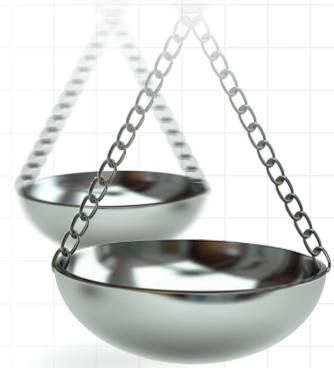
Short Communication

For reprint orders, please contact: reprints@futuremedicine.com



Journal of **Comparative Effectiveness Research**

Thromboembolic and bleeding events with rivaroxaban in clinical practice in Spain: impact of inappropriate doses (the EMIR study)

Marcelo Sanmartín Fernández*[1], Francisco Marín[2], Carles Rafols[3], Fernando Arribas[4], Vivencio Barrios[5], Juan Cosín-Sales[6] & Manuel Anguita Sánchez[7]

[1]Department of Cardiology, Hospital Ramón y Cajal, Madrid, Spain
[2]Department of Cardiology, Hospital Clínico Universitario Virgen de la Arrixaca, IMIB-Arrixaca, University of Murcia, CIBERCV, Murcia, Spain
[3]Department of Medical Affairs, Bayer Hispania, Barcelona, Spain
[4]Department of Cardiology, Hospital Universitario 12 de Octubre; Department of Medicine, Facultad de Medicina, Universidad Complutense de Madrid (UCM); Instituto de Investigación Sanitaria Hospital 12 de Octubre (imas12); CIBERCV, Madrid, Spain
[5]Department of Cardiology, Hospital Ramón y Cajal; Alcalá University, Madrid, Spain
[6]Department of Cardiology, Hospital Arnau de Vilanova, Valencia, Spain
[7]Department of Cardiology, Hospital Universitario Reina Sofia, IMIBIC, University of Córdoba, Córdoba, Spain
*Author for correspondence: msanfer@me.com

Aim: To analyze the frequency and variables related to inappropriate rivaroxaban dosage in clinical practice and its impact on outcomes after 2 years. **Materials & methods:** Postauthorization, observational, multicenter study, in which atrial fibrillation patients, treated with rivaroxaban ≥6 months were included. **Results:** A total of 1421 patients (74.2 ± 9.7 years, CHA_2DS_2-VASc 3.5 ± 1.6) were included. Overall, 22.9% received rivaroxaban 15 mg. The proper dose of rivaroxaban was taken by 83.3% (9.7% underdosed, 7.0% overdosed). Older age and renal insufficiency were associated with inadequate rivaroxaban dosage. There was a trend toward higher all-cause mortality among underdosed patients (adjusted hazard ratio 1.39; 95% CI 0.75–2.58), and more bleedings in overdosed patients (2.29 vs 0.80 events/100 patient-years; p = 0.14). **Conclusion:** In clinical practice, rivaroxaban is properly dosed in most patients.

First draft submitted: 17 December 2020; Accepted for publication: 12 February 2021; Published online: 31 March 2021

Keywords: atrial fibrillation • dosage • major bleeding • overdosage • rivaroxaban • stroke • underdosage

Most patients with nonvalvular atrial fibrillation (NVAF) require anticoagulation therapy to reduce the risk of ischemic stroke and systemic embolism [1]. Direct oral anticoagulants (DOACs) have a wide therapeutic window and provide a predictable anticoagulant effect [2]. Clinical trials have shown that DOACs have a better risk–benefit profile than vitamin K antagonists (VKAs) [3].

Given the potentially major differences between 'real-life' patients and those included in clinical trials [4,5], it is mandatory to ascertain whether the results observed in clinical trials can be extended to everyday practice and whether these drugs are properly used [6–13]. In fact, data from a meta-analysis suggest that the effectiveness and safety of DOACs in clinical practice may differ not only between the drugs themselves, but also in terms of the results of their respective pivotal clinical trials [14]. This could be associated, at least in part, with inappropriate dosage of DOACs, which could in turn lead to more frequent thromboembolic or bleeding events [6–13]. As a result, it is necessary to determine the factors underlying incorrect prescription of DOACs and their impact on clinical outcomes [15].

The dosage of DOACs depends on various clinical characteristics, with rivaroxaban being the simplest to adjust, as it relies only on renal function [2]. The aims of this study were to analyze the use of rivaroxaban in clinical practice and to determine the frequency and predictors of inappropriate dosing, along with its possible impact on thromboembolic and bleeding events after 2 years of follow-up.

Future Medicine

Materials & methods

EMIR (**E**studio observacional para la identificación de los factores de riesgo asociados a eventos cardiovasculares **mayores** en pacientes con **fi**brilación auricular no valvular tratados con un anticoagulante oral directo [**R**ivaroxaban] ["Observational study to identify risk factors associated with major cardiovascular events in patients with NVAF treated with a DOAC [rivaroxaban]") was a postauthorization, observational and multicenter study aimed at ascertaining the predictors of major cardiovascular events in NVAF patients treated with rivaroxaban for at least 6 months by different specialists in Spain. Patients were followed up for 2.5 years. In this study, the appropriateness of the dosage of rivaroxaban and the related outcomes (thromboembolic events and major bleeding) were analyzed after 2 years of follow-up. Overdosage was defined as creatinine clearance (Cockcroft–Gault) <50 ml/min with rivaroxaban 20 mg and underdosage as creatinine clearance ≥50 ml/min with rivaroxaban 15 mg.

The study population comprised NVAF patients aged ≥18 years of both sexes who had been treated with rivaroxaban for at least 6 months before being enrolled. The study population excluded patients participating in a clinical trial, patients starting treatment with rivaroxaban after the inclusion period and patients with severe cognitive impairment, chronic infectious disease, systemic autoimmune disease, active cancer or significant liver insufficiency. All patients gave their written consent prior to enrollment. The study was approved by each participating Institutional Review Board.

Baseline data were recorded using a specific electronic case report form and included biodemographic data (age, sex, level of dependency, type of atrial fibrillation [AF]), physical examination (weight, BMI, heart rate, blood pressure), thromboembolic data ($CHADS_2$ [congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or TIA or thromboembolism (doubled)] and CHA_2DS_2-VASc [congestive heart failure, hypertension, age ≥75 years [doubled], diabetes mellitus, prior stroke or TIA or thromboembolism [doubled], vascular disease, age 65–74 years, sex category]), bleeding data (HAS-BLED [hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR [international normalized ratio], elderly, drugs/alcohol]), cardiovascular risk factors (hypertension, dyslipidemia, diabetes, smoking status), concomitant structural or vascular disease (heart failure, ischemic heart disease, renal insufficiency, prior cerebrovascular disease, peripheral artery disease, aortic plaque, venous thromboembolic disease and prior systemic embolism). Conditions that increase the risk of bleeding (e.g., labile INR in patients taking VKAs before starting rivaroxaban, alcohol intake, falls) were also recorded. Dependency was classified as autonomous (no dependency), partial dependency to daily activities or complete dependency to daily activities.

Previous antithrombotic treatment before starting rivaroxaban therapy, current dose of rivaroxaban, and the appropriateness of this dose (correct dose, overdosage or underdosage) were analyzed. For the purpose of this analysis, overdosage was considered to have occurred when a patient with a Cockcroft–Gault creatinine clearance <50 ml/min was taking rivaroxaban 20 mg and underdosage when a patient with a Cockcroft–Gault creatinine clearance ≥50 ml/min was taking rivaroxaban 15 mg. Factors associated with prescribing inadequate doses of rivaroxaban, underdosage and overdosage were also analyzed.

Thromboembolic events (stroke, transient ischemic attack, systemic embolism or myocardial infarction), and major bleeding (following International Society of Thrombosis and Haemostasis definition) [16]. In addition, during this period, all-cause death and cardiovascular death that included sudden cardiac death and death from heart failure, myocardial infarction, arrhythmia or percutaneous or surgical coronary revascularization were analyzed. Outcomes were analyzed according to the appropriateness of the rivaroxaban dosage.

Statistical methods

Categorical variables were expressed as absolute (n) and relative frequencies (%). Continuous variables were expressed as mean and standard deviation. Categorical variables were compared using the chi-square test or the Fisher exact test when appropriate. When 2 means were compared, the t-test or the Mann–Whitney test was used, as applicable. A bivariate logistic regression analysis was performed to evaluate which factors were associated with an inadequate dose. The analysis also included age, sex, previous major bleeding, diabetes, type of AF (paroxysmal vs permanent), ischemic heart disease, coronary revascularization, use of aspirin or clopidogrel, renal insufficiency, prior stroke and the level of dependency. A bivariate logistic regression analysis was performed to evaluate which factors were associated with underdosage or overdosage. The analysis included age, sex, previous major bleeding, diabetes, type of AF (permanent vs paroxysmal), ischemic heart disease, coronary revascularization, concomitant use of aspirin or clopidogrel, prior stroke, dependency, anemia (baseline hemoglobin <12 g/dl), falls in the previous

year, and treatment with verapamil, dronedarone or amiodarone. Those factors with a p-value < 0.150 in the bivariate analysis were included in the multivariate analysis through automatic forward stepwise selection.

The analysis was based on events during the 2 years of follow-up after the baseline visit. Follow-up time in years from the date of the baseline visit to the last follow-up (maximum 2 years) was calculated. The event rate was calculated using the following formula: rate = event/time (years)*100. The Fisher exact test was used to compare events between patients who received the appropriate dosage and those who did not (underdosage and overdosage).

Unadjusted and adjusted Cox models were constructed to estimate event rates at 2 years. The time in years from the baseline visit to the first recorded event or to last follow-up visit in cases of not presenting the event (maximum 2 years), was calculated. To calculate variables associated with overdosing/underdosing, a logistic regression was performed, with 16 factors included for over/underdosing and 13 factors for inadequate dosing. All representative factors were included in the analysis. Hazard ratios were adjusted for age, sex, type of AF, diabetes, hypertension, previous major bleeding, ischemic stroke + systemic embolism + transient ischemic attack, congestive heart failure, vascular disease (peripheral artery and/or aortic plaque), smoking, alcohol use and renal insufficiency (glomerular filtration rate <60 ml/min). Hazard ratios with 95% CIs were presented. Missing data or lost values were not imputed to avoid information bias. Missing data for important variables were controlled by filters when data were collected from the electronic case report form. A level of statistical significance of 0.05 was applied in all the statistical tests. The data were analyzed using the statistical package SPSS (v18.0 or superior).

Results

A total of 1503 patients were initially enrolled in the study. After excluding 82 patients because of lack of data or inconsistent data, 1421 patients were finally analyzed.

Table 1 shows the baseline clinical characteristics of the study population. Mean age was 74.2 ± 9.7 years, 55.5% of patients were men, and total or partial dependency was reported in 9.9% of patients. The mean CHA_2DS_2-VASc score was 3.5 ± 1.6 and the mean HAS-BLED score was 1.6 ± 1.0. Major comorbidities were common, such as heart failure in 22.7%, ischemic heart disease in 16.5%, renal insufficiency in 15.8% and prior cerebrovascular disease in 12.5%.

A total of 1096 patients (77.1%) were taking rivaroxaban 20 mg and 325 (22.9%) were taking rivaroxaban 15 mg. At baseline, 238 patients (16.7%) were taking an inadequate dose of rivaroxaban, namely, underdosage in 138 (9.7%) and overdosage in 100 (7.0%), according to the Cockcroft–Gault equation. If estimated glomerular filtration rate is taken into consideration, the percentage of patients underdosed and overdosed would have been, respectively, 14.8 and 3.7% according to the MDRD-4 formula and 12.1 and 5.4% according to CKD-EPI. After 2 years of follow-up, mean creatinine clearance (Cockcroft–Gault) increased slightly from 76.0 ± 30.5 ml/min at baseline to 77.0 ± 33.8 ml/min (p = 0.014). The number of overdosed patients decreased from 100 (7.0%) to 47 (3.3%) during the study period.

At baseline, compared with patients taking the proper dose of rivaroxaban, underdosed patients were older (78.4 ± 8.7 vs 73.0 ± 9.6 years; p < 0.001) and less autonomous (77.9 vs 91.9%; p < 0.001) and had a higher thromboembolic risk (CHA_2DS_2-VASc score: 4.0 ± 1.7 vs 3.4 ± 1.5; p < 0.001), a higher bleeding risk (HAS-BLED score: 2.0 ± 1.0 vs 1.5 ± 1.0; p < 0.001) and more frequent renal insufficiency (31.9 vs 12.9%; p < 0.001). Compared with patients taking the proper dose of rivaroxaban, overdosed patients were older (82.3 ± 5.6 vs 73.0 ± 9.6 years; <0.001) and less autonomous (82.7 vs 91.9%; p = 0.003) and had lower weight (67.4 ± 9.7 vs 80.7 ± 15.9 Kg; p < 0.001), a higher thromboembolic risk (CHA_2DS_2-VASc score: 4.2 ± 1.3 vs 3.4 ± 1.5; p < 0.001), and a higher bleeding risk (HAS-BLED score: 1.9 ± 0.9 vs 1.5 ± 1.0; p < 0.001) and more frequent renal insufficiency (28.0 vs 12.9%; p < 0.001). However, diabetes was less frequent in this group (16.0 vs 27.5%; p = 0.013; Table 1).

Factors associated with the prescription of an inadequate dose of rivaroxaban are reported in Table 2. In the bivariate analysis, older age, female sex, renal insufficiency, prior cerebrovascular disease and partial or total dependency were associated with inappropriate dosage. Of note, labile INR did not have any impact on dosage. However, in the multivariate analysis, the only remaining independent factors were age (OR 1.09; 95% CI 1.07–1.11; p < 0.001) and renal insufficiency (OR 2.00; 95% CI 1.41–2.84; p < 0.001). Variables associated with underdosage and overdosage are reported in Table 3. In the bivariate analysis, older age, permanent AF (versus paroxysmal AF), dependency (versus autonomous) and anemia were associated with underdosage. However, in the multivariate analysis, the only remaining independent factors were age (OR 1.04; 95% CI 1.02–1.07; p < 0.001) and dependency (OR 2.13; 95% CI 1.43–3.18; p = 0.003). In the bivariate analysis, old age, female sex, absence

Table 1. Clinical characteristics of the study population at baseline (n = 1421).

Clinical characteristics	Total (n = 1421; 100%)	Proper dose (n = 1183; 83.3%)	Underdosed (n = 138; 9.7%)	p-value (underdosage vs proper dose)	Overdosed (n = 100; 7.0%)	p-value (overdosage vs proper dose)
Biodemographic data						
Age (years)	74.2 ± 9.7	73.0 ± 9.6	78.4 ± 8.7	**<0.001**	82.3 ± 5.6	**<0.001**
Sex (men), n (%)	788 (55.5)	673 (56.9)	74 (53.6)	0.464	41 (41.0)	**0.002**
Level of dependency, n (%) – No dependency – Partial dependency – Total dependency	 1,249 (87.9) 126 (8.9) 14 (1.0)	 1,066 (91.9) 88 (7.6) 6 (0.5)	 102 (77.9) 21 (16.0) 8 (6.1)	 <0.001	 81 (82.7) 17 (17.3) 0	 0.003
Type of AF, n (%) – Paroxysmal – Persistent – Long-standing persistent AF – Permanent	 569 (40.0) 259 (18.2) 53 (3.7) 532 (37.4)	 481 (40.9) 218 (18.5) 46 (3.9) 431 (36.6)	 48 (34.8) 22 (15.9) 3 (2.2) 65 (47.1)	 0.103	 40 (40.4) 19 (19.2) 4 (4.0) 36 (36.4)	 0.998
Physical examination						
Systolic blood pressure (mmHg)	131.5 ± 16.4	131.8 ± 16.2	128.1 ± 16.8	**0.031**	132.5 ± 17.2	0.763
Diastolic blood pressure (mmHg)	76.2 ± 10.5	76.6 ± 10.6	73.8 ± 10.1	**0.007**	75.0 ± 9.4	0.231
Heart rate (bpm)	71.9 ± 14.8	71.7 ± 14.9	71.8 ± 14.0	0.835	75.4 ± 14.8	**0.008**
Weight (kg)	79.7 ± 15.8	80.7 ± 15.9	80.3 ± 15.2	0.579	67.4 ± 9.7	**<0.001**
BMI (kg/m^2)	29.1 ± 4.9	29.3 ± 4.9	29.3 ± 5.3	0.693	26.0 ± 3.7	**<0.001**
Risk stratification						
$CHADS_2$ score	2.0 ± 1.2	1.9 ± 1.2	2.4 ± 1.4	**<0.001**	2.3 ± 1.1	**<0.001**
CHA_2DS_2-VASc score	3.5 ± 1.6	3.4 ± 1.5	4.0 ± 1.7	**<0.001**	4.2 ± 1.3	**<0.001**
2MACE score	2.4 ± 1.0	2.4 ± 1.0	2.6 ± 1.2	0.060	2.4 ± 0.7	0.155
HAS-BLED score	1.6 ± 1.0	1.5 ± 1.0	2.0 ± 1.0	**<0.001**	1.9 ± 0.9	**<0.001**
Cardiovascular risk factors						
Hypertension, n (%) – Systolic blood pressure >160 mmHg, n (%)	1,119 (78.7) 51 (3.6)	938 (79.3) 41 (4.4)	104 (75.4) 4 (3.8)	0.285 0.999	77 (77.0) 6 (7.8)	0.589 0.161
Dyslipidemia, n (%)	784 (55.2)	664 (56.1)	68 (49.3)	0.125	52 (52.0)	0.425
Diabetes, n (%)	381 (26.8)	325 (27.5)	39 (28.3)	0.844	16 (16.0)	**0.013**
Smoking, n (%) – Current – Ex-smoker <1 year – Ex-smoker >1 year	119 (8.4) 72 (5.1) 24 (1.7) 23 (1.6)	109 (9.2) 63 (5.4) 23 (1.9) 23 (1.9)	7 (5.1) 6 (4.3) 1 (0.8) 0	0.104 0.492	3 (3.0) 3 (3.0) 0 0	**0.035** **0.567**
Vascular disease						
Heart failure, n (%)	323 (22.7)	260 (22.0)	42 (30.4)	0.104	21 (21.0)	0.724
Ischemic heart disease, n (%) – Revascularization, n (%)	235 (16.5) 183 (12.9)	196 (16.6) 153 (12.9)	28 (20.2) 21 (15.2)	0.634 0.453	11 (11.0) 9 (9.0)	0.095 0.256
Renal insufficiency,† n (%) – Severe renal insufficiency	225 (15.8) 14 (1.0)	153 (12.9) 14 (9.2)	44 (31.9) 0	**<0.001** **0.043**	28 (28.0) 0	**<0.001** **0.132**
Prior cerebrovascular disease, n (%)	177 (12.5)	137 (11.6)	24 (17.4)	**0.048**	16 (16.0)	0.190
Peripheral artery disease, n (%)	58 (4.1)	47 (4.0)	8 (5.8)	0.310	3 (3.0)	0.792
Aortic plaque, n (%)	46 (3.2)	35 (3.0)	4 (2.9)	0.999	7 (7.0)	**0.039**
Venous thromboembolic disease, n (%)	32 (2.3)	26 (2.2)	4 (2.9)	0.545	2 (2.0)	0.999
Prior systemic embolism, n (%)	14 (1.0)	13 (1.1)	0	0.383	1 (1.0)	0.999
Other conditions						
Labile INR, n (%)	372 (26.2)	304 (25.7)	44 (31.9)	0.118	24 (24.0)	0.709
Drugs or alcohol, n (%)	129 (9.1)	121 (10.2)	3 (2.2)	**0.002**	5 (5.0)	0.092
Medication usage predisposing to bleeding‡, n (%)	119 (8.4)	93 (7.9)	20 (14.5)	**0.008**	6 (6.0)	0.503
Cancer, n (%)	83 (5.8)	61 (5.2)	14 (10.1)	**0.017**	8 (8.0)	0.226
Falls in the last year, n (%)	86 (6.1)	65 (5.5)	10 (7.2)	0.400	11 (11.0)	**0.025**

†Glomerular filtration rate <60 ml/min (investigator assessment).
‡Nonsteroidal anti-inflammatory drugs or antiplatelets at least once a week.
Bold terms indicate significant p-values.
AF: Atrial fibrillation; eFGR: Estimated glomerular filtration rate; INR: International normalized ratio.

Table 1. Clinical characteristics of the study population at baseline (n = 1421) (cont.).

Clinical characteristics	Total (n = 1421; 100%)	Proper dose (n = 1183; 83.3%)	Underdosed (n = 138; 9.7%)	p-value (underdosage vs proper dose)	Overdosed (n = 100; 7.0%)	p-value (overdosage vs proper dose)
Previous major bleeding, n (%) – Gastrointestinal – Intracranial – Hematuria – Others	46 (3.2) 17 (1.2) 8 (0.6) 8 (0.6) 13 (0.8)	40 (3.4) 16 (1.3) 7 (0.6) 6 (0.5) 13 (1.0)	4 (2.92) 1 (0.73) 1 (0.73) 1 (0.73) 1 (0.73)	0.999 0.999 0.566 0.513 0.593	2 (2.0) 0 0 1 (1.0) 1 (1.0)	0.767 0.517 0.999 0.309 0.999
No severe cognitive impairment, n (%)	33 (2.3)	24 (2.0)	8 (5.8)	**0.014**	1 (1.0)	0.715
Hepatic failure, n (%)	11 (0.8)	7 (0.6)	3 (2.2)	0.077	1 (1.0)	0.478
Biochemical parameters						
Hemoglobin (g/dl)	14.1 ± 1.7	14.1 ± 1.6	13.7 ± 1.8	**0.036**	13.7 ± 1.6	**0.033**
Creatinine clearance, ml/min (Cockroft–Gault) eFGR, ml/min/1.73m^2 (MDRD4) eFGR, ml/min/1.73m^2 (CKD-EPI)	76.0 ± 30.5 74.8 ± 21.5 69.6 ± 18.8	78.2 ± 31.1 76.7 ± 21.3 71.7 ± 18.2	67.5 ± 17.1 73.5 ± 19.8 66.9 ± 15.0	<0.001 0.023 <0.001	41.6 ± 7.7 54.3 ± 12.9 49.8 ± 11.8	<0.001 <0.001 <0.001

†Glomerular filtration rate <60 ml/min (investigator assessment).
‡Nonsteroidal anti-inflammatory drugs or antiplatelets at least once a week.
Bold terms indicate significant p-values.
AF: Atrial fibrillation; eFGR: Estimated glomerular filtration rate; INR: International normalized ratio.

Table 2. Factors associated with inadequate dosage†.

Independent variables	Bivariate analysis						Multivariate analysis					
	Dependent variable						Dependent variable					
	B	Standard error	p-value	OR	95% CI lower limit	95% CI upper limit	B	Standard error	p-value	OR	95% CI lower limit	95% CI upper limit
Age	0.09	0.01	**0.000**	1.10	1.08	1.12	0.09	0.01	**0.000**	1.09	1.07	1.11
Sex (women vs men)	0.35	0.14	**0.02**	1.41	1.07	1.87						
Prior major bleeding	-0.30	0.44	0.50	0.74	0.31	1.76						
Type 2 diabetes	-0.26	0.17	0.13	0.77	0.55	1.08						
Type of AF (permanent vs paroxysmal)	0.25	0.16	0.12	1.28	0.94	1.75						
Revascularization	0.17	0.14	0.23	1.19	0.90	1.57						
Aspirin	0.17	0.275	0.53	1.18	0.70	1.99						
Clopidogrel	0.38	0.44	0.38	1.46	0.62	3.44						
Renal insufficiency‡	1.07	0.17	**0.000**	2.92	2.11	4.04	0.69	0.18	**0.000**	2.00	1.41	2.84
Prior cerebrovascular disease	0.43	0.20	**0.03**	1.54	1.05	2.26						
Partial dependency	0.92	0.21	**0.000**	2.52	1.67	3.80						
Total dependency	2.05	0.56	0.000	7.77	2.66	22.65						

†Only those factors with a p-value < 0.150 in the bivariate analysis were included in the multivariate analysis.
‡Glomerular filtration rate <60 ml/min (Investigator assessment).
Bold terms indicate significant p-values.
AF: Atrial fibrillation; OR: Odds ratio.

of Type 2 diabetes, dependency and falls in the previous year were associated with overdosage. However, the only remaining independent factors were age (OR 1.13; 95% CI 1.10–1.16; p < 0.001) and absence of Type 2 diabetes (OR 0.47; 95% CI 0.26–0.85; p = 0.013).

Clinical outcomes after 2 years of follow-up are presented in Table 4. Cumulative time was 2537.56 years. Annual rates for death, thromboembolic events (stroke, transient ischemic attack, systemic embolism or myocardial infarction), and major bleeding were 2.68, 0.71 and 0.95 events per 100 patient-years, respectively in total population. The equivalent values for underdosed and overdosed patients were 5.76, 0.89 and 1.33 events per 100 patient-years and 3.43, 1.14 and 2.29, respectively. There was a trend toward higher all-cause mortality among underdosed patients (unadjusted HR 2.51; 95% CI 1.36–4.63; adjusted HR 1.39; 95% CI 0.75–2.58; Supplementary Table 1). No significant differences were found in cardiovascular mortality among underdosed

Table 3. Factors associated with underdosage and overdosage†.

Independent variables	Factors associated with underdosage											
	Bivariate analysis						Multivariate analysis					
	Dependent variable						Dependent variable					
	B	Standard error	p-value	OR	95% CI lower limit	95% CI upper limit	B	Standard error	p-value	OR	95% CI lower limit	95% CI upper limit
Age	0.06	0.01	**0.000**	1.06	1.04	1.08	0.04	0.01	**0.000**	1.04	1.02	1.07
Sex (women vs men)	0.08	0.18	0.65	1.09	0.76	1.54						
Previous bleeding	-0.13	0.53	0.81	0.88	0.31	2.50						
Type 2 diabetes	0.10	0.20	0.62	1.11	0.75	1.64						
Type of AF (permanent vs paroxysmal)	0.41	0.20	**0.04**	1.51	1.02	2.24						
Revascularization	0.22	0.25	0.39	1.24	0.76	2.03						
Prior cardiac disease	0.27	0.18	0.14	1.31	0.92	1.87						
Antiplatelet therapy	0.14	0.31	0.64	1.16	0.63	2.11						
Prior cerebrovascular disease	0.44	0.24	0.07	1.56	0.97	2.49						
Dependency (dependency vs autonomous)	1.08	0.23	**0.000**	2.94	1.86	4.64	0.76	0.20	**0.000**	2.13	1.43	3.18
Anemia	0.64	0.27	**0.02**	1.89	1.11	3.20						
Falls in the last year	0.22	0.35	0.54	1.24	0.63	2.46						
Verapamil	-18.98	14210.36	0.99	0.000	0.000	.						
Dronedarone	0.072	0.62	0.91	1.07	0.32	3.60						
Amiodarone	-0.34	0.33	0.30	0.71	0.38	1.35						
	Factors associated with overdosage											
	Bivariate analysis						Multivariate analysis					
	Dependent variable						Dependent variable					
Age	0.13	0.02	**0.000**	1.13	1.10	1.17	0.12	0.02	**0.000**	1.13	1.10	1.16
Sex (women vs men)	0.63	0.21	**0.003**	1.87	1.24	2.83						
Previous bleeding	-0.52	0.73	0.47	0.59	0.14	2.48						
Type 2 diabetes	-0.80	0.30	**0.006**	0.45	0.25	0.80	-0.75	0.30	**0.013**	0.47	0.26	0.85
Type of AF (permanent vs paroxysmal)	-0.04	0.24	0.86	0.96	0.60	1.53						
Revascularization	-0.43	0.36	0.23	0.65	0.32	1.32						
Prior cardiac disease	0.003	0.21	0.99	1.003	0.67	1.51						
Antiplatelet therapy	0.09	0.36	0.82	1.09	0.53	2.22						
Prior cerebrovascular disease	0.32	0.29	0.27	1.37	0.78	2.40						
Dependency (dependency vs autonomous)	0.69	0.28	**0.015**	1.99	1.14	3.47						
Anemia	0.24	0.35	0.49	1.27	0.64	2.53						
Falls in the last year	0.72	0.34	**0.035**	2.05	1.05	4.01						
Verapamil	0.64	1.07	0.55	1.90	0.23	15.57						
Dronedarone	-0.02	0.74	0.97	0.98	0.23	4.17						
Amiodarone	0.16	0.32	0.63	1.17	0.62	2.19						

†Only those factors with a p-value <0.150 in the bivariate analysis were included in the multivariate analysis.
Bold terms indicate significant p-values.
AF: Atrial fibrillation; OR: Odds ratio.

patients (0.44 vs 0.75 events per 100 patient-years; p = 0.99). More bleedings were recorded in overdosed patients, although the difference was not significant (2.29 vs 0.80 events per 100 patient-years; p = 0.14; Table 4).

Discussion

The main findings of this study are as follows: approximately 17% of patients treated with rivaroxaban for NVAF received off-label doses, more commonly the lower dose; advanced age and high dependency explained most of

Table 4. Clinical outcomes at 2-year follow-up.

Events	Total population (n = 1421)		Proper dose (n = 1183)		Underdosage (n = 138)		p-value (underdosed vs proper dose)	Overdosage (n = 100)		p-value (overdosed vs proper dose)
	n of events	Annual rate of events† (cumulative time = 2537.56 years)	n of events	Annual rate of events† (cumulative time = 2136.99 years)	n of events	Annual rate of events† (cumulative time = 225.59 years)		n of events	Annual rate of events† (cumulative time = 174.98 years)	
Death	68	2.68	49	2.29	13	5.76	**0.01**	6	3.43	0.47
– CV death	18	0.71	16	0.75	1	0.44	0.99	1	0.57	0.99
– Heart failure death	11	0.43	9	0.42	1	0.44	0.99	1	0.57	0.99
Thromboembolic events‡	18	0.71	14	0.66	2	0.89	0.92	2	1.14	0.69
– Ischemic stroke + SE + TIA	13	0.51	10	0.47	1	0.44	0.99	2	1.14	0.46
– Ischemic stroke	10	0.39	7	0.33	1	0.44	0.99	2	1.14	0.29
– Myocardial infarction	5	0.20	4	0.19	1	0.44	0.79	0	0.00	0.99
Major bleeding	24	0.95	17	0.80	3	1.33	0.60	4	2.29	0.14
– Fatal bleeding	2	0.08	1	0.05	1	0.44	0.36	0	0	0.99
– Intracranial bleeding	7	0.28	6	0.28	0	0	0.99	1	0.57	0.85

†Events per 100 patient-years.
‡Thromboembolic events: ischemic stroke + transient ischemic attack + systemic embolism + myocardial infarction.
CV: Cardiovascular; SE: Systemic embolism; TIA: Transient ischemic attack.

the underdosing prescriptions; after a 2-year follow-up period, rates of thromboembolic or bleeding complications were lower than expected based on data from other prospective real-world registries.

The ROCKET-AF trial, which was performed in a population with a high thromboembolic risk, showed that rivaroxaban was at least as effective as warfarin for the prevention of stroke or systemic embolism with the same risk of major bleeding, but with a lower risk of fatal and intracranial bleeding [17]. Compared with the rivaroxaban arm of the ROCKET-AF trial, both the number of comorbidities and the thromboembolic risk were lower ($CHADS_2$ score 3.5 vs 2.0), even though the patients in our study were slightly older [17]. The XANTUS study was the first real-world, prospective and observational study of patients treated with rivaroxaban for prevention of stroke in AF, with a thromboembolic risk that was similar to that reported in our study [18]. Other studies of NVAF patients treated with rivaroxaban in Spain have revealed a similar clinical profile [19–22]. Therefore, these data suggest that the EMIR population is highly representative.

In the EMIR study, the proportion of patients taking 20 and 15 mg of rivaroxaban (77 and 23%, respectively) was similar to that of the ROCKET-AF trial (20 mg dose: 79.3%) and the XANTUS real-world study (79 and 21%, respectively) [17,18]. We found that approximately 83% of patients were taking the correct dose of rivaroxaban according to approved recommendations, 10% of patients were underdosed and 7% were overdosed. Remarkably, during the study, the proportion of overdosed patients decreased to only 3%. As a result, our data showed that in most cases, rivaroxaban is adequately prescribed in clinical practice, and that only a small proportion of patients are underdosed. However, there were relevant differences in the numbers according to the method used to estimate renal function and this could have an impact on the appropriateness of dosage in clinical practice.

Various studies have analyzed the frequency of inappropriate dosing of rivaroxaban. In the XANTUS study, 15% of patients with a creatinine clearance ≥50 ml/min received rivaroxaban 15 mg, whereas 36% of patients with a creatinine clearance <50 ml/min received rivaroxaban 20 mg [18]. In a preplanned pooled analysis of the XANTUS, XANAP (Asia) and XANTUS-EL (Latin America and EMEA Region) registries, 18.3% of patients with a creatinine clearance ≥50 ml/min received rivaroxaban 15 mg [23].

Although other authors have found that a higher risk of bleeding may be associated with the use of low doses of DOACs [9], in our study, advanced age and dependency, but not bleeding risk, were associated with underdosage. In fact, we found thromboembolic and bleeding risk to be similar in underdosed and overdosed patients. Many authors report that underdosage is more common in elderly patients, particularly in those with creatinine clearance consistent with the dose reduction criteria [7,24,25]. Of note, some studies, but not all, have shown that dependency and frailty, that are commonly observed in elderly patients, may be associated with underdosage [26,27]. However, dosage of DOACs should be performed according to the summary of product characteristics [2]. This is very

relevant, since some studies have shown that inadequate prescription may be associated with worse outcomes and that this is more evident when adjustment of the DOACs prescribed is more complex [10–12,15,26,28,29]. Thus, recent data from the GARFIELD-AF registry have shown a higher risk of all-cause mortality – mainly cardiovascular – for underdosing [29]. We recorded numerically higher rates of death and thromboembolic and bleeding outcomes in underdosed patients, although these numbers did not reach statistical significance, likely due to the low number of events during follow-up. On the other hand, frailty is frequent in patients with AF and is associated with adverse clinical outcomes, partially due to lower rates of adequate anticoagulation in this population [30,31]. As a result, the dosage of rivaroxaban should also be based on renal function in this population.

Although less common, overdosage is also recorded with rivaroxaban. In our study, the proportion of overdosed patients decreased from 7 to 3% over time. Due to pharmacovigilance safety reasons, the investigators were advised in case of inappropriate dosage according to the summary of product characteristics (Cockcroft–Gault creatinine clearance). Then, the investigators could modify the dosage according to their clinical criteria, but this only occurred in case of overdosing during the second year of follow-up. While study results vary, most are similar to those we report [19,21,32–34]. Of note, after 2 years of treatment with rivaroxaban, renal function remained stable. Compared with patients prescribed warfarin, patients treated with DOACs may experience a less pronounced decline in renal function [35], thus indicating an added value in the management of patients with NVAF compared with VKAs [36].

After 2 years of follow-up, rates for death, thromboembolic events and major bleeding were 2.68, 0.71 and 0.95 events per 100 patient-years, respectively. The equivalent values were 1.9, 1.7 and 3.6 per 100 patient-years, respectively, in the ROCKET-AF trial (rivaroxaban-arm) and 1.9, 1.8 and 2.1 per 100 patient-years, respectively in the XANTUS study [17,18]. Therefore, in clinical practice, thromboembolic and bleeding events are less frequent than in the pivotal clinical trial, likely because of differences in the patients' clinical profile. Of note, bleeding outcomes occur more frequently during the first weeks after initiating treatment, and in the EMIR study, patients were on continuous rivaroxaban therapy, thus potentially leading these events to be underrepresented.

In addition, real-life studies have shown lower rates of thromboembolic complications of rivaroxaban compared with warfarin [14,37]. These data strongly suggest that rivaroxaban can be safely used in clinical practice.

Study limitations

Our study is subject to a series of limitations. First, as this was an observational study, no control group was available, and only indirect comparisons could be made with data from other studies. Second, although rivaroxaban was prescribed appropriately in most patients, a limited number of patients were underdosed or overdosed and this reduced the power of the study to detect differences. However, the meticulousness of the data recorded and the consistency of the results with available evidence reduce this potential bias. Third, medication adherence was not assessed and this could have an impact on the results. However, the number of events was low, suggesting that rivaroxaban persistence was high. Finally, as follow-up was limited to 2 years, it is uncertain whether thromboembolic or bleeding events could vary beyond this period.

Conclusion

Our study confirms that dosing of rivaroxaban for prevention of thromboembolic events in patients with NVAF is appropriate in most patients in current clinical practice in Spain. Older age and renal insufficiency are the main predictors of inadequate prescription. After a 2-year follow-up period, rates of death and thromboembolic and major bleeding events are low. There was a trend toward a higher risk of death among underdosed patients. As a result, adequate prescription of rivaroxaban according to renal function should be strongly encouraged.

Summary points

- Published data suggest that the effectiveness and safety of direct oral anticoagulants in clinical practice may differ from their respective pivotal clinical trials.
- This could be associated, at least in part, with inappropriate dosage of direct oral anticoagulants, which could in turn lead to more frequent thromboembolic or bleeding events.
- In Spain, patients taking rivaroxaban are old and have a high thromboembolic risk.
- Dosage of rivaroxaban is properly performed in most patients in Spain.
- Older age and renal insufficiency are the main predictors of inadequate prescription.
- After 2 years of treatment, rates of death, thromboembolic events, major bleeding, and fatal bleeding are low.
- There is a trend toward a higher death risk among underdosed patients.
- There is a trend toward a higher bleeding risk among overdosed patients.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/cer-2020-0286

Financial & competing interests disclosure

M Sanmartín Fernandez has received speaker and advisory fees from the following companies in the past 3 years: Bayer, Boehringer-Ingelheim, BMS and Pfizer. F Marín has received consultancy/lecturing fees from Bayer, Boehringer Ingelheim, Pfizer, Bristol Myers Squibb and Daiichi Sankyo. C Rafols is an employee of the Medical Department, Bayer Hispania SL. Bayer Hispania SL is the sponsor of the EMIR study. F Arribas has received consultancy/lecture fees and research funding from Daiichi Sankyo, Pulse Dynamics, Medtronic, Boston Scientific, Bayer, Bristol Myers Squibb, Arrhythmia Network Technology SL/BAROSTIM, Abbott, Novartis, Janssen-Cilag, Biosensors, Edwards Lifesciences. He has also received financial compensation from Bayer for participating in the EMIR registry. V Barrios has received consultancy/lecture fees from Bayer, BMS/Pfizer, Boehringer Ingelheim and Daiichi Sankyo. He has also received financial compensation from Bayer for participating in the EMIR registry. J Cosín-Sales has received financial compensation from Bayer for participating in the EMIR registry. M Anguita Sánchez has received financial compensation from Bayer for participating in the EMIR registry. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Editorial and writing assistance was provided by Content Ed Net (Madrid, Spain) with funding from Bayer Hispania.

Acknowledgments

The Supplementary Material details the names of the EMIR Study Investigators.

Data sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical conduct of research

The study was approved by each participating Institutional Review Board. All patients gave their written consent prior to enrollment.

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Kirchhof P, Benussi S, Kotecha D *et al.* 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur. Heart J.* 37(38), 2893–2962 (2016).
2. Steffel J, Verhamme P, Potpara TS *et al.* The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Eur. Heart J.* 39(16), 1330–1393 (2018).
3. Ruff CT, Giugliano RP, Braunwald E *et al.* Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 383(9921), 955–962 (2014).

•• **This meta-analysis of pivotal clinical trials showed that compared with warfarin, direct oral anticoagulants (DOACs) have a better benefit-risk profile.**

4. Barrios V, Escobar C. From clinical trials to clinical practice. Experience with rivaroxaban in the anticoagulant treatment of patients with non-valvular atrial fibrillation. *Semergen* 43(3), 222–229 (2017).
5. Barón-Esquivias G, Marín F, Sanmartín Fernandez M. Rivaroxaban in patients with atrial fibrillation: from ROCKET AF to everyday practice. *Expert Rev. Cardiovasc. Ther.* 15(5), 403–413 (2017).
6. Santos J, António N, Rocha M, Fortuna A. Impact of direct oral anticoagulants off-label doses on clinical outcomes of atrial fibrillation patients: a systematic review. *Br. J. Clin. Pharmacol.* 86(3), 533–547 (2020).

•• **This systematic review showed that prescribing off-label DOAC doses was associated with an increased risk of adverse events.**

7. Yagi N, Suzuki S, Arita T *et al.* Creatinine clearance and inappropriate dose of rivaroxaban in Japanese patients with non-valvular atrial fibrillation. *Heart Vessels* 35(1), 110–117 (2020).
8. Briasoulis A, Gao Y, Inampudi C *et al.* Characteristics and outcomes in patients with atrial fibrillation receiving direct oral anticoagulants in off-label doses. *BMC Cardiovasc. Disord.* 20(1), 42 (2020).

• **In this study, a significant number of patients received higher or lower dose of dabigatran and rivaroxaban than recommended, with a low impact on outcomes.**

9. Miyazaki M, Matsuo K, Uchiyama M *et al.* Inappropriate direct oral anticoagulant dosing in atrial fibrillation patients is associated with prescriptions for outpatients rather than inpatients: a single-center retrospective cohort study. *J. Pharm. Health Care Sci.* 6, 2 (2020).

10. Cho MS, Yun JE, Park JJ *et al.* Pattern and impact of off-label underdosing of non-vitamin k antagonist oral anticoagulants in patients with atrial fibrillation who are indicated for standard dosing. *Am. J. Cardiol.* 125(9), 1332–1338 (2020).
11. Cerdá M, Cerezo-Manchado JJ, Johansson E *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.* 8(3), 165–178 (2019).
12. Steinberg BA, Shrader P, Pieper K *et al.* Frequency and outcomes of reduced dose non-vitamin k antagonist anticoagulants: results from ORBIT-AF II (The Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II). *J. Am. Heart Assoc.* 7(4), e007633 (2018).
13. Ruiz Ortiz M, Esteve-Pastor MA, Roldán I, Muñiz J, Marín F, Anguita M. Prognostic impact of inappropriate -doses of direct oral anticoagulants in clinical practice. *Rev. Esp. Cardiol.* 73(4), 329–330 (2020).

•• **This study showed that inappropriately low dose of DOACs was associated with a higher risk of stroke.**

14. Escobar C, Martí-Almor J, Pérez Cabeza A, Martínez-Zapata MJ. Direct oral anticoagulants versus vitamin K antagonists in real-life patients with atrial fibrillation. A systematic review and meta-analysis. *Rev. Esp. Cardiol.* 72(4), 305–316 (2019).
15. Moudallel S, Steurbaut S, Cornu P, Dupont A. Appropriateness of DOAC prescribing before and during hospital admission and analysis of determinants for inappropriate prescribing. *Front. Pharmacol.* 9, 1220 (2018).
16. Schulman S, Kearon C. Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J. Thromb. Haemost.* 3(4), 692–694 (2005).
17. Patel MR, Mahaffey KW, Garg J *et al.* Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N. Engl. J. Med.* 365(10), 883–891 (2011).
18. Camm AJ, Amarenco P, Haas S *et al.* XANTUS: a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation. *Eur. Heart J.* 37(14), 1145–1153 (2016).

•• **XANTUS was the first prospective observational study with rivaroxaban in clinical practice, showing a low risk of stroke and bleeding.**

19. Martí E, Segado A, Pastor-Galán I *et al.* Use of rivaroxaban for the prevention of stroke in patients with nonvalvular atrial fibrillation in Spain. *Future Cardiol.* 14(3s), 3–8 (2018).
20. Pérez Cabeza AI, González Correa JA, Chinchurreta Capote PA *et al.* Drug persistence and outcomes in a cohort of patients with nonvalvular atrial fibrillation treated with rivaroxaban after 2 years of follow-up in clinical practice. *Future Cardiol.* 14(3s), 9–16 (2018).
21. Muñiz Lobato S, Tarrazo Tarrazo C, González Fernández E, Morán Alcalá M. Clinical profile, adequacy of dosage and thromboembolic and bleeding outcomes in patients with nonvalvular atrial fibrillation treated with rivaroxaban in a regional hospital of Asturias, Spain. *Future Cardiol.* 14(3s), 17–24 (2018).
22. Cerezo-Manchado JJ, Navarro-Almenzar B, Elvira-Ruiz G *et al.* Effectiveness and safety of rivaroxaban in a cohort of 142 patients with nonvalvular atrial fibrillation treated with rivaroxaban for the prevention of stroke. *Future Cardiol.* 14(3s), 31–37 (2018).
23. Kirchhof P, Radaideh G, Kim YH *et al.* Global prospective safety analysis of rivaroxaban. *J. Am. Coll. Cardiol.* 72(2), 141–153 (2018).

• **This worldwide prospective real-world study showed low bleeding and stroke rates in rivaroxaban-treated patients with atrial fibrillation.**

24. Brun Guinda D, Callen Garcia O, Ondiviela Perez J *et al.* Clinical profile, management and outcomes in a cohort of elderly and highly comorbid patients with nonvalvular atrial fibrillation treated with rivaroxaban in routine practice. *Future Cardiol.* 14(3s), 39–45 (2018).
25. Khan F, Huang H, Datta YH. Direct oral anticoagulant use and the incidence of bleeding in the very elderly with atrial fibrillation. *J. Thromb. Thrombolysis* 42(4), 573–578 (2016).
26. Mostaza JM, Jiménez MJR, Laiglesia FJR *et al.* Clinical characteristics and type of antithrombotic treatment in a Spanish cohort of elderly patients with atrial fibrillation according to dependency, frailty and cognitive impairment. *J. Geriatr. Cardiol.* 15(4), 268–274 (2018).
27. Saczynski JS, Sanghai SR, Kiefe CI *et al.* Geriatric elements and oral anticoagulant prescribing in older atrial fibrillation patients: SAGE-AF. *J. Am. Geriatr. Soc.* 68(1), 147–154 (2020).
28. Cho MS, Yun JE, Park JJ *et al.* Outcomes After use of standard- and low-dose non-vitamin K oral anticoagulants in Asian patients with atrial fibrillation. *Stroke* STROKEAHA118023093 (2018).
29. Camm AJ, Cools F, Virdone S *et al.* Mortality in patients with atrial fibrillation receiving nonrecommended doses of direct oral anticoagulants. *J. Am. Coll. Cardiol.* 76(12), 1425–1436 (2020).

• **In GARFIELD-AF, most patients received the recommended DOAC doses. However, prescribing nonrecommended doses was associated with an increased risk of death.**

30. Villani ER, Tummolo AM, Palmer K *et al.* Frailty and atrial fibrillation: a systematic review. *Eur. J. Intern. Med.* 56, 33–38 (2018).
31. Wilkinson C, Todd O, Clegg A, Gale CP, Hall M. Management of atrial fibrillation for older people with frailty: a systematic review and meta-analysis. *Age Ageing* 48(2), 196–203 (2019).
32. Coleman CI, Turpie AGG, Bunz TJ, Eriksson D, Sood NA, Baker WL. Effectiveness and safety of rivaroxaban vs. warfarin in non-valvular atrial fibrillation patients with a non-sex-related CHA2DS2-VASc score of 1. *Eur. Heart J. Cardiovasc. Pharmacother.* 5(2), 64–69 (2019).

33. Beyer-Westendorf J, Camm AJ, Coleman CI, Tamayo S. Rivaroxaban real-world evidence: validating safety and effectiveness in clinical practice. *Thromb. Haemost.* 116(Suppl. 2), S13–S23 (2016).

34. Weir MR, Berger JS, Ashton V *et al.* Impact of renal function on ischemic stroke and major bleeding rates in nonvalvular atrial fibrillation patients treated with warfarin or rivaroxaban: a retrospective cohort study using real-world evidence. *Curr. Med. Res. Opin.* 33(10), 1891–1900 (2017).

35. Pastori D, Ettorre E, Lip GYH *et al.* Association of different oral anticoagulants use with renal function worsening in patients with atrial fibrillation: a multicentre cohort study. *Br. J. Clin. Pharmacol.* 86(12), 2455–2463 (2020).

36. Barrios V, Górriz JL. Atrial fibrillation and chronic kidney disease: focus on rivaroxaban. *J. Comp. Eff. Res.* 4(6), 651–656 (2015).

37. Alberts M, Chen YW, Lin JH, Kogan E, Twyman K, Milentijevic D. Risks of stroke and mortality in atrial fibrillation patients treated with rivaroxaban and warfarin. *Stroke* 51(2), 549–555 (2020).