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Clinical profile and management of rivaroxaban in patients with atrial fibrillation in routine practice in Spain: data from six nationwide studies

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Abstract

Aims: To analyze the clinical profile and management of patients with nonvalvular atrial fibrillation taking rivaroxaban in routine practice in Spain.

Methods: Clinical data from the observational studies HEROIC (cardiology and hematology; n=1,727), EMIR (cardiology; n=1,493), BRONCE-AP (primary care; n=133), SILVER-AP (primary care; n=457), ALADIN (internal medicine and neurology; n=249), and ESPARTA (internal medicine; n=110) of patients taking rivaroxaban were analyzed. The clinical profile was compared with those of the XANTUS and ROCKET-AF studies.

Results: Overall, mean age was 74.9±9.4 years, CHA_2DS_2-VASc score was 3.7±1.5, and 43.2% had a HAS-BLED score ≥3. Patients included in the HEROIC and EMIR studies were older and more frequently had a creatinine clearance <50 mL/min and a higher thromboembolic risk than those in the XANTUS study, and patients included in the ALADIN study were older and had more prior cerebrovascular disease, but a lower thromboembolic risk than those in the ROCKET-AF trial. In those studies with available data, medication adherence and satisfaction with rivaroxaban were high.

Conclusion: Bearing in mind differences according to the clinical setting of each study, atrial fibrillation patients taking rivaroxaban in Spain were elderly and had a high thromboembolic risk. Medication adherence and satisfaction with rivaroxaban were high.

Keywords: atrial fibrillation, clinical practice, rivaroxaban, ROCKET-AF, Spain, XANTUS.

Citation

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Introduction

Cardioembolic stroke in patients with atrial fibrillation (AF) is associated with significant morbidity and mortality.[1] Prevention of cardioembolic stroke is the main therapeutic approach for improving prognosis among the AF population.[2] Until the last decade, antiplatelet agents and vitamin K antagonists (VKA) were the antithrombotic therapies used for the prevention of thromboembolic complications in nonvalvular AF (NVAF). However, due to the lack of efficacy of antiplatelet agents for the prevention of stroke, and the limitations of VKA (e.g. periodic monitoring of anticoagulant effect, many food and drug–drug interactions, slow onset and end of action), many patients with AF have not traditionally received the appropriate antithrombotic treatment.[3–5] Not only clinical trials but also studies performed in clinical practice have shown that overall, direct oral anticoagulants (DOACs) have at least a similar efficacy to VKA for the prevention of stroke, with a better safety profile, mainly due to a lesser risk of intracranial hemorrhage.[6,7] Fortunately, the introduction of DOACs in clinical practice has increased the proportion of patients receiving oral anticoagulation for the prevention of stroke or systemic embolism in AF patients.[8–10] Nevertheless, a significant proportion of patients with a high thromboembolic risk remain without anticoagulant treatment, particularly elderly or frail patients.[10,11]

Rivaroxaban was the first once-daily DOAC to be marketed. The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) trial included 14,264 patients with NVAF at high risk of stroke. In

this study, compared with warfarin, rivaroxaban was at least as effective as warfarin for the prevention of stroke or systemic embolism in patients with AF (non-inferior in the intention-to-treat population; superior with regard to safety in the as-treated population), but with a marked reduction in the risk of critical bleeding (31%), fatal bleeding (50%), and intracranial hemorrhage (33%).[12] Observational studies are important to ascertain whether the results of the clinical trials can be applied to "real-world".[13,14] Xarelto® for Prevention of Stroke in Patients with Atrial Fibrillation (XANTUS) was the first international prospective and observational study of AF patients treated with rivaroxaban in routine practice.[15] A recent meta-analysis of "real-world" with NVAF showed that compared with VKA, rivaroxaban significantly reduced the risk of ischemic stroke by 17% and intracranial hemorrhage by 34%, with a similar risk of major bleeding.[7]

Studies performed in routine practice may help determine in which patients DOACs are being prescribed, and whether they are being used properly. Although in recent years a number of studies on the use of rivaroxaban in clinical practice in Spain have been published, these studies have been limited to one single center or healthcare area or to a specific medical specialty.[16–22] In this context, it is important to analyze the clinical management of rivaroxaban not limited to a specific area or specialty in Spain. The aim of this analysis was to determine the clinical profile and use in clinical practice of patients taking rivaroxaban in Spain, using data from the following studies: HEROIC (*Perfil de pacientes con fibrilación auricular novalvular tratados con rivaroxaban en España: la desigualdad en el acceso a los anticoagulantes orales directos*)[23]; EMIR (*Estudio observacional para la identificación de los factores de riesgo asociados a eventos cardiovasculares mayores en pacientes con fIbrilación auricular no valvular tratados con un anticoagulante oral directo Rivaroxaban*)[24,25]; BRONCE-AP (*Estudio observacional de corte transversal para evaluar el uso de recursos y las características sociodemográficas y clínicas de los pacientes diagnosticados de FANV con riesgo de ictus o embolia sistémica, en tratamiento anticoagulante y que son atendidos en consultas de atención primaria*)[26,27]; SILVER-AP (*Estudio observacional de corte transversal para evaluar las características sociodemográficas y clínicas de los pacientes diagnosticados de FANV con riesgo de ictus o embolia sistémica, que reciben tratamiento para el control adecuado de su coagulación y que son atendidos en consultas de atención primaria*)[26–28]; ALADIN (*Validación del cuestionario ACTS en pacientes con Fibrilación Auricular tratados con anticoagulantes orales en consultas de medicina interna y neurología de España*)[29–31]; ESPARTA (*Estudio sobre el seguimiento en la práctica clínica de las recomendaciones sobre el tratamiento con anticoagulantes orales en pacientes con fibrilación auricular de edad avanzada*).[32–34] In addition, our data were compared with those of the XANTUS study[15,35] and the ROCKET-AF trial.[12]

Methods

The HEROIC study was an observational, cross-sectional, and multicenter study of patients with NVAF treated with rivaroxaban in specialist practice (cardiology 70.8%, hematology 25.0%, and internal medicine 4.2%). It was performed to assess the impact of the 2013 Therapeutic Positioning Report of the Spanish Agency of Medicines and Sanitary Products on the reasons for prescribing rivaroxaban in this population, the clinical profile of patients with NVAF treated with rivaroxaban, and how long it took to access the treatment in National Health System hospitals in Spain.[23]

The EMIR study is an ongoing postmarketing, observational, multicenter, prospective, and nationwide study aimed to identify those risk factors associated with major cardiovascular events among patients with NVAF who are under rivaroxaban treatment for at least 6 months before inclusion and attend the cardiology units at Spanish hospitals and private clinics. In this study, baseline data from the EMIR database have been reported.[24,25]

The BRONCE-AP study was an observational, cross-sectional, and multicenter study that included patients with NVAF attended by primary care physicians from those autonomous communities in which the primary care physician had to refer the patient to the specialist to start treatment with DOACs (8 autonomous communities). Patients had to be on chronic treatment with anticoagulants, but on current treatment with DOACs for at least 3 months.[26,27]

The SILVER-AP study was an observational, cross-sectional, and multicenter study that included patients with NVAF attended by primary care physicians from those autonomous communities in which the primary care physician could prescribe DOACs directly (9 autonomous communities). Patients had to be on chronic treatment with anticoagulants, but on current treatment with DOACs for at least 3 months.[26-28]

The ALADIN study was a cross-sectional and multicenter study aimed to validate the satisfaction questionnaire Anti-Clot-Treatment Scale (ACTS) in outpatients with NVAF treated with oral anticoagulants for at least 3 months and attended internal medicine and neurology departments in Spain.[29–31]

The ESPARTA study was an observational, cross-sectional, and multicenter study in which patients aged ≥75 years with NVAF, with stable treatment with oral anticoagulants for at least 3 months before inclusion and treated in internal medicine departments in Spain, were included. The aim of this study was to evaluate, in this population, the adherence to the clinical practice recommendations of the 'Therapeutic Positioning Report of the Spanish Agency of Medicines and Sanitary Products'.[32–34]

All the studies were observational, and no specific diagnostic or therapeutic actions were taken for participating in them. Except for the EMIR study that was prospective, but only baseline data were reported, the rest of the studies had a cross-sectional design. All the studies were approved by the appropriate Clinical Research Ethics Committees, and in every

study, all patients signed the written informed consent before inclusion.

In each study, data were collected from the medical history and physician interview and were entered into a specific electronic case report form. Biodemographic data (age, sex); type of AF; history of cerebrovascular disease; renal function (creatinine clearance); and $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores were recorded. High thromboembolic risk was defined as a CHA_2DS_2-VASc score ≥2 and high bleeding risk as a HAS-BLED score ≥3.[2]

The clinical profiles of patients included in the HEROIC and EMIR studies (patients attended by cardiologists or hematologists) were compared with those of the XANTUS study, and those of the ALADIN study (patients attended by internists and neurologists) with those of the ROCKET-AF trial as they had a similar risk profile (i.e. age, thromboembolic risk), respectively.

Anticoagulant treatment before starting rivaroxaban was recorded. Among patients who had taken VKA, the reasons for switching to rivaroxaban were analyzed. Adequate international normalized ratio (INR) control was defined as the time in the therapeutic range ≥60% according to the direct method (percent time with INR values within therapeutic range) and ≥65% according to the Rosendaal method.[36] Polymedication was defined as using five or more prescription drugs at the moment of the visit. With regard to rivaroxaban therapy, duration of treatment, the dosage prescribed, and medication persistence were recorded. Medication adherence was assessed at the moment of the study.[37,38]

Treatment satisfaction with rivaroxaban was determined with the Anti-Clot Treatment Scale (ACTS) questionnaire. ACTS is a patient-reported questionnaire that includes 12 items about the burdens of anticoagulant therapy and 3 items about the benefits of anticoagulant treatment. Patients are asked to report their experiences with anticoagulants during the last 4 weeks on a 5-point scale of intensity (from not at all -1- to extremely -5-). The ACTS Burdens score ranges from 12 to 60 points and the ACTS Benefits from 3 to 15 points. Higher scores in the ACTS Burdens indicate lesser burden (higher satisfaction) with anticoagulant therapy and higher scores in the ACTS Benefits represent higher benefit (higher satisfaction) with anticoagulant treatment.[29]

Statistical analysis

Quantitative variables were described with mean and standard deviation and qualitative variables as absolute (n) and relative (%) frequencies. In the bivariate analyses, to compare two means, parametric (Student's t-test) or non-parametric (Mann–Whitney U test) statistical tests were performed based on the sample distribution. To compare percentages, the chi-square test or Fisher test were used, according to the sample size. Statistical significance was set at a *p*-value <0.05. The statistical analysis was performed using the SAS statistics package, version 9.4.

Results

In the HEROIC and EMIR studies, a total of 1,727 and 1,493 patients taking rivaroxaban were included, respectively. In the BRONCE-AP study, of 246 patients, 133 (54.1%) were taking rivaroxaban. In the SILVER-AP study, of 790 patients, 457 (57.8%) were taking rivaroxaban. In the ALADIN study, of 1,337 patients, 249 (18.6%) were taking rivaroxaban (165 from the neurology department and 84 from the internal medicine department). In the ESPARTA study, of 837 patients, 110 (13.1%) were taking rivaroxaban. Therefore, a total of 4,169 patients taking rivaroxaban were included for the final analysis of this study.

The clinical characteristics of the study population are reported in Table 1. Overall, mean age was 74.9±9.4 years, 53.6% of patients were men, 43.2% had permanent AF, and 17.6% had prior cerebrovascular disease. In all, 93.7% of patients had a high thromboembolic risk (CHA2DS2-VASc ≥2), and 43.2% of patients had a high bleeding risk (HAS-BLED ≥3). In the HEROIC and EMIR studies, 117 (6.8%) and 121 (8.1%) patients had valvular heart disease (other than significant mitral stenosis or prosthetic valve).

Compared with the XANTUS study, patients included in the HEROIC and EMIR studies were older (74.3±9.6 *versus* 71.5±10.0 years; $p<0.001$), more commonly women (45.9 *versus* 40.8%; $p<0.001$), and more frequently had permanent AF (36.7 *versus* 27.0%; $p<0.001$), a creatinine clearance <50 mL/min (12.9 *versus* 9.1%; $p<0.001$), and a higher thromboembolic risk (CHA_2DS_2-VASc ≥2: 92.7 *versus* 87.3%; $p<0.001$), but less prior cerebrovascular disease (13.5 *versus* 19.0%; $p<0.001$) (Table 2).

Compared with the ROCKET-AF trial (rivaroxaban arm), patients included in the ALADIN study were older (75.6±9.4 *versus* 73.0 years; $p<0.001$), more commonly women (46.2 *versus* 39.7%; $p=0.04$), and had more prior cerebrovascular disease (64.3 *versus* 54.9%; $p=0.004$), but a lower thromboembolic risk ($CHADS_2$ 3.3±1.1 *versus* 3.5±0.9; $p=0.005$) (Table 3).

With regard to the antithrombotic treatment, 57.7% of our patients took VKA before starting treatment with rivaroxaban, mainly acenocoumarol (89.5%). Poor INR control was the most common reason (68.9% of patients taking VKA) for switching from VKA to rivaroxaban. Overall, the mean duration of treatment with rivaroxaban at baseline was 14.1±11.5 months. With regard to the dosage of rivaroxaban, 74.1% of patients were taking rivaroxaban 20 mg, and the remaining 25.9% rivaroxaban 15 mg. In the EMIR study, a total of 300 patients (20.1%) had a creatinine clearance <50 mL/min; underdosing was observed in 153 patients (10.4%), and overdosing in 121 patients (8.2%). Polymedication was reported in 75.0, 78.3, and 86.4% of patients included in the BRONCE-AP, ALADIN, and ESPARTA studies, respectively. In all, 92.7% of patients were adherent to rivaroxaban in the study (Table 4).

Compared with the XANTUS study, more patients included in the HEROIC and EMIR studies were taking VKA before starting treatment with rivaroxaban (51.4 *versus* 45.5%; $p<0.001$). The dosage of rivaroxaban was similar among patients included

Table 1. Clinical characteristics of patients taking rivaroxaban included in the different observational studies in Spain.*

	HEROIC[23] (n=1,727)	EMIR[24,25] (n=1,493)	BRONCE-AP[26,27] (n=133)	SILVER-AP[26–28] (n=457)	ALADIN[29–31] (n=249)	Overall (n=4,059)
Age, years	74.4±9.6	74.1±9.7	76.1±8.5	78.9±8.0	75.6±9.4	74.9±9.4
Sex, male (%)	53.0	55.5	48.9	51.4	53.8	53.6
Permanent AF (%)	—	36.7	42.9	64.6	—	43.2
Prior cerebrovascular disease (%)	14.8	12.0	19.5	20.6	64.3	17.6
CrCl <50 mL/min (%)	6.8	20.1	21.8	26.5	—	14.9
$CHADS_2$, High risk (≥2) (%)	2.1±1.2 67.9	1.9±1.2 —	2.3±1.4 71.4	2.6±1.2 80.5	3.3±1.1 —	2.2±1.2 70.6
CHA_2DS_2-VASc High risk (≥2) (%)	3.6 ± 1.5 92.7	3.4±1.5 —	4.0±1.8 91.7	4.3±1.6 98.0	4.9±1.4 —	3.7±1.5 93.7
HAS-BLED High risk (≥3) (%)	2.4 ± 0.9 45.6	1.5±1.0 —	1.9±1.0 26.3	2.3±1.0 39.2	2.4±1.3 —	2.0±1.0 43.2

AF, atrial fibrillation; CrCl, creatinine clearance.

*Calculated with the available data for each study.

$CHADS_2$: Congestive heart failure, Hypertension, Age >75, Diabetes mellitus, prior Stroke; CHA_2DS_2-VASc: Congestive heart failure, Hypertension, Age ≥75, Diabetes mellitus, prior Stroke, Vascular disease, Age 65-74, Sex category (female); HAS-BLED: Hypertension, Abnormal liver/renal function, Stroke history, Bleeding history or predisposition, Labile INR, Elderly, Drug/alcohol usage.

Table 2. Clinical characteristics of patients taking rivaroxaban included in the HEROIC, EMIR, and XANTUS studies*.

	HEROIC[23] (n=1,727)	EMIR[24,25] (n=1,493)	HEROIC + EMIR (n=3,220)	XANTUS study[15] (n=6,784)	$P_{HEROIC+EMIR}$ *versus* XANTUS
Age (years)	74.4±9.6	74.1±9.7	74.3±9.6	71.5+10.0	<0.001
Sex (male; %)	53.0	55.5	54.1	59.2	<0.001
Permanent AF (%)	—	36.7	36.7	27.0	<0.001
Prior cerebrovascular disease (%)	14.8	12.0	13.5	19.0	<0.001
CrCl <50 mL/min (%)	6.8	20.1	12.9	9.1	<0.001
$CHADS_2$ High risk (≥2) (%)	2.1±1.2 67.9	1.9±1.2 —	2.0±1.2 67.9	2.0+1.3 59.2	NS <0.001
CHA_2DS_2-VASc High risk (≥2) (%)	3.6±1.5 92.7	3.4±1.5 —	3.5±1.5 92.7	3.4+1.7 87.3	0.004 <0.001
HAS-BLED High risk (≥3) (%)	2.4±0.9 45.6	1.5±1.0 —	2.0±0.9 45.6	— —	— —

AF, atrial fibrillation; CrCl, creatinine clearance; NS, not significant;

*Calculated with the available data for each study.

$CHADS_2$: Congestive heart failure, Hypertension, Age >75, Diabetes mellitus, prior Stroke; CHA_2DS_2-VASc: Congestive heart failure, Hypertension, Age ≥75, Diabetes mellitus, prior Stroke, Vascular disease, Age 65-74, Sex category (female); HAS-BLED: Hypertension, Abnormal liver/renal function, Stroke history, Bleeding history or predisposition, Labile INR, Elderly, Drug/alcohol usage.

in the XANTUS study and the HEROIC and EMIR studies. Compared with the HEROIC and EMIR studies, in the ROCKET-AF trial (rivaroxaban arm), more patients were taking VKA before starting treatment with rivaroxaban (62.3 *versus* 51.4%; $p<0.001$), and more patients were taking rivaroxaban 20 mg (79.4 *versus* 76.8%; $p=0.03$) (Table 5). In the XANTUS study and ROCKET-AF trial, 79.9 and 85.7% of patients remained on rivaroxaban therapy after 329 days and 1 year of treatment, respectively.

Table 3. Clinical characteristics of patients included in the ALADIN study and ROCKET-AF trial*.

	ALADIN[29–31] (n=249)	ROCKET-AF[12] (rivaroxaban arm) (n=7,131)	$P_{ALADIN\ versus\ ROCKET\text{-}AF}$
Age (years)	75.6±9.4	73.0	<0.001
Sex (male; %)	53.8	60.3	0.04
Permanent AF (%)	—	81.1	—
Prior cerebrovascular disease (%)	64.3	54.9	0.004
CrCl <50 mL/min (%)	—	20.6	—
$CHADS_2$ High risk (≥2) (%)	3.3±1.1 —	3.5±0.9 100	0.005 —
CHA_2DS_2-VASc High risk (≥2) (%)	4.9±1.4 —	— 100	— —
HAS-BLED High risk (≥3) (%)	2.4±1.3 —	— 62.5	— —

AF, atrial fibrillation; CrCl, creatinine clearance;

*Calculated with the available data for each study.

$CHADS_2$: Congestive heart failure, Hypertension, Age >75, Diabetes mellitus, prior Stroke; CHA_2DS_2-VASc: Congestive heart failure, Hypertension, Age ≥75, Diabetes mellitus, prior Stroke, Vascular disease, Age 65-74, Sex category (female); HAS-BLED: Hypertension, Abnormal liver/renal function, Stroke history, Bleeding history or predisposition, Labile INR, Elderly, Drug/alcohol usage.

Satisfaction of treatment with rivaroxaban using the ACTS scale was specifically analyzed in the BRONCE-AP, SILVER-AP, and ALADIN studies. Overall, in our study, the mean ACTS burden and benefit scores were 52.3±6.9 and 12.1±2.2, respectively. In the SILVER-AP study, the mean ACTS burden and benefit scores were higher among patients taking rivaroxaban for 12 months or more compared with those patients taking rivaroxaban for less than 12 months (53.1±6.5 *versus* 50.3±8.0; $p<0.001$, and 12.2±2.3 *versus* 11.8±2.3; $p=0.008$, respectively). In the XANTUS study, after switching from VKA to rivaroxaban, the ACTS burden and benefit scores significantly increased at month 3 (Table 6).

Discussion

Our study included more than 4,100 patients with NVAF, attended by different specialties (i.e. primary care, cardiology, internal medicine, neurology, and hematology) throughout Spain, treated with rivaroxaban for the prevention of stroke or systemic embolism. In our study, patients were elderly (mean age 75 years), nearly 50% of patients were women, and up to 18% of patients had prior cerebrovascular disease. In addition, thromboembolic risk was high, and more than 40% of patients had a high bleeding risk. Compared with the XANTUS study,[15] patients included in the HEROIC and EMIR studies were older, had more frequently a creatinine clearance <50 mL/min, and a higher thromboembolic risk, and compared with the ROCKET-AF study (rivaroxaban arm),[12] patients included in the ALADIN study were older and had more prior cerebrovascular disease, but a lower thromboembolic risk. Overall, our patients had a lower thromboembolic and bleeding risk than those included in the ROCKET-AF trial but a higher thromboembolic risk than those included in the XANTUS study.[12,15] ROCKET-AF was the clinical trial that included those patients with the highest thromboembolic risk among all DOAC trials.[39-41] When rivaroxaban was introduced in clinical practice, it was mainly prescribed in patients with a better clinical profile,[13–15] or among patients with a high bleeding risk.[22] However, as our study has shown, the experience with rivaroxaban has increased in routine practice, it is prescribed in different clinical settings, and its use has been extended to the entire AF population, regardless of the clinical profile of patients. Therefore, this study exhibits an accurate description of the clinical profile and management of NVAF patients taking rivaroxaban in Spain and may complement, in our country, the information provided by the ROCKET-AF trial and the XANTUS study.

In the HEROIC and EMIR studies, between 7 and 8.1% of patients had valvular heart disease.[23–25] As is well known, DOACs are contraindicated in patients with AF and mechanical prosthetic valves or moderate to severe mitral stenosis (usually of rheumatic origin), but they can be used in patients with other native valvular disease.[42] Thus, a recent meta-analysis of four phase III AF clinical trials has shown that the overall efficacy and safety of DOACs were independent of the presence of valvular heart disease.[43]

With regard to the antithrombotic treatment, in our study, nearly 58% of our patients were taking VKA before starting treatment with rivaroxaban. This percentage was higher than that reported in other studies performed in Europe or the United States in routine practice, but lower than that in the ROCKET-AF trial.[12,15,44,45] This is because in Spain, the reimbursement for the initial prescription of DOACs is limited in the majority of the autonomous communities to some specific conditions, such as poor INR control or a high intracranial bleeding risk.[46] In fact, in our study, poor INR control was the most common reason (69% of patients taking VKA) for switching from VKA to rivaroxaban. This is very relevant, as in Spain, up to 40–50% of patients taking VKA have inadequate anticoagulation control. Considering that approximately 30% of all oral anticoagulants prescribed in Spain correspond to DOACs and the remaining 70% to VKA, these data strongly suggest that DOACs are underused in Spain.[47,48]

Table 4. Antithrombotic treatment of patients included in different observational studies in Spain.*

	HEROIC[23] (n=1,727)	EMIR[24,25] (n=1,493)	BRONCE-AP[26,27] (n=133)	SILVER-AP[26–28] (n=457)	ESPARTA[32–34] (n=110)	Overall*
Previous use of VKA (%)	57.0	44.9	89.5	97.2	39.1	57.7
Warfarin	15.1	—	1.7	3.2	4.7	10.5
Acenocoumarol	84.9	—	98.3	96.8	95.3	89.5
Switch due to poor INR control (%)	64.8	68.2	83.1	75.7	67.4	68.9
Previous use of heparin (%)	6.2	2.2	10.5	2.6	0	4.2
Previous use of other DOACs (%)	2.9	2.7	0	0	1.8	2.3
Duration of treatment with rivaroxaban (months)	—	—	14.7±10.8	13.5± 11.1	15.6±14.1	14.1±11.5
Rivaroxaban (%)						
20 mg	—	76.8	69.9	70.2	59.1	74.1
15 mg	—	22.0	30.1	29.8	40.9	25.9
Adherence to rivaroxaban treatment (%)†	—	—	97.9	97.2	68.2	92.7

DOACs, direct oral anticoagulants; INR, international normalized ratio; VKA, vitamin K antagonists.

*Calculated with the available data for each study.
†The Haynes–Sackett test was applied in the BRONZE-AP and SILVER-AP studies. The Morisky–Green test was applied in the ESPARTA study.

Table 5. Antithrombotic treatment of patients included in the HEROIC, EMIR, and XANTUS studies and ROCKET-AF trial.*

	HEROIC[23] (n=1,727)	EMIR[24,25] (n=1,493)	HEROIC + EMIR (n=3,220)	XANTUS study[15] (n=6,784)	$P_{\text{HEROIC+EMIR } versus \text{ XANTUS}}$	ROCKET-AF[12] (rivaroxaban arm) (n=7,131)	$P_{\text{HEROIC+EMIR } versus \text{ ROCKET-AF}}$
Previous use of VKA (%)	57.0	44.9	51,4	45.5	<0.001	62.3	<0.001
Warfarin	15.1	—	15.1	—	—	—	—
Acenocoumarol	84.9	—	84.9	—	—	—	—
Switch due to poor INR control (%)	64.8	457 (68.2)		—	—	—	—
Previous use of heparin (%)	6.2	2.2	4.3	3.2	0.004	—	—
Previous use of other DOACs (%)	2.9	2.7	2.8	3.2	NS	0	<0.001
Duration of treatment with rivaroxaban (months)	—	—	—	11.0±3.8	—	23.6	—
Rivaroxaban (%)							
20 mg	—	76.8	76.8	78.7	NS	79.4	0.03
15 mg	—	22.0	22.0	21.3	NS	20.6	NS

DOACs, direct oral anticoagulants; INR, international normalized ratio; NS, not significant; VKA, vitamin K antagonists.

*Calculated with the available data for each study.

Polymedication was reported in 75–86% of our patients. Drug–drug interactions with rivaroxaban are uncommon. In the ROCKET-AF trial, polymedication was associated with a higher risk of bleeding but not of stroke. Importantly, the efficacy and safety of rivaroxaban were independent of the number of concomitant drugs and the use of ≥1 combined cytochrome P450 3A4 and P-glycoprotein inhibitors.[49]

Table 6. Satisfaction of treatment with rivaroxaban in the BRONCE-AP, SILVER-AP, ALADIN, and XANTUS studies.*

	BRONCE-AP[26,27] (n=133)	SILVER-AP[26–28] (n=457)	ALADIN[29–31] (n=249)	Overall	XANTUS study[35] (n=1,291)	
					Baseline	At month 3
Burden scale	54.1± 6.0	51.4±7.5	54.6±6.2	52.3±6.9	50.5±8.4	54.4
<12 months of treatment	—	50.3±8.0	—	—		
≥12 months of treatment	—	53.1±6.5	—	—		
Benefit scale	12.1± 2.3	12.0±2.3	12.4±2.1	12.1±2.2	10.3±2.7	11.4
<12 months of treatment	—	11.8±2.3	—	—		
≥12 months of treatment	—	12.2±2.3	—	—		

*Calculated with the available data for each study.

With regard to the suitability of dosage of rivaroxaban, in the EMIR study, underdosing was observed in 10.4% of patients and overdosing, in 8.2%.[24] In the XANTUS study, of patients with a creatinine clearance ≥50 mL/min, 15% received rivaroxaban 15 mg, and of patients with moderate or severe renal impairment, 36% of patients received rivaroxaban 20 mg.[15] Remarkably, underdosing with rivaroxaban has not been associated with an increased risk of stroke.[50] However, despite the observation that prescription of inappropriate doses seems lower with rivaroxaban compared with other DOACs, it is common in real-world clinical practice,[51] and this may have a negative impact on outcomes.[7] Therefore, it is mandatory to prescribe the appropriate dosage of DOACs according to the clinical characteristics of the patients.

Medication persistence was high in the XANTUS study (80%) and in the ROCKET-AF trial (86% at year one).[12,15] In a recent retrospective study, approximately 96 and 91% of patients remained on rivaroxaban therapy after 1 and 2 years of treatment, respectively.[17] In our study, adherence with rivaroxaban was high (93%) at the moment of being included in the study. Medication persistence is essential in patients with chronic conditions, such as AF. All these data indicate that medication persistence and adherence are high among patients taking rivaroxaban in routine practice.

Not only AF but also anticoagulation treatment is associated with poorer quality of life.[52] Although it has been reported that satisfaction with treatment is high among patients with AF chronically anticoagulated with VKA,[53] the XANTUS study demonstrated that switching from VKA to rivaroxaban was associated with an improvement of quality of life.[35] In our study, satisfaction with rivaroxaban was high (low burden and high benefit with anticoagulant treatment), particularly among patients chronically anticoagulated.

Although including data from different studies may increase the risk of bias, the high number of patients included throughout Spain, the similar study designs, and the accuracy of data recorded may diminish this risk. Of note, not all variables could be recorded in all studies, and some analyses were not performed with the data of the six studies. In addition, comparing our data with those of the XANTUS and the ROCKET-AF studies has some limitations, as these studies had a different design and inclusion criteria. However, due to the importance of these studies about the use of rivaroxaban, these comparisons may be of interest. Finally, the results of our study can be applied only to patients with a similar clinical profile and health care system.

Conclusion

NVAF patients taking rivaroxaban for the prevention of stroke in routine practice in Spain were elderly and had a high thromboembolic risk, and more than 40% of patients had a high bleeding risk. Patients included in the HEROIC and EMIR studies were older and had more renal insufficiency and a higher thromboembolic risk than those in the XANTUS study, and patients included in the ALADIN study were older and had more prior cerebrovascular disease, but a lower thromboembolic risk than those in the ROCKET-AF trial (rivaroxaban arm), suggesting that in Spain, rivaroxaban is prescribed in a wide range of NVAF patients. Approximately 58% of patients were taking VKA before starting treatment with rivaroxaban, with poor INR control being the main reason for switching. However, according to guidelines, treatment naïve patients with NVAF should start anticoagulant treatment with DOACs, instead of VKA. Overall, 74% of patients were taking rivaroxaban 20 mg, and 26% rivaroxaban 15 mg. In the majority of patients, rivaroxaban was properly prescribed, even better than with other DOACs, likely due to its high simplicity of use (i.e. a single daily dose and dosage adjustment only according to renal function). Medication adherence and satisfaction with rivaroxaban were high. All these data strongly suggest that rivaroxaban is a good alternative for the treatment of NVAF patients.

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