)	1.916	0.698–5.258	0.207
Creatinine clearance	1.024	0.997–1.052	0.080
Previous thromboembolism	**4.229**	**1.517–11.791**	**0.006**
Dabigatran 110 mg	1	–	–
Apixaban 2,5 mg	0.243	0.051–1.148	0.074
Apixaban 5 mg	0.959	0.382–2.404	0.928
Dabigatran 150 mg	1.62	0.628–4.175	0.318
Rivaroxaban 15 mg	0.506	0.1961.307	0.159
Rivaroxaban 20 mg	1.544	0.591–4.020	0.375
Age	**1.072**	**1.022–1.125**	**0.005**
Gender (male)	**2.096**	**1.180–3.722**	**0.012**
Platelet aggregation inhib.-yes	**7.052**	**2.277–21.838**	**0.001**

P-value < 0.05. The reference category Rivaroxaban 15 mg was chosen because this treatment group had the highest proportion of TE events. *In the treatment group Rivaroxaban 20 mg no TE events were observed.
The reference category dabigatran 110 mg was chosen because the dabigatran treatment group had the highest proportion of bleeding events.

Of note, the clinical profile of patients in our series differed according to the DOAC administered. These different profiles do not appear to be random but are in line with recent publications analyzing characteristics of patients prescribed with DOAC in routine practice.[23,24] There is a higher margin of renal failure and low gastrointestinal bleeding risk of apixaban in the elderly,[3] that together with data of the RELY- trial[2] it shows a lower risk of ischemic stroke, independent of age. However, an interaction between age and bleeding risk might explain the differences in prescriptions.[25]

Our population was older and glomerular filtration was worse than in pivotal studies. Median CHADSVASC was also higher, reflecting the fact that real-world patients present more comorbidities than subjects selected in randomized trials. However, our bleeding and thrombotic rates were similar to those in clinical trials. As a whole, patient characteristics in our study differed from pivotal trials, pointing out potential higher risk for clinical complications in our patients. Nevertheless, instead of showing the expected worse outcomes, our results confirm the benefits of DOACs in terms of similar efficacy and lower rates of adverse events compared to acenocoumarol. The contribution of real-world studies is of paramount importance, as shown by previous experiences with other drugs such as ceriva statine in hyperlipidemia, or sibutramine and rimonabant in obesity. In these examples, daily practice did not confirm the safety and efficacy of these drugs postulated in clinical trials. The implications of extending the results of randomized trials to the general population affected by NVAF are far-reaching. A recent publication points out the superiority of all three direct anticoagulants against acenocoumarol in terms of cost-effectiveness in a Spanish setting.[26] In the absence of scientific evidence based on clinical or economic data, administrative restrictions for DOACs appear to be unnecessary.

Stroke rates in our study (1.6 events/100 patients-years) were similar to those reported in pivotal trials ranging from 1.1 to 1.7 events/100 patients-years. Similarly, rates of major bleeding (2.4/100 patients-years), NMCR bleeding (5/100 patients-years) and intracranial bleeding (0.5/100 patients-years) in our study were in the range of those reported in randomized trials. Increasing age and previous stroke/TIA were independent predictors of efficacy, in accordance with previous studies.[27–32]

Although risk factors for bleeding during DOACs therapy have yet to be fully elucidated, and limited data is available on the clinical value of various bleeding risk scores in this setting, the HAS-BLED is the most widely used score with the best evidence for predicting the risk of hemorrhage.[10] In our study, increasing age, concurrent aspirin use, and male gender were independent predictors of bleeding. Multiple studies have highlighted the increased propensity of bleeding in elderly patients [7,30,31,33,34] and in those taking the combination of oral anticoagulants plus antiplatelet drugs.[35–37,39] The influence of gender on bleeding rates is more controversial, with some studies confirming our own.[38–40]

Although no head-to-head comparisons between DOACs have been performed, a series of systematic reviews and meta-analysis of RCT and observational studies have compared efficacy and safety of DOACs. In general, compared

with warfarin and apixaban offering, DOACs have the most favorable profile.[41–43] In our study we did not observe statistically significant differences between specific DOACs.

It is unknown whether all DOACs have similar rates of switching. Information on this matter in the literature is rare, although it is a frequent issue in clinical practice.[44] A distinctive feature of our study is that we analyzed DOACs discontinuation, dose adjustments and patterns of crossover between DOACs. A recent meta-analysis in patients with NVAF reviewed studies comparing DOAC-to-DOAC switch prevalence, showing that switching across DOACs is frequent, affecting up to 11% of patients during their life-time.[45] Among DOACs, apixaban had lower risk of DOAC-to-DOAC switch compared to dabigatran and rivaroxaban, but no data was available in this study regarding specific causes of switch. Another case series showed a higher cross-over rate with dabigatran.[46] These results resembled our own study, where almost 10% of patients underwent dose adjustments or switched to another DOAC, with the highest percentages in dabigatran users (13.6%) and the lowest in patients prescribed apixaban (3.9%). Furthermore, apixaban was the most often chosen DOAC as an alternative option. The lower bleeding rate observed with apixaban treatment in comparison to rivaroxaban and dabigatran in multiple real-world studies[23,24,47,48] and its lowest dependence on renal function may influence these treatment decisions.

Concerning evaluation of the appropriateness of dosing, the incidence of off-label use in our study was 23.8%, being underdosing much more common (22%) than over-dosing (1.8%). This numbers are in line with previous studies reporting non-recommended dosing in up to 30% of NVAF patients, the majority due to underdosing.[40,49] A bias towards greater concern of bleeding amongst physicians might be a main underlying factor.[50] It should be taken into consideration, that in real clinical practice appropriateness cannot always be defined straight-forward. For instance, in our study 36/56 (64%) of patients strictly speaking underdosed with rivaroxaban, were older than 80 years and/or had a creatinine clearance between 50—60 ml/min. Due to the small sample size, we did not analyze differences in outcomes in these cases. Although data in this regard have not been consistent, there are concerns for a potential increase of bleeding or TE events in these cases.[40]

Finally, it must be highlighted that our program for DOACs management in NVAF patients harmonizes with the recently published guidelines of the ESC which emphasize the importance of implementing an integrated care of AF across all healthcare levels (ABC pathway) to maximize treatment safety and efficacy.[9] Although patients on DOACs, unlike those on VKA, need no routine laboratory monitoring, it is essential that anticoagulation clinics get involved and provide guidance surrounding DOACs management. Our program offers a solid and updated reference, spreads knowledge, targets all levels of care and integrates clinical management. In our opinion, centralized follow-up within Hematology Units should be stratified based on patient risk level for TE bleeding complications.

Strengths of our study are first, that clinical and analytic data were collected prospectively, allowing for good data quality, and second, the fact that treatment decisions followed a consensus protocol between acting physicians. The small number of patients, the narrow time of follow-up and the special conditions applying to the Spanish Health Care System are limitations of our study that may reduce the generalization of our conclusions. Another limitation results from the fact that our study could not compare the performance of our program with the previous situation. As a consequence, no statement about potential superiority can be made.

Conclusions

To conclude, our study complements the scant data available on the use of DOACs in NVAF patients in Spain. Confirming a good safety and effectiveness profile, it analyses the pattern of switching between DOACs and it offers a solid model based on consensus protocols under the surveillance of specialized Units.

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Conflicts of interest

The authors declare that they do not have any conflicts of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.rce.2023.03.007.

References

1. Apenteng PN, Murray ET, Holder R, Hobbs FDR, Fitzmaurice DA. An international longitudinal registry of patients with atrial fibrillation at risk of stroke (GARFIELD): The UK protocol. BMC Cardiovasc Disord. 2013;13, doi:10.1186/1471-2261-13-31.
2. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Eng J Med. 2009;361(12):1139–51, doi:10.1056/nejmoa0905561.
3. Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Eng J Med. 2011;365(11):981–92, doi:10.1056/nejmoa1107039.
4. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Eng J Med. 2011;365(10):883–91, doi:10.1056/nejmoa1009638.
5. Carmo J, Costa FM, Ferreira J, Mendes M. Dabigatran in real-world atrial fibrillation: Meta-analysis of observational comparison studies with vitamin K antagonists. Thromb Haemost. 2009;116(4):754–63, doi:10.1160/TH16-03-0203.
6. Huisman MV, Rothman KJ, Paquette M, Teutsch C, Diener HC, Dubner SJ, et al. Two-year follow-up of patients treated with dabigatran for stroke prevention in atrial fibrillation: Global Registry on Long-Term Antithrombotic Treatment in Patients with Atrial Fibrillation (GLORIA-AF) registry. Am Heart J. 2018;198:55–63, doi:10.1016/j.ahj.2017.08.018.

7. Camm AJ, Amarenco P, Haas S, Hess S, Kirchhof P, Kuhls S, et al. XANTUS: A real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation. Eur Heart J. 2016;37(14):1145–53, doi:10.1093/eurheartj/ehv466.
8. Li X, Deitelzweig S, Keshishian A, Hamilton M, Horblyuk R, Gupta K, et al. Effectiveness and safety of apixaban versus warfarin in non-valvular atrial fibrillation patients in ''real-world'' clinical practice: A propensity-matched analysis of 76,940 patients. Thromb Haemost. 2017;117(6):1072–82, doi:10.1160/TH17-01-0068.
9. 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), doi:10.1093/eurheartj/ehw210.
10. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J. 2021;42(5):373–498, doi:10.1093/eurheartj/ehaa612.
11. Anguita Sánchez M, Bertomeu Martínez V, Ruiz Ortiz M, Cequier Fillat Á, Roldán Rabadán I, Muñiz García J, et al. Direct oral anticoagulants versus vitamin K antagonists in real-world patients with nonvalvular atrial fibrillation. The FANTASIIA study. Rev Esp Cardiol (English Edition). 2020;73(1):14–20, doi:10.1016/j.rec.2019.02.021.
12. Ramagopalan SV, Sicras-Mainar A, Polanco-Sanchez C, Carroll R, de Bobadilla JF. Patient characteristics and stroke and bleeding events in nonvalvular atrial fibrillation patients treated with apixaban and Vitamin K antagonists: A Spanish real-world study. J Comp Eff Res. 2019;8(14):1201–12, doi:10.2217/cer-2019-0079.
13. Cerdá M, Cerezo-Manchado JJ, Johansson E, Martínez F, Fernández M, Varela A, et al. Facing real-life with direct oral anticoagulants in patients with nonvalvular atrial fibrillation: Outcomes from the first observational and prospective study in a Spanish population. J Comp Eff Res. 2019;8(3):165–78, doi:10.2217/cer-2018-0134.
14. Kaatz S, Ahmad D, Spyropoulos AC, Schulman S. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: Communication from the SSC of the ISTH. J Thromb Haemost. 2015;13(11):2119–26, doi:10.1111/jth.13140.
15. R Core Team. https://www.R-project.org/, 2021 [consultada el 3 de septiembre de 2022].
16. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. J R Stat Soc Ser B (Methodological). 2015;57(1):289–300, doi:10.2307/2346101.
17. de la Figuera M, Prieto MA, Marín N, Egocheaga I, Cinza S. Diferencias en el manejo de los pacientes con fibrilación auricular según inicie el tratamiento con anticoagulantes orales de acción directa el médico de atención primaria o el especialista. Estudios SILVER-AP y BRONCE-AP. Semergen. 2017;44(5), doi:10.1016/j.semerg.2017.09.005.
18. de la Figuera M, Cinza S, Marín N, Egocheaga I, Prieto MA. Clinical characteristics of patients with atrial fibrillation treated with direct oral anticoagulants attended in primary care setting. The SILVER-AP study. Aten Primaria. 2018;50(6):359–67, doi:10.1016/j.aprim.2017.05.009.
19. Gomez-Lumbreras A, Cortes J, Giner-Soriano M, Quijada-Manuitt MA, Morros R. Characteristics of Apixaban-Treated Patients, Evaluation of the Dose Prescribed, and the Persistence of Treatment: A Cohort Study in Catalonia. J Cardiovasc Pharmacol Ther. 2018;23(6):494–501, doi:10.1177/1074248418778544.
20. Mostaza JM, Suárez Fernández C, Castilla Guerra L, Suriñach JM, Tamarit J, et al. Type and doses of oral anticoagulants and adherence to anticoagulant treatment in elderly patients with atrial fibrillation: The ESPARTA study. J Comp Eff Res. 2018;7(3):223–32, doi:10.2217/cer-2017-0034.
21. Peris Vidal J, Ferreiro Argüelles M, Hidalgo Urbano RJ, et al. Patients with non-valvular atrial fibrillation treated with rivaroxaban in Spain: unequal access to oral direct anticoagulants (HEROIC study). Cardiocore. 2018;53(4):159–65, doi:10.1016/j.carcor.2018.04.002.
22. Rodríguez-Bernal CL, Santa-Ana-Téllez Y, García-Sempere A, Hurtado I, Peiró S, Sanfélix-Gimeno G. Clinical outcomes of nonvitamin K oral anticoagulants and acenocoumarol for stroke prevention in contemporary practice: A population-based propensity-weighted cohort study. Br J Clin Pharmacol. 2021;87(2):632–43, doi:10.1111/bcp.14430.
23. Rutherford OCW, Jonasson C, Ghanima W, Söderdahl F, Halvorsen S. Comparison of dabigatran, rivaroxaban, and apixaban for effectiveness and safety in atrial fibrillation: A nationwide cohort study. Eur Heart J Cardiovasc Pharmacother. 2020;6(2):75–85, doi:10.1093/ehjcvp/pvz086.
24. van Ganse E, Danchin N, Mahé I, Mahé I, Hanon O, et al. Comparative safety and effectiveness of oral anticoagulants in nonvalvular atrial fibrillation: The NAXOS study. Stroke. 2020;51(7):2066–75, doi:10.1161/STROKEAHA.120.028825.
25. Grymonprez M, Steurbaut S, de Backer TL, Petrovic M, Lahousse L, Noordam R, Mueller T, Laranjeira L, Lilly E. Effectiveness and safety of oral anticoagulants in older patients with atrial fibrillation: A systematic review and meta-analysis. Front Pharmacol. 2020;11:1663–9812, doi:10.3389/fphar.2020.583311.
26. Monreal-Bosch M, Soulard S, Crespo C, Brand S, Kansal A. Comparación del coste-utilidad de los anticoagulantes orales de acción directa en la prevención de ictus en la fibrilación auricular no valvular en España (Comparison of the cost-utility of direct oral anticoagulants for the prevention of stroke in patients with atrial fibrillation in Spain). Rev Neurol. 2017;64(6):247–56, doi:10.33588/rn.6406.2016311.
27. Marinigh R, Lip GYH, Fiotti N, Giansante C, Lane DA. Age as a risk factor for stroke in atrial fibrillation patients: Implications for thromboprophylaxis. J Am Coll Cardiol. 2010;56(11):827–37, doi:10.1016/j.jacc.2010.05.028. Elsevier USA.
28. Olesen JB, Lip GYH, Hansen ML, Hansen PR, Tolstrup JS, Lindhardsen J, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: Nationwide cohort study. BMJ. 2011;342(7792):d124, doi:10.1136/bmj.d124.
29. Hijazi Z, Lindbäck J, Alexander JH, Hanna M, Held C, Hylek E, 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, doi:10.1093/eurheartj/ehw054.
30. Kim TH, Yang PS, Yu HT Jang E, Uhm JS, Kim JY, et al. Age threshold for ischemic stroke risk in atrial fibrillation cohort data covering the entire Korean population. Stroke. 2018;49(8):1872–9, doi:10.1161/STROKEAHA.118.021047.
31. Graham DJ, Reichman ME, Wernecke M, Hsueh YH, Izem R, Southworth MR, et al. Stroke, bleeding, and mortality risks in elderly medicare beneficiaries treated with dabigatran or rivaroxaban for nonvalvular atrial fibrillation. JAMA Intern Med. 2016;176(11):1662–71, doi:10.1001/jamainternmed.2016.5954.
32. 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), doi:10.1161/JAHA.117.005657.
33. Tamayo S, Peacock WF, Patel M, Sicignano N, Hopf KP, Fields LE, et al. Characterizing major bleeding in patients with nonvalvular atrial fibrillation: A pharmacovigilance study of 27 467 patients taking Rivaroxaban. Clin Cardiol. 2015;38(2):63–8, doi:10.1002/clc.22373.
34. Akhtar T, Fratti JDC, Mattumpuram J, Fugar S, Uprety A, Nwaichi C, et al. Factors associated with bleeding events in patients on rivaroxaban for non-valvular atrial fibrillation: A real-world experience. Int J Cardiol. 2020;320:78–82, doi:10.1016/j.ijcard.2020.06.032.
35. Steinberg BA, Shrader P, Thomas L, Ansell J, Fonarow GC, Gersh BJ, et al. Off-label dosing of non-vitamin K antagonist oral anticoagulants and adverse outcomes: The ORBIT-AF II registry. J Am Coll Cardiol. 2016;68(24):2597–604, doi:10.1016/j.jacc.2016.09.966.
36. Kumar S, Danik SB, Altman RK, Barrett CD, Lip GYH, Chatterjee S, et al. Non-vitamin K antagonist oral anticoagulants and antiplatelet therapy for stroke prevention in patients with atrial fibrillation: A meta-analysis of randomized controlled trials. Cardiol Rev. 2016;24(5):218–23, doi:10.1097/CRD.0000000000000088.
37. Lemesle G, Ducrocq G, Elbez Y, van Belle E, Goto S, Cannon CP, et al. Vitamin K antagonists with or without long-term antiplatelet therapy in outpatients with stable coronary artery disease and atrial fibrillation: Association with ischemic and bleeding events. Clin Cardiol. 2017;40(10):932–9, doi:10.1002/clc.22750.
38. Raccah BH, Perlman A, Zwas DR, Hochberg-Klein S, Masarwa R, Muszkat M, et al. Gender differences in efficacy and safety of direct oral anticoagulants in atrial fibrillation: Systematic review and network meta-analysis. Ann Pharmacother. 2018;52:1135–42, doi:10.1177/1060028018771264.
39. Goodman SG, Wojdyla DM, Piccini JP, et al. Factors associated with major bleeding events: Insights from the ROCKET AF trial (rivaroxaban once-daily oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation). J Am Coll Cardiol. 2014;63:891–900, doi:10.1016/j.jacc.2013.11.013.
40. Vinereanu D, Stevens SR, Alexander JH, et al. Clinical outcomes in patients with atrial fibrillation according to sex during anticoagulation with apixaban or warfarin: a secondary analysis of a randomized controlled trial. Eur Heart J. 2015;36:3268–75, doi:10.1093/eurheartj/ehv447.
41. Ntaios G, Papavasileiou V, Makaritsis K, Vemmos K, Michel P, Lip GYH. Real-world setting comparison of nonvitamin-K antagonist oral anticoagulants versus vitamin-K antagonists for stroke prevention in atrial fibrillation: A systematic review and meta-analysis. Stroke. 2017;48(9):2494–503, doi:10.1161/STROKEAHA.117.017549.
42. Malik AH, Yandrapalli S, Aronow WS, Panza JA, Cooper HA. Meta-analysis of direct-acting oral anticoagulants compared with warfarin in patients &75 years of age. Am J Cardiol. 2019;123(12):2051–7, doi:10.1016/j.amjcard.2019.02.060.
43. Menichelli D, del Sole F, di Rocco A, Farcomeni A, Vestri A, Violi F, et al. Real-world safety and efficacy of direct oral anticoagulants in atrial fibrillation: A systematic review and meta-analysis of 605 771 patients. Eur Heart J Cardiovasc Pharmacother. 2021;7(FI1):f11–9, doi:10.1093/ehjcvp/pvab002.
44. Manzoor BS, Walton SM, Sharp LK, Galanter WL, Lee TA, Nutescu EA. High number of newly initiated direct oral anticoagulant users switch to alternate anticoagulant therapy. J Thromb Thrombolysis. 2017;44(4):435–41, doi:10.1007/s11239-017-1565-2.
45. Romoli M, Marchetti G, Bernardini F, Urbinati S. Switching between direct oral anticoagulants: A systematic review and meta-analysis. J Thromb Thrombolysis. 2021, doi:10.1007/s11239-020-02367-2.
46. Marchetti G, Bernardini F, Romoli M, Urbinati S. Switching across direct oral anticoagulants: A real-life-setting pilot prospective study. J Cardiovasc Med (Hagerstown). 2021;22(6):453–8, doi:10.2459/JCM.0000000000001118.
47. Yao X, Abraham NS, Sangaralingham LR, Bellolio MF, McBane RD, Shah, et al. Effectiveness and safety of dabigatran, rivaroxaban, and apixaban versus warfarin in nonvalvular atrial fibrillation. J Am Heart Assoc. 2016;5(6), doi:10.1161/JAHA.116.003725.
48. Staerk L, Gerds TA, Lip GYH, Ozenne B, Bonde AN, Lamberts M, et al. Standard and reduced doses of dabigatran, rivaroxaban and apixaban for stroke prevention in atrial fibrillation: a nationwide cohort study. J Intern Med. 2018;283(1):45–55, doi:10.1111/joim.126833.
49. Ruiz Ortiz M, Muñiz J, Míguez PR, Roldán I, Marín F, Esteve-Pastor MA, et al. Inappropriate doses of direct oral anticoagulants in real-world clinical practice: Prevalence and associated factors. A subanalysis of the FANTASIIA registry. Europace. 2018;20(10):1577–83, doi:10.1093/europace/eux316.
50. Devereaux PJ, Anderson DR, Gardner MJ, Putnam W, Flowerdew GJ, Brownell BF, et al. Differences between perspectives of physicians and patients on anticoagulation in patients with atrial fibrillation: Observational study. Br Med J. 2001;323(7323):1218–21, doi:10.1136/bmj.323.7323.1218.