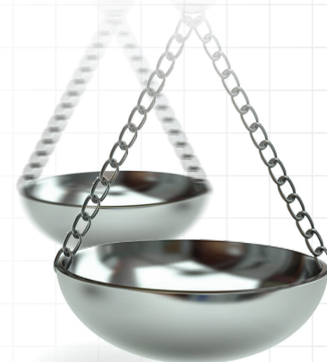




Rivaroxaban for the prevention of outcomes in patients with atrial fibrillation in clinical practice: an indirect comparison of national and international registries

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Objective: To analyze the effectiveness and safety of rivaroxaban in patients with atrial fibrillation (AF).

Methods: The clinical profile and outcomes of the EMIR study were indirectly compared with those of ROCKET-AF, eight other Spanish observational studies and XANTUS. **Results:** In EMIR, mean age was 74.2 years and CHA₂DS₂-VAsC was 3.5. In the rivaroxaban arm of the ROCKET-AF trial, mean age was 73 years and CHADS₂ was 3.5, whereas in the Spanish studies mean age ranged from 74.9 years to 78.4 years and CHA₂DS₂-VAsC from 3.5 to 4.3. In EMIR, rates of stroke/systemic embolism, major adverse cardiovascular events, cardiovascular death and major bleeding were 0.57, 1.07, 0.63 and 1.04 events/100 patient-years, respectively. In ROCKET-AF, these numbers were 1.7, 3.91, 1.53 and 3.6 events/100 patient-years, respectively. In the Spanish studies, rates of stroke and major bleeding were 0–1.8 and 0.22–4.2 events/100 patient-years, respectively. In XANTUS, rates of stroke, major adverse cardiovascular events and major bleeding were 0.7, 1.8 and 2.1 events/100 patient-years, respectively. **Conclusion:** Despite the fact that rivaroxaban is prescribed for elderly patients with a high thromboembolic risk, rates of outcomes remain low.

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Keywords: atrial fibrillation • direct oral anticoagulant • EMIR • MACE • registry • rivaroxaban • stroke

Atrial fibrillation (AF) is the most common cardiac arrhythmia all around the world, currently reaching epidemic numbers [1]. Ischemic stroke is the most devastating complication associated with AF, and anticoagulation represents the cornerstone for the prevention of thromboembolic events in the AF population [2]. However, despite anticoagulation, patients remain at risk of cardiovascular complications, including myocardial infarction or cardiovascular death [3]. As a result, not only stroke but also overall cardiovascular disease prevention should be considered in the comprehensive management of the AF population [2].

Direct oral anticoagulants (DOACs) exhibit a better benefit–risk profile than vitamin K antagonists [4]. Remarkably, the greater rates of anticoagulation shown in the last years, particularly through a higher use of DOACs in clinical practice, have translated into a reduction of ischemic stroke [5,6]. Rivaroxaban is a once-daily direct anticoagulant that effectively reduces the risk of stroke with a good safety profile. The ROCKET-AF trial showed in a high-risk population that rivaroxaban was at least as effective as warfarin for the prevention of stroke or systemic embolism, with a lower risk of fatal and intracranial hemorrhages [7]. However, it is important to ascertain whether these good results can be extended to the overall real-life population with AF [8]. The EMIR study was designed to evaluate the performance of the cardiovascular risk 2MACE score in AF patients treated with rivaroxaban. Overall, this study showed that the risk of adverse events (stroke, major cardiovascular events [MACE] and bleeding) in elderly patients with many comorbidities anticoagulated with rivaroxaban in Spain was low [9].

However, in the last years a number of national and international studies on the use of rivaroxaban in clinical practice have been published [10–25]. As a result, it is important to ascertain whether the results of the EMIR study are comparable to other registries of patients anticoagulated with rivaroxaban. The aim of this narrative review was to evaluate, through indirect comparisons between different national or international real-life studies, the clinical profile and outcomes of patients with AF anticoagulated with rivaroxaban. Additionally, data from the EMIR study were compared with three other observational and prospective studies of patients treated with different DOACs [10–25].

Methods

EMIR was a noninterventional and observational study that included patients ≥ 18 years old with AF, taking rivaroxaban according to clinical practice ≥ 6 months before being enrolled. Patients with a valvular prosthesis or rheumatic mitral stenosis were excluded from the study. Patients were recruited from 79 Spanish centers (hospitals and private clinics) and followed up during 2.5 years with four visits (baseline, 12 months, 24 months and study end) that should coincide with any of the patients' routine visits. In the EMIR study, MACE were defined as a combination of nonfatal myocardial infarction, revascularization and cardiovascular death (death for coronary events, progressive heart failure death and sudden cardiac death) [9].

ROCKET-AF was a double-blind clinical trial in which 14,264 patients with nonvalvular AF who were at increased risk for stroke were randomized to receive either rivaroxaban or dose-adjusted warfarin. The median duration of treatment exposure was 590 days, with a median follow-up period of 707 days [7].

In addition to the EMIR study, eight other Spanish observational studies (one with a prospective design and seven with a retrospective design) of patients with AF taking rivaroxaban for the prevention of stroke or systemic embolism were analyzed. Brun *et al.* performed a retrospective study of AF patients who had started rivaroxaban therapy between May 2013 and February 2017 in the cardiology department of two hospitals from Huesca. Mean duration of treatment was 30.5 months [10]. Cerdá *et al.* developed an observational and prospective study of all patients with AF, with or without prior stroke, who had attended the Oral Anticoagulant Treatment Unit of the Hemostasis and Thrombosis Department of the University Hospital Vall d' Hebron from Barcelona and who had started treatment with any DOAC between January 2015 and September 2017. Mean follow-up was 1.7 years [11]. Gavin *et al.* designed a retrospective study that included all patients with AF who had started treatment with rivaroxaban for the prevention of thromboembolic events in the hematology unit of a tertiary hospital between February 2012 and June 2016 (mean follow-up of 16.5 months) [12]. Pérez Cabeza *et al.* analyzed, in a retrospective study, the drug persistence and outcomes after 2 years of follow-up in a cohort of patients with AF in whom rivaroxaban had been prescribed during the first quarter of 2014 by cardiologists or internists, in the sanitary area of Costa del Sol (Malaga, Spain) [13]. Muñiz *et al.* developed a retrospective study that included all patients with AF who had started anticoagulant treatment with rivaroxaban for the prevention of stroke or systemic embolism between July 2013 and May 2017 (mean follow-up of 26.6 months) in a regional hospital in Asturias (Hospital

San Agustín, Aviles, Spain) [14]. Martí *et al.* retrospectively analyzed patients with AF that had started treatment with rivaroxaban for the prevention of stroke from July 2012 to December 2015 (mean duration of treatment of 29.7 months) in a healthcare area of 330,000 inhabitants of Valencia (Spain) [15]. Pimentel *et al.* performed a retrospective study of AF patients treated with rivaroxaban in the cardiology department of the tertiary hospital San Juan de la Cruz at Ubeda (Jaen, Spain), between November 2012 and January 2017 (median follow-up of 24 months) [16]. Caro *et al.* developed a retrospective study that included all AF patients who had started treatment with rivaroxaban for the prevention of stroke or systemic embolism between December 2012 and December 2015 (mean follow-up period of 22.7 months) from two health areas belonging to two tertiary hospitals (Hospital Vega Baja [Alicante, Spain], and University Hospital Clínico Virgen de la Arrixaca [El Palmar, Spain]) [17].

Furthermore, one international study of patients taking rivaroxaban for the prevention of thromboembolic events was included. Thus, the XANTUS study was the first international, real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in AF. This study included patients with AF newly started on rivaroxaban who were followed up at ~3-month intervals for 1 year, or for at least 30 days after permanent discontinuation (mean treatment duration of 329 days) [21].

Additionally, in order to put into context the results of rivaroxaban compared with those of other DOACs, three prospective registries of patients with AF taking any DOAC were also included for analysis (one developed in Spain and two international studies performed in different countries across Europe). The FANTASIIA registry included consecutive AF outpatients on anticoagulant therapy, either with vitamin K antagonists or DOACs, from 50 Spanish centers between 1 June 2013 and 15 October 2014 (median follow-up of 32.4 months). For this analysis, the 533 patients receiving DOACs were included [18–20]. GLORIA-AF was a large, prospective, global registry program run in three phases, assessing the long-term safety and effectiveness of dabigatran in patients with newly diagnosed AF in clinical practice. For this analysis, patients from phase II, enrolled between 2011 and 2014 with a mean follow-up of 18.0 months, were included [22–24]. ETNA-AF-Europe was a prospective, multicenter, postauthorization, observational study enrolling patients treated with edoxaban in ten European countries. Data from 852 sites that completed the 1-year follow-up (mean and median follow-up of 352 and 366 days, respectively) were analyzed [25].

With the exception of the ROCKET-AF trial, all other studies had an observational design. All studies were approved by the appropriate clinical research ethics committees. In each study, data were collected from the medical history and physician interview. Biodemographic data, comorbidities and thromboembolic and bleeding risk were recorded if available. Information regarding thromboembolic and bleeding events, as well as death, was recorded from all studies if available and expressed as annual rates (events per 100 patient-years).

Statistical analysis

A descriptive analysis was performed. Quantitative variables were described with mean and standard deviation and qualitative variables as absolute (n) and relative (%) frequencies. Outcomes were expressed as absolute (n) and relative (%) frequencies, as well as events per 100 patient-years. The data were analyzed using the statistical package SPSS (v18.0 or superior).

Results

EMIR study versus ROCKET-AF trial

In the EMIR study, a total of 1433 patients were included. Mean age was 74.2 years, 55.5% of patients were men, mean CHA₂DS₂-VAsC score was 3.5 and HAS-BLED score was 1.6 (Table 1). Rates of stroke, MACE, cardiovascular death and major bleeding were 0.57, 1.07, 0.63 and 1.04 events per 100 patient-years, respectively (Table 2).

In the ROCKET-AF trial, 7131 patients were included in the rivaroxaban arm. Median age was 73 years, 60.3% of patients were men, and mean CHADS₂ score was 3.5 (Table 1). Rates of stroke or systemic embolism, MACE, cardiovascular death and major bleeding were 1.7, 3.91, 1.53 and 3.6 events per 100 patient-years, respectively (Table 2).

EMIR study versus observational Spanish studies of AF patients taking rivaroxaban, including the FANTASIIA study

A total of eight studies were included. The number of patients included in these studies ranged from 111 to 732 (total no.: 2516; 3949 with the EMIR study). Mean age ranged from 74.9 to 78.4 years (vs 74.2 years in the EMIR

Table 1. Baseline clinical characteristics of the EMIR study and the ROCKET-AF trial.

	EMIR study (n = 1433)	ROCKET-AF trial (rivaroxaban arm; n = 7131)
Age (years)	74.2	73
Sex (men), n (%)	795 (55.5)	4300 (60.3)
Permanent atrial fibrillation, n (%)	535 (37.5)	5786 (81.1)
CHA ₂ DS ₂ -VASc score	3.5	–
CHADS ₂ score	–	3.5
HAS-BLED score	1.6	–
Hypertension, n (%)	1137 (79.3)	6436 (90.3)
Diabetes, n (%)	388 (27.1)	2878 (40.4)
Previous coronary disease, n (%)	235 (16.4)	1182 (16.6) [†]
Prior cerebrovascular disease, n (%)	179 (12.5)	3916 (54.9) [‡]
Renal insufficiency (<60 ml/min/1.73m ²), n (%)	350 (24.7)	1474 (20.7) [§]
Underdosing, n (%)	138 (9.7)	0

[†]Myocardial infarction.
[‡]Includes systemic embolism.
[§]<50 ml/min.
Underdosing of rivaroxaban was defined as taking rivaroxaban 15 mg/daily when creatinine clearance was ≥50 ml/min.
–: Not available.
Table created with data from [7,9].

Table 2. Outcomes of the EMIR study and the ROCKET-AF trial.

	EMIR study (n = 1433)	ROCKET-AF trial (rivaroxaban arm; n = 7131)
Stroke + systemic embolism n (%) Annual rate	23 (1.6) 0.57	188 (2.6) [†] 1.7
Major bleeding n (%) Annual rate	29 (2.0) 1.04	395 (5.6) 3.6
MACE n (%) Annual rate	30 (2.1) 1.07	433 (6.13) 3.91
Myocardial infarction n (%) Annual rate	5 (0.3) 0.16	101 (1.43) 0.91
Cardiovascular death n (%) Annual rate	20 (1.4) 0.63	170 (2.41) 1.53
Death from any cause n (%) Annual rate	87 (6.1) 2.73	208 (2.95) 1.87

[†]On treatment.
In the EMIR study, MACE were defined as a combination of nonfatal myocardial infarction, revascularization, cardiovascular death (death from coronary events, progressive heart failure death and sudden cardiac death). In the ROCKET-AF trial, MACE were defined as a combination of stroke, non-central nervous system embolism, vascular death, myocardial infarction.
MACE: Major adverse cardiovascular events.
Table created with data from [7,9].

study); CHA₂DS₂-VASc score ranged from 3.5 to 4.3 (vs 3.5 in the EMIR study), and HAS-BLED score ranged from 1.3 to 2.3 (vs 1.6 in the EMIR study; Table 3). Rates of stroke (the definition differed between studies) ranged from 0 to 1.8 (2.3 including transient ischemic attack) events per 100 patient-years (vs 0.57 in the EMIR study); major bleeding rates ranged from 0.22 to 4.2 events per 100 patient-years (vs 1.04 in the EMIR study); only one study reported data for MACE (2.0 vs 1.07 events per 100 patient-years, respectively) and two studies reported information about the rates of cardiovascular death (2.0 vs 0.63 events per 100 patient-years; Table 4). The study of Cerdá *et al.* [11] included patients taking not only rivaroxaban prospectively but also other DOACs. Rates of ischemic stroke and major bleeding are reported in Figure 1.

Additionally, data from the FANTASIA study were reported. In the FANTASIA trial, 533 patients taking DOACs were analyzed. Mean age was 73.3 years, 53.8% of patients were men and mean CHA₂DS₂-VASc score

Table 3. Baseline clinical characteristics of different observational studies of patients with atrial fibrillation anticoagulated with rivaroxaban in Spain, including the FANTASIA study.

	EMIR study (n = 1433)	Brun et al. (n = 137)	Cerdá et al. (n = 663)	Gavín et al. (n = 243)	Pérez Cabeza et al. (n = 111)	Muñiz et al. (n = 189)	Martí et al. (n = 230)	Pimentel et al. (n = 211)	Caro et al. (n = 732)	FANTASIA direct oral anticoagulants (n = 533)
Age (years)	74.2	78.2	77.8	78.4	74.9	76.0	76.9	76.7	76.4	73.3
Sex (men), n (%)	795 (55.5)	82 (59.9)	299 (45.1)	128 (52.5)	58 (52.3)	93 (49.2)	126 (54.8)	104 (49.3)	333 (45.5)	287 (53.8)
Permanent atrial fibrillation, n (%)	535 (37.5)	77 (56.2)	–	–	29 (26.2)	124 (65.6)	–	–	341 (46.6)	222 (41.7)
CHA ₂ DS ₂ -VAsC score	3.5	3.5	4.0	3.7	3.6	4.1	4.3	3.8	3.9	3.67
HAS-BLED score	1.6	–	–	–	1.3	2.1	1.7	2.0	2.3	1.95
Hypertension, n (%)	1137 (79.3)	–	564 (85.1)	181 (74.6)	93 (83.8)	–	183 (79.6)	175 (83.0)	640 (87.5)	425 (79.7)
Diabetes, n (%)	388 (27.1)	–	173 (26.1)	63 (25.8)	28 (25.2)	–	87 (37.8)	61 (29.0)	194 (26.5)	145 (27.2)
Previous coronary disease, n (%)	235 (16.4)	–	–	–	20 (18.0)	–	–	27 (12.8)	83 (11.3)	79 (14.9)
Prior cerebrovascular disease, n (%)	179 (12.5)	–	123 (18.6)	–	16 (14.4) [†]	56 (29.6) [†]	40 (17.4) [†]	30 (14.2)	123 (16.8)	111 (20.9) [†]
Renal insufficiency (estimated glomerular filtration rate <60 ml/min/1.73 m ²), n (%)	350 (24.7)	25 (18.2) [‡]	229 (34.5) [‡]	–	19 (17.1)	42 (22.2) [§]	70 (30.5) [‡]	–	180 (24.6) [‡]	72 (13.5)
Underdosing, n (%)	138 (9.7)	43 (31.4)	20 (3.0)	–	–	12 (6.3)	28 (12.2)	–	88 (12.0)	13 (7.0) [¶]

† Prior stroke.

‡ Creatinine clearance <50 ml/min.

§ Estimated glomerular filtration rate <50 ml/min/1.73m².

¶ A substudy of FANTASIA [18] showed that among 190 patients taking rivaroxaban, 13 (7.0%) were underdosed.

Underdosing of rivaroxaban was defined as taking rivaroxaban 15 mg/daily when creatinine clearance was ≥50 ml/min.

–: Not available.

Table created with data from [9–20].

Table 4. Outcomes of different observational studies of patients with atrial fibrillation anticoagulated with rivaroxaban in Spain, including the FANTASIIA study.

	EMIR study (n = 1433)	Brun et al. (n = 137)	Cerdá et al. (n = 663)	Gavin et al. (n = 243)	Perez Cabeza et al. (n = 111)	Muñiz et al. (n = 189)	Martí et al. (n = 230)	Pimente et al. (n = 211)	Caro et al. (n = 732)	FANTASIIA direct oral anticoagulants (n = 533)
Stroke n (%)	23 (1.6)	0	5 (0.7) [†]	–	4 (3.6)	–	2 (0.9)	–	25 (3.4)	–
Annual rate	0.57		0.5		–	0.45	0.4	2.3 [‡]	1.8	0.40
Major bleeding n (%)	29 (2.0)	5 (3.6)	9 (1.3)	6 (2.4)	0	–	11 (4.8)	–	44 (6.0)	–
Annual rate	1.04	1.43	0.8	1.7		0.22	1.9	4.2	3.2	2.13
MACE n (%)	30 (2.1)	–	–	7 (2.8)	–	–	–	–	–	–
Annual rate	1.07			2.0						
Myocardial infarction n (%)	5 (0.3)	–	–	–	0	–	–	–	15 (2.0)	–
Annual rate	0.16								1.0	
Cardiovascular death n (%)	20 (1.4)	–	–	–	2 (1.8)	–	–	–	28 (3.8)	–
Annual rate	0.63				–				2.0	1.20
Death from any cause n (%)	87 (6.1)	–	–	–	–	–	–	–	76 (10.4)	–
Annual rate	2.73								5.5	3.77

[†] Ischemic stroke.

[‡] Stroke + transient ischemic attack.

In the EMIR study, MACE were defined as a combination of nonfatal myocardial infarction, revascularization, cardiovascular death (death from coronary events, progressive heart failure death and sudden cardiac death). Gavin et al. MACE: stroke, transient ischemic attack, systemic embolism or myocardial infarction.

MACE: Major adverse cardiovascular events; –: Not available.

Table created with data from [9–20].

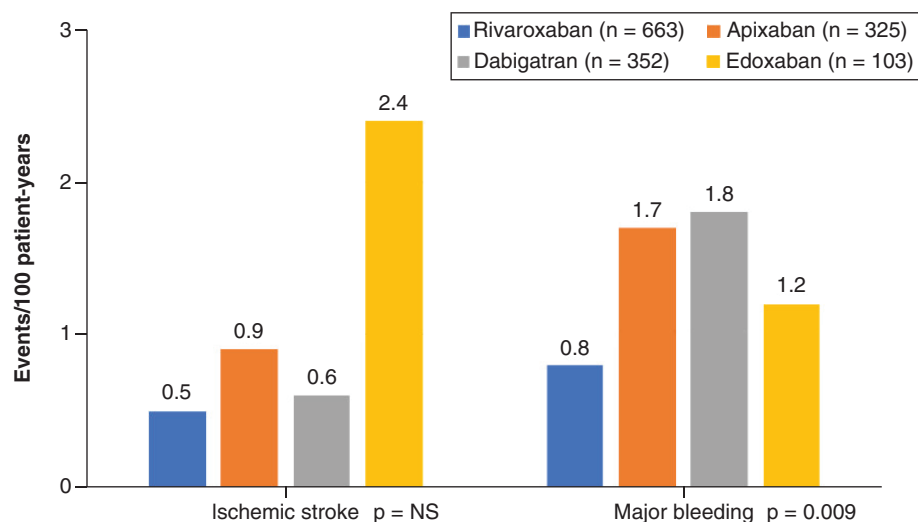


Figure 1. Main results of Cerdá et al. study.

NS: Not significant.

Figure created with data from [11].

Table 5. Baseline clinical characteristics of the EMIR study and different European observational and prospective studies of patients with atrial fibrillation anticoagulated with direct oral anticoagulants.

	EMIR, rivaroxaban (n = 1433)	XANTUS, rivaroxaban ^{††} (n = 6784)	GLORIA-AF Europe, dabigatran ^{‡‡} (n = 7108)	ETNA-AF Europe, edoxaban (n = 13,092)
Age (years)	74.2	71.5	73.0	73.6
Sex (men), n (%)	795 (55.5)	4016 (59.2)	3791 (53.3)	7430 (56.8)
Permanent atrial fibrillation, n (%)	535 (37.5)	1835 (27.0)	1019 (14.3)	2864 (21.9)
CHA ₂ DS ₂ -VASc score	3.5	3.4	3.0	3.1
HAS-BLED score	1.6	–	1.0	2.5
Hypertension, n (%)	1137 (79.3)	5065 (74.7)	5217 (73.4)	10,088 (77.1)
Diabetes, n (%)	388 (27.1)	1333 (19.6)	1510 (21.2)	2879 (22.0)
Previous coronary disease, n (%)	235 (16.4)	688 (10.1) [†]	1167 (16.4)	560 (4.3) [†]
Prior cerebrovascular disease, n (%)	179 (12.5)	1291 (19.0) [‡]	1107 (15.6)	778 (5.9) [#]
Renal insufficiency (<60 ml/min), n (%)	350 (24.7)	640 (9.4) [§]	89 (1.3) [¶]	–
Underdosing, n (%)	138 (9.7)	572 (8.4)	–	–

[†]Myocardial infarction.

[‡]Includes systemic embolism.

[§]Creatinine clearance <50 ml/min.

[¶]Defined as the presence of chronic dialysis or renal transplantation or serum creatinine ≥200 μmol/l.

[#]Prior stroke.

^{††}In XANTUS, patients were enrolled from centres in Europe, Israel and Canada.

^{‡‡}Baseline

Characteristics correspond to the entire European population included in the study (n = 7108), not only those treated with dabigatran.

Underdosing of rivaroxaban was defined as taking rivaroxaban 15 mg/daily when creatinine clearance was ≥50 ml/min.

–: Not available.

Table created with data from [9,21–25].

was 3.67 (Table 3). Rates of stroke, cardiovascular death and major bleeding were 0.40, 1.20 and 2.13 events per 100 patient-years, respectively (Table 4).

EMIR study versus European prospective registries of patients taking DOACs

With regard to those registries of patients taking rivaroxaban, in the XANTUS study, mean age was 71.5 years (vs 74.2 years in the EMIR study) and CHA₂DS₂-VASc score was 3.4 (vs 3.5 in the EMIR study; Table 5). Rates of stroke and major bleeding were 0.7 events per 100 patient-years (vs 0.57 in the EMIR study) and 2.1 events per 100 patient-years (vs 1.04 in the EMIR study), respectively. Additionally, in the XANTUS study, the rate of MACE

Table 6. Outcomes of the EMIR study and different European observational and prospective international studies of patients with atrial fibrillation anticoagulated with direct oral anticoagulants.

	EMIR, rivaroxaban (n = 1433)	XANTUS, rivaroxaban [‡] (n = 6784)	GLORIA-AF Europe, dabigatran (n = 2675)	ETNA-AF Europe, edoxaban (n = 13,092)
Stroke				
n (%)	23 (1.6)	43 (0.6)	28 (1.0)	70 (0.5) [†]
Annual rate	0.57	0.7	0.70	0.56
Major bleeding				
n (%)	29 (2.0)	128 (1.9)	35 (1.3)	132 (1.0)
Annual rate	1.04	2.1	0.87	1.05
MACE				
n (%)	30 (2.1)	108 (1.6)	–	–
Annual rate	1.07	1.8		
Myocardial infarction				
n (%)	5 (0.3)	27 (0.4)	20 (0.7)	66 (0.5)
Annual rate	0.16	0.4	0.50	0.52
Cardiovascular death				
n (%)	20 (1.4)	49 (0.7)	37 (1.4)	206 (1.6)
Annual rate	0.63	–	0.92	1.63
Death from any cause				
n (%)	87 (6.1)	118 (1.7)	100 (3.7)	442 (3.4)
Annual rate	2.73	1.9	2.48	3.50

[†]Ischemic stroke.
[‡]In XANTUS, patients were enrolled from centres in Europe, Israel and Canada.
In the EMIR study, MACE were defined as a combination of nonfatal myocardial infarction, revascularization, cardiovascular death (death from coronary events, progressive heart failure death and sudden cardiac death). In the XANTUS study, MACE were defined as a combination of stroke, systemic embolism, transient ischemic attack, myocardial infarction.
MACE: Major adverse cardiovascular events; –: Not available.
Table created with data from [9,21–25].

was 1.8 events per 100 patient-years (vs 1.07 in the EMIR study; [Table 6](#)). When compared with other European studies in which other DOACs were analyzed (GLORIA-AF Europe and ETNA-AF Europe studies), mean age ranged from 73.0 years to 73.6 years (vs 74.2 years in the EMIR study), CHA₂DS₂-VASc score ranged from 3.0 to 3.1 (vs 3.5 in the EMIR study) and HAS-BLED score ranged from 1.0 to 2.5 (vs 1.6 in the EMIR study; [Table 5](#)). Rates of stroke (the definition differed between studies) ranged from 0.56 to 0.70 events per 100 patient-years (vs 0.57 in the EMIR study), major bleeding rates ranged from 0.87 to 1.05 events per 100 patient-years (vs 1.04 in the EMIR study) and the rates of cardiovascular death ranged from 0.92 to 1.63 events per 100 patient-years (vs 0.63 in the EMIR study; [Table 6](#)).

Discussion

The EMIR study showed in a wide sample of real-life patients with AF that rivaroxaban was prescribed in elderly patients with a high thromboembolic risk. Despite that, rates of thromboembolic, cardiovascular and major bleeding events remained low. These numbers were in the range of or were even better than those reported in other national or international registries.

The ROCKET-AF trial was the study that included those patients with the highest thromboembolic risk and the greatest number of comorbidities when compared with the other pivotal clinical trials [7,26–28]. As a result, it was necessary to ascertain whether the results of the ROCKET-AF trial could be applied to real-life patients [8,29]. On the other hand, the clinical profile of patients for which rivaroxaban is prescribed has changed over time. Thus, as experience with rivaroxaban has increased, its prescription has been extended to the whole AF population, including those patients with a more challenging clinical profile [16,30]. In this context, the present study provided relevant and current information. In the EMIR study, patients were slightly older than in the ROCKET-AF trial, and despite the fact that they had a high thromboembolic risk and a great number of comorbidities, these were lower than in the ROCKET-AF trial [7,9]. Compared with other Spanish registries of patients taking rivaroxaban, the number of patients included in the EMIR study was markedly higher. Interestingly, overall, these studies showed that in Spain, rivaroxaban had been prescribed in elderly patients, with a high thromboembolic risk and a great number of conditions, in line with the data reported in the EMIR study [9–17]. Additionally, the XANTUS study exhibited a clinical profile similar to that of the EMIR study [21]. In summary, all these data are consistent and indicate that rivaroxaban is prescribed for the whole spectrum of the AF population, including patients with more complex disease.

In the EMIR study [9], the rate of stroke was low (0.57 events per 100 patient-years). This was much lower than that reported in the ROCKET-AF trial [7] but similar to that of the XANTUS study and other Spanish registries [10–17,21]. With regard to major bleeding, the EMIR study showed lower rates than those observed in the ROCKET-AF trial and some national and international registries of patients treated with rivaroxaban, such as the XANTUS study [7,9–17,21]. In addition, rates of stroke and bleeding events in the EMIR study were similar to those reported with other DOACs [7,18–20,22–25]. Although disparities in the clinical profiles of patients among the registries could explain, at least in part, some differences in the numbers, it should be emphasized that the EMIR study is a contemporary registry, and consequently, the more experience with the use of rivaroxaban and in the management of AF could have had some impact on the results. In fact, in the EMIR study, around 17% of patients were taking an inappropriate dose of rivaroxaban (vs 19% in the XANTUS study); underdosing was observed in 9.7% and 8.4% of patients, respectively [9,21]. In the Spanish observational studies, underdosing with rivaroxaban ranged from 3.0% to 31.4% [10–18]. These figures could be higher with other DOACs, likely related to the simplicity of dose adjustment with rivaroxaban, only depending on renal function [9,31,32]. Thus, in the FANTASIA study, 32% of patients did not receive the proper dose [18]. In another study, underdosing was observed in one out of five patients taking DOACs [32]. This is very relevant, as underdosing is associated with an increased risk of stroke, without reducing the risk of bleeding [33,34]. As a result, prescribing the appropriate dose of DOACs according to the summary of product characteristics should be encouraged in order to provide the highest benefit [2].

The risk of MACE was specifically analyzed in the EMIR study [9]. Remarkably, despite anticoagulation, AF patients have a high risk for myocardial infarction or cardiovascular death [2,3]. In fact, the European guidelines recommend a comprehensive approach in the management of patients with AF that includes the prevention of not only thromboembolic events but also cardiovascular disease [2]. Unfortunately, this has not been fully analyzed in real-life studies. For example, only Gavin *et al.* and the XANTUS study specifically investigated this point, but not other registries, including those with other DOACs [12,21]. On the other hand, it is difficult to compare the rates of MACE among these studies, as the definition of MACE differed among them. In any case, the rate of MACE of the EMIR study was markedly lower than that of the ROCKET-AF trial and similar to those observed in the real-life studies with rivaroxaban [7,9,12,21]. As no head-to-head clinical trials between DOACs are available, observational studies can provide relevant information on the comparative effectiveness and safety of DOACs. However, these studies cannot be considered individually, since differences in the data can be the result of disparities in the clinical profile and methods [11,35]. By contrast, meta-analysis can show more accurate information. In this context, previous meta-analyses have reported that the use of rivaroxaban could be associated with a lower risk of ischemic events in the AF population [36–38].

This narrative review has some limitations. As no control groups are available in observational studies, no definite conclusions can be obtained from these studies (this occurred in national and international registries, including XANTUS, GLORIA-AF and ETNA-AF). However, these studies best reflect clinical practice, as no specific diagnostic or therapeutic intervention is performed for being included. On the other hand, data were taken from different studies, with particular inclusion criteria, follow-up and outcomes definitions. Therefore, only an indirect comparison can be performed between the studies and no more than hypothesis can be suggested. However, the high number of patients included throughout Spain and the robustness of the international registries may reduce these potential biases.

Conclusion

National and international registries confirm that in clinical practice, despite the fact that rivaroxaban is prescribed in elderly patients with a high thromboembolic risk and many comorbidities, rates of outcomes such as stroke, MACE, myocardial infarction, death and major bleeding are low. Therefore, rivaroxaban should be considered as a first-line therapy in the comprehensive management of patients with AF, to reduce the risk of not only thromboembolic complications but also cardiovascular disease. Using the appropriate dose of DOACs is highly recommended to obtain the maximum benefit.

Future perspective

Although the information provided by clinical trials is important, real-life studies are necessary to determine whether the results can be extended to the whole population [8]. Additionally, as observational studies cannot control all potential bias, it is important to compare data between different real-world evidence studies. In this context, as the

information provided was consistent between different studies, we can conclude that rivaroxaban represents a good choice for anticoagulation in AF patients, even in elderly patients with many comorbidities.

Summary points

- The ROCKET-AF trial demonstrated that rivaroxaban was effective and safe in patients with atrial fibrillation (AF). However, it is important to analyze whether the results of the clinical trials can be extended to the real-life population.
- The EMIR study included patients taking rivaroxaban over a 2.5-year period in Spain.
- As observational studies cannot control all potential bias, it is also important to compare data between different real-world evidence studies.
- This study's aim was to analyze the effectiveness and safety of rivaroxaban in patients with AF in clinical practice through different national and international registries.
- In the EMIR study, a total of 1433 patients were included (mean age: 74.2 years; CHA₂DS₂-VASc: 3.5). Rates of stroke/systemic embolism, major adverse cardiovascular events, cardiovascular death and major bleeding were 0.57, 1.07, 0.63 and 1.04 events/100 patient-years, respectively.
- Rates of outcomes were lower than those reported in the ROCKET-AF trial but were in line with those of the Spanish observational studies (rivaroxaban), XANTUS (rivaroxaban), FANTASIA (any direct oral anticoagulant, in Spain), GLORIA-AF Europe (dabigatran) and ETNA-AF Europe (edoxaban).
- In clinical practice, national and international registries consistently show that despite the fact that rivaroxaban is prescribed for elderly patients with a high thromboembolic risk, rates of outcomes such as stroke, major adverse cardiovascular events, myocardial infarction, death and major bleeding remain low.

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