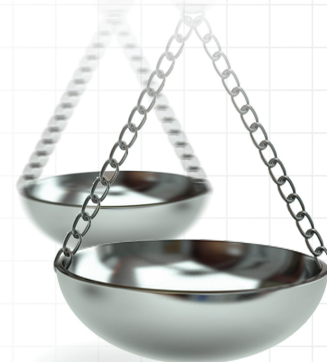




Non-embolic outcomes in patients with cardiovascular disease and atrial fibrillation treated with rivaroxaban

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Francisco Marín^{*,1} , Marcelo Sanmartín Fernández² , Gonzalo Barón-Esquivias^{3,4} , Vivencio Barrios⁵ , Iñaki Lekuona⁶ , Alejandro I Pérez-Cabeza⁷ , Jaime Masjuan⁸ , Esther Recalde del Vigo⁹, José Manuel Vázquez Rodríguez¹⁰ , Roman Freixa-Pamias¹¹ , Vanessa Roldán Schilling¹² , Fernando Arribas^{13,14} , Carles Rafols Priu¹⁵  & Manuel Anguita Sánchez¹⁶ 

¹Department of Cardiology, Hospital Clínico Universitario Virgen de la Arrixaca, IMIB-Arrixaca, University of Murcia, CIBERCV, Murcia, Spain

²Department of Cardiology, Hospital Universitario Ramon y Cajal, Madrid, Spain

³Department of Cardiology, Hospital Universitario Virgen del Rocío, Universidad de Sevilla, Sevilla, Spain

⁴Unidad Cardiovascular, Instituto de Biología de Sevilla. Centro de Investigación en Red Cardiovascular, Madrid, Spain

⁵Department of Cardiology, University Hospital Ramón y Cajal, Alcalá University, Madrid, Spain

⁶Hospital Galdakao-Usansolo, Bizkaia, Spain

⁷Department of Cardiology, Virgen de la Victoria University Hospital, Málaga, Spain

⁸Servicio de Neurología, Hospital Universitario Ramón y Cajal, IRYCIS, Departamento de Medicina, Universidad de Alcalá. Red INVICTUS, Madrid, Spain

⁹Hospital Universitario de Basurto, Centro Médico San Juan de Dios, Bizkaia, Spain

¹⁰Department of Cardiology, Complejo Hospitalario Universitario A Coruña, INIBIC, CIBERCV, A Coruña, Spain

¹¹Department of Cardiology, Hospital Moisès Broggi, Barcelona, Spain

¹²Department of Haematology & Clinical Oncology, Hospital Universitario Morales Meseguer. University of Murcia, Murcia, Spain

¹³Department of Cardiology, Hospital Universitario 12 de Octubre, Department of Medicine, Facultad de Medicina, Universidad Complutense de Madrid (UCM), Madrid, Spain

¹⁴Instituto de Investigación Sanitaria Hospital 12 de Octubre (imas12), CIBERCV, Madrid, Spain

¹⁵Department of Medical Affairs, Bayer Hispania, Barcelona, Spain

¹⁶Department of Cardiology, Hospital Reina Sofía Córdoba, IMIBIC, University of Córdoba, Córdoba, Spain

*Author for correspondence: fcomarino@hotmail.com; fr.marino@um.es

Aim: It is not well known how comorbidities may change the prognosis of atrial fibrillation (AF) patients. This study was aimed to analyze the impact of cardiovascular disease on this population. **Materials & methods:** EMIR was a multicenter, prospective study, including 1433 AF patients taking rivaroxaban for ≥ 6 months. Data were analyzed according to the presence of vascular disease. **Results:** Coronary artery disease was detected in 16.4%, peripheral artery disease/aortic plaque in 6.7%, vascular disease in 28.3%. Patients with coronary artery disease had higher rates (per 100 patient-years) of major adverse cardiovascular events (2.98 vs 0.71; $p < 0.001$) and cardiovascular death (1.79 vs 0.41; $p = 0.004$). Those with vascular disease had higher rates of thromboembolic events (1.47 vs 0.44; $p = 0.007$), major adverse cardiovascular events (2.03 vs 0.70; $p = 0.004$), and cardiovascular death (1.24 vs 0.39; $p = 0.025$). Patients with peripheral artery disease/aortic plaque had similar rates. **Conclusion:** AF patients with vascular disease have a higher risk of non-embolic outcomes.

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Keywords: atrial fibrillation • bleeding • coronary artery disease • EMIR • MACE • myocardial infarction • peripheral artery disease • rivaroxaban • stroke • vascular disease

Stroke is the most devastating complication associated with atrial fibrillation (AF) [1]. Anticoagulation markedly reduces the risk of thromboembolic outcomes in AF patients [2]; however, relevant residual cardiovascular risk (mainly coronary artery disease [CAD], heart failure and cardiovascular death) persists despite antithrombotic



therapy [3,4]. Atherosclerotic cardiovascular disease and AF are common conditions that frequently co-occur. Of note, the presence of one entity may precipitate/exacerbate the development of the other and *vice versa*. In fact, both conditions share risk factors and comorbidities. In addition, the hypercoagulability, systemic inflammation, oxidative stress, platelet activation and endothelial dysfunction that commonly occur in these patients promote both thromboembolism and atherothrombosis, leading to an increased risk of ischemic stroke and myocardial infarction [3–7]. In this context, the most recent European guidelines recommend a comprehensive approach in the management of patients with AF, with the aim of reducing not only the risk of stroke, but also that of vascular disease [7].

Rivaroxaban is a once-daily direct anticoagulant that safely and effectively reduces the risk of stroke [8,9]. However, it is important to determine whether the results of clinical trials are applicable under real-world conditions [10,11]. The EMIR study (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] [‘Observational study to identify risk factors associated with major cardiovascular events in patients with nonvalvular atrial fibrillation treated with a direct oral anticoagulant [rivaroxaban]’]) evaluated risk 2 major adverse cardiovascular events (MACE) score in AF patients treated with rivaroxaban, showing the frequency of MACE is lower among high-risk patients prescribed with rivaroxaban in clinical practice [12,13].

This study analyzed the impact of atherosclerotic vascular disease, defined as the presence of previous CAD or peripheral artery disease/aortic plaque, on clinical profile and outcomes in AF patients anticoagulated with rivaroxaban in the EMIR population.

Materials & methods

The design and methods of the EMIR study have been described elsewhere [12,13]. Briefly, EMIR was a prospective and observational study that included adult patients with a diagnosis of AF treated with rivaroxaban for at least 6 months before enrollment. All patients had to give their written informed consent before being included in the study and were followed up for 2.5 years according to routine clinical practice. The exclusion criteria were prosthetic heart valves, severe valvopathy, chronic infections, systemic autoimmune diseases, active cancer, severe liver or renal insufficiency and severe cognitive impairment. The study was approved by the local ethics committees. For the purpose of this study, we performed a retrospective analysis of the EMIR database, although all the end points were prospectively collected.

Baseline data, including biodemographic parameters, scales (CHA₂DS₂-VASc, HAS-BLED, 2MACE), cardiovascular risk factors and history of vascular disease were collected from the patients’ clinical history and via interview and recorded on a specific electronic case report form. Data were analyzed in the overall study population and according to the presence of vascular disease, which was defined as the presence of baseline CAD, cerebrovascular disease or peripheral artery disease. The presence of coronary heart disease, vascular disease and aortic plaque were recorded from the electronic clinical history of patients, according to physicians’ criteria. Chronic kidney disease was defined as an estimated glomerular filtration rate <60 ml/min/1.73 m² according to the MDRD-4 formula [14].

Outcomes (MACE, thromboembolic events, major bleeding, myocardial infarction, revascularization, cardiovascular death and all-cause mortality) during the study were evaluated by an independent scientific committee. MACE included a combination of non-fatal myocardial infarction, revascularization and cardiovascular death (ischemic heart disease, progressive heart failure and sudden cardiac death). Thromboembolic events included a combination of stroke, systemic embolism and/or transient ischemic attack, together with myocardial infarction. Major bleeding was defined according to definition of the International Society of Thrombosis and Hemostasis [15]. Events were analyzed in the overall study population and according to the presence of previous CAD, peripheral artery disease/aortic plaque and vascular disease. In addition, predictors of MACE, thromboembolic events and major bleeding in patients with previous CAD or vascular disease were determined.

Statistical methods

Qualitative variables were expressed as absolute and relative frequencies. Quantitative variables were reported with measures of central tendency (mean) and dispersion (standard deviation). Qualitative variables were compared using the chi-square test or the Fisher exact test, as required. The *t*-test was used to compare two means. Incident rates were calculated for each event in the overall study population and according to the presence of previous CAD, peripheral artery disease/aortic plaque and vascular disease. Multivariate logistic regression analyses were performed to assess predictors of MACE, thromboembolic events and major bleeding (dependent variables). The

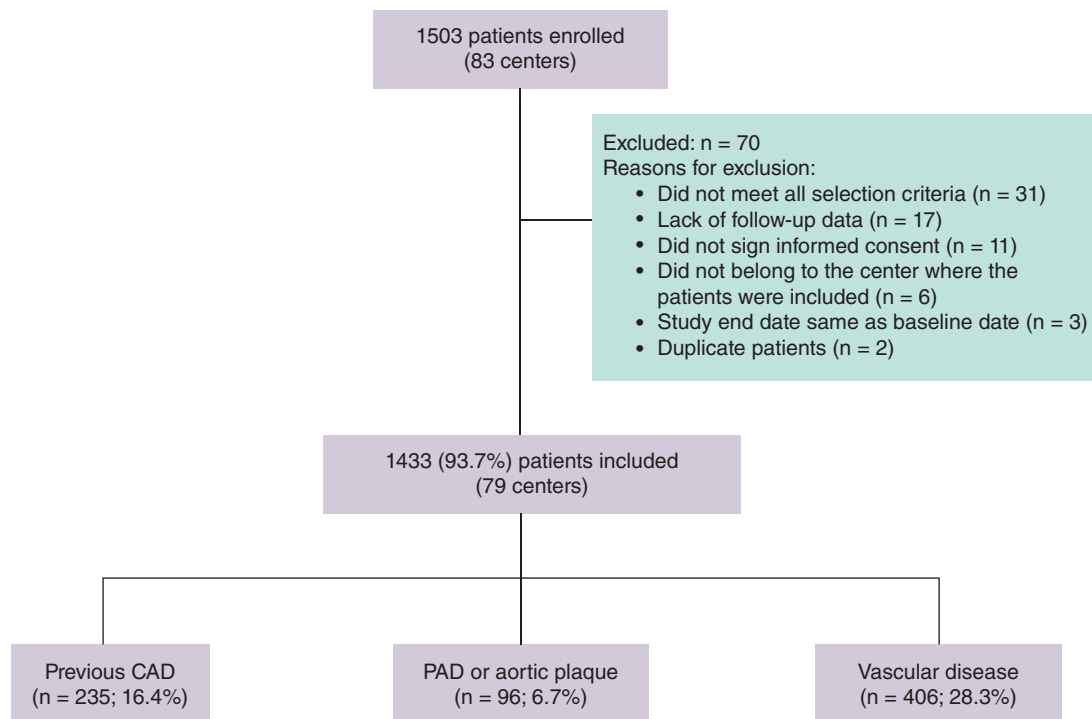


Figure 1. Flow chart of the study population.

Vascular disease: previous CAD and/or previous cerebrovascular disease and/or PAD.
CAD: Coronary artery disease; PAD: Peripheral artery disease.

independent variables were age (continuous variable), sex (female vs male), BMI (continuous variable), type of AF (permanent vs paroxysmal), CAD, coronary revascularization, concomitant use of antiplatelet agents, heart failure, previous cerebrovascular disease, peripheral artery disease, dependence level (dependent vs autonomous), diabetes, hypertension, hyperlipidemia, smoking, chronic kidney disease, previous bleeding, liver failure, pulmonary disease, cancer, alcohol use, non-severe dementia, CHA₂DS₂-VASc (discrete quantitative), HAS-BLED (discrete quantitative) and 2MACE ≥ 3 . The multivariate models were constructed by including those factors with $p < 0.150$ in the bivariate analysis using automatic forward stepwise selection. Only the significant factors were finally included in the model. Statistical significance was set at <0.05 for all tests. The data were analyzed using the statistical package SPSS (v18.0 or higher).

Results

The initial study population comprised 1503 patients from 83 Spanish centers (hospitals and private clinics). After the exclusion of 70 patients, 1433 (93.7%) patients from 79 Spanish centers, were included in the final analysis. At baseline, 235 (16.4%) had CAD, 96 (6.7%) peripheral artery disease/aortic plaque and 406 (28.3%) vascular disease (Figure 1).

Table 1 presents the baseline clinical characteristics overall and according to the presence of previous CAD, peripheral artery disease/aortic plaque and vascular disease. Mean age was 74.2 ± 9.7 years, 55.5% of patients were male, 37.5% had permanent AF, mean CHA₂DS₂-VASc was 3.5 ± 1.5 , mean HAS-BLED was 1.6 ± 1.0 , and 26.9% had a 2MACE score ≥ 3 . Compared with patients without CAD, those with ischemic heart disease were more commonly men, had higher CHA₂DS₂-VASc and HAS-BLED scores, and more frequently had diabetes, heart failure and peripheral artery disease. In addition, a greater proportion of patients presented with 2MACE ≥ 3 . Compared with patients without peripheral artery disease/aortic plaque, those with peripheral artery disease/aortic plaque were older, had higher CHA₂DS₂-VASc and HAS-BLED scores and more frequently had hypertension, diabetes, heart failure and chronic kidney disease. In addition, a greater proportion of patients had 2MACE ≥ 3 . Compared with patients without vascular disease, those with vascular disease were older and more commonly men

Table 1. Baseline clinical characteristics of the study population overall and according to the presence of coronary artery disease, peripheral artery disease/aortic plaque or vascular disease.										
	Total population (n = 1433; 100%)	No previous CAD (n = 1198; 83.6%)	Previous CAD (n = 235; 16.4%)	p-value	No PAD/aortic plaque (n = 1337; 93.3%)	PAD/aortic plaque (n = 96; 6.7%)	p-value	No vascular disease (n = 1027; 71.7%)	Vascular disease † (n = 406; 28.3%)	p-value
Biodemographic data										
Age, years	74.2 ± 9.7	74.0 ± 9.7	74.8 ± 9.6	0.215	74.0 ± 9.7	77.1 ± 8.3	0.002	73.6 ± 9.7	75.6 ± 9.6	<0.001
Sex (male), n (%)	795 (55.5)	613 (51.2)	182 (77.4)	<0.001	733 (54.8)	62 (64.6)	0.063	523 (50.9)	272 (67.0)	<0.001
Permanent AF, n (%)	535 (37.5)	437 (36.5)	98 (41.7)	0.130	492 (36.8)	43 (44.8)	0.118	367 (35.7)	168 (41.4)	0.047
BMI, kg/m²	29.1 ± 4.9	29.2 ± 4.9	28.8 ± 4.8	0.214	29.1 ± 5.0	29.4 ± 4.1	0.200	29.2 ± 5.0	28.8 ± 4.6	0.175
Risk stratification										
CHA2DS2-VASc score	3.5 ± 1.5	3.4 ± 1.5	4.1 ± 1.6	<0.001	3.4 ± 1.5	4.9 ± 1.4	<0.001	3.1 ± 1.3	4.6 ± 1.6	<0.001
2MACE score ≥3, n (%)	385 (26.9)	223 (18.6)	162 (68.9)	<0.001	337 (25.2)	48 (50.0)	<0.001	110 (10.7)	275 (67.7)	<0.001
HAS-BLED score	1.6 ± 1.0	1.5 ± 1.0	1.8 ± 1.0	<0.001	1.5 ± 1.0	2.0 ± 1.0	<0.001	1.3 ± 0.9	2.1 ± 1.1	<0.001
Cardiovascular risk factors										
Hypertension, n (%)	1137 (79.3)	948 (79.1)	189 (80.4)	0.654	1,051 (78.6)	86 (89.6)	0.010	803 (78.2)	334 (82.3)	0.086
Diabetes, n (%)	388 (27.1)	296 (24.7)	92 (39.1)	<0.001	350 (26.2)	38 (39.6)	0.004	242 (23.6)	146 (36.0)	<0.001
Vascular disease										
Previous coronary disease, n (%)	235 (16.4)	0	235 (100)	<0.001				0	235 (57.9)	<0.001
Heart failure, n (%)	326 (22.7)	234 (19.5)	92 (39.1)	<0.001	293 (21.9)	33 (34.4)	0.005	199 (19.4)	127 (31.3)	<0.001
Previous cerebrovascular disease, n (%)	179 (12.5)	143 (11.9)	36 (15.3)	0.152	162 (12.1)	17 (17.7)	0.109	0	179 (44.1)	<0.001
Peripheral artery disease, n (%)	58 (4.0)	38 (3.2)	20 (8.5)	<0.001				0	58 (14.3)	<0.001
Chronic kidney disease, n (%)	350 (24.4)	286 (23.9)	64 (27.6)	0.262	313 (23.4)	37 (38.9)	0.001	242 (23.6)	108 (26.8)	0.244
† Vascular disease was defined as the presence of previous CAD and/or previous cerebrovascular disease and/or PAD. AF: Atrial fibrillation; CAD: Coronary artery disease; MACE: Major cardiovascular event; PAD: Peripheral artery disease.										

and had more permanent AF, higher CHA₂DS₂-VASc and HAS-BLED scores, as well as more frequent diabetes and heart failure. In addition, more patients had 2MACE ≥ 3 .

The mean follow-up was 2.2 ± 0.6 years (median: 2.5 years; interquartile range: 2.2–2.6 years). The incident rates of relevant events were calculated based on 1425 patients (Table 2). Overall, annual percentages of stroke + systemic embolism + transient ischemic attack, MACE, cardiovascular death, death from any cause and major bleeding were 0.72, 1.07, 0.63, 2.73 and 1.04%, respectively. Compared with patients with no previous CAD at baseline, those with ischemic heart disease had a greater annual frequency of MACE, coronary revascularization, cardiovascular death and death from any cause, with a trend toward more thromboembolic outcomes and major bleeding. Compared with patients without previous vascular disease at baseline, those with vascular disease had higher incidence rates of stroke + systemic embolism + transient ischemic attack, MACE, coronary revascularization, cardiovascular death, death from any cause and major bleeding. By contrast, no significant differences were found regarding outcomes according to the presence of peripheral artery disease/aortic plaque.

Multivariate logistic regression analyses were performed to determine the potential predictors of MACE events, thromboembolic events and major bleeding (Table 3). The concomitant use of antiplatelet agents and older age were independent predictive factors associated with MACE in patients with previous CAD, whereas antiplatelet agents and heart failure were independent predictive factors associated with MACE in patients with vascular disease. On the other hand, permanent AF and previous stroke were independently associated with the development of thromboembolic events in patients with previous CAD, and permanent AF was associated with the development of thromboembolic events in patients with vascular disease. Finally, chronic kidney disease was an independent predictor for major bleeding in patients with previous CAD and vascular disease.

Discussion

Although, it is known that the presence of comorbidities may have a negative impact on the prognosis of AF patients, it has not been well established how cardiovascular disease may impact on AF patients. This is even more relevant among patients taking direct oral anticoagulants. Our study of a wide sample of real-life patients with AF anticoagulated with rivaroxaban showed that patients with atherosclerotic vascular disease have a worse clinical profile and a much higher risk of MACE (cardiac mortality, coronary revascularization, non-fatal myocardial infarction), thromboembolic events and cardiovascular mortality than patients without vascular disease.

In the EMIR study, rivaroxaban was prescribed in high-risk patients, as in the pivotal clinical trial and in other real-life registries [11,16]. In addition, our study showed, in line with the ROCKET-AF substudies [17–19], that patients with CAD, peripheral artery disease/aortic plaque and vascular disease had a worse clinical profile, with more comorbidities and a higher thromboembolic and bleeding risk than patients without these conditions. As a result, our data are representative of this population. Therefore, the management of these patients is more challenging and requires a comprehensive, holistic approach addressing all aspects of prevention of cardiovascular disease [7].

In the EMIR study, patients with ischemic heart disease had greater incidence rates of MACE, coronary revascularization, cardiovascular death and death from any cause. In the ROCKET-AF trial, rates of cardiovascular death and myocardial infarction were higher in patients who had previously had myocardial infarction than in those who had not. Of note, among patients with previous myocardial infarction, the risk of ischemic cardiac events fell by 14% in those treated with rivaroxaban than in those treated with warfarin, although the difference was not significant [17]. A meta-analysis of nine trials from various clinical scenarios (AF, acute coronary syndrome, prophylaxis and treatment of deep venous thrombosis/pulmonary embolism), showed that compared with the control groups, rivaroxaban was associated with an 18% reduction in the risk of myocardial infarction [20]. As a result, although the risk of outcomes is higher in patients with CAD, this risk remains low among real-world AF patients taking rivaroxaban, likely owing to its beneficial effects on these outcomes [21]. A trend toward more major bleeding was observed; however, and is probably associated with the more frequent use of antiplatelet agents in this population [22]. Of note, the AFIRE trial showed that in patients with AF and stable CAD, rivaroxaban in monotherapy had a similar efficacy but better safety profile than the combination of rivaroxaban and a single antiplatelet agent [23].

In our study, similar outcomes were observed regardless of the presence of peripheral artery disease/aortic plaque. Although this could be explained by the low number of patients included in this subgroup, in the pivotal ROCKET AF clinical trial, patients with peripheral artery disease did not have a higher risk of stroke or systemic embolism [18]. However, in the EMIR study, patients with vascular disease had a higher risk of thromboembolic

Table 2. Events during follow-up in the overall study population and according to the presence of coronary artery disease, peripheral artery disease/aortic plaque, or vascular disease.

	Total (n = 1,425)	No previous CAD (n = 1,190)	Previous CAD (n = 235)	p-value	No PAD/aortic plaque (n = 1,329)	PAD/aortic plaque (n = 96)	p-value	No vascular disease (n = 1,019)	Vascular disease [†] (n = 406)	p-value
Thromboembolic events [§]										
Patients, n (%)	21 (1.5)	14 (1.2)	7 (3.0)	0.036	20 (1.5)	1 (1.0)	0.716	11 (1.1)	10 (2.5)	0.050
Incident rate events (%) [‡]	0.66	0.52	1.39	0.075	0.67	0.47	0.999	0.48	1.13	0.085
Stroke + SE + TIA										
Patients, n (%)	23 (1.6)	16 (1.3)	7 (3.0)	0.084	22 (1.6)	1 (1.0)	0.999	10 (1.0)	13 (3.2)	0.002
Incident rate events (%) [‡]	0.72	0.60	1.39	0.119	0.74	0.47	0.999	0.44	1.47	0.007
Major bleeding										
Patients, n (%)	29 (2.0)	22 (1.8)	7 (3.0)	0.306	29 (2.2)	0	0.255	14 (1.4)	15 (3.7)	0.005
Incident rate events (%) [‡]	1.04	0.86	1.99	0.055	1.11	0	0.204	0.65	2.03	0.002
MACE										
Patients, n (%)	30 (2.1)	16 (1.3)	14 (6.0)	<0.001	26 (1.9)	4 (4.2)	0.136	14 (1.4)	16 (3.9)	0.002
Incident rate events (%) [‡]	1.07	0.71	2.98	<0.001	0.98	2.35	0.148	0.70	2.03	0.004
Myocardial infarction										
Patients, n (%)	5 (0.3)	4 (0.3)	1 (0.4)	0.592	5 (0.4)	0	0.999	4 (0.4)	1 (0.2)	0.999
Incident rate events (%) [‡]	0.16	0.15	0.20	0.999	0.17	0	0.999	0.17	0.11	0.999
Revascularization										
Patients, n (%)	9 (0.6)	4 (0.3)	5 (2.1)	0.008	7 (0.5)	2 (2.1)	0.118	3 (0.3)	6 (1.5)	0.019
Incident rate events (%) [‡]	0.28	0.15	0.99	0.014	0.24	0.94	0.235	0.13	0.68	0.035
Cardiovascular death										
Patients, n (%)	20 (1.4)	11 (0.9)	9 (3.8)	0.002	17 (1.3)	3 (3.1)	0.145	9 (0.9)	11 (2.7)	0.010
Incident rate events (%) [‡]	0.63	0.41	1.79	0.004	0.57	1.41	0.292	0.39	1.24	0.025
Death from any cause										
Patients, n (%)	87 (6.1)	59 (5.0)	28 (11.9)	<0.001	79 (5.9)	8 (8.3)	0.345	42 (4.1)	45 (11.1)	<0.001
Incident rate events (%) [‡]	2.73	2.20	5.56	<0.001	2.66	3.75	0.453	1.83	5.08	<0.001

[†] Vascular disease was defined as the presence of previous CAD and/or previous cerebrovascular disease and/or PAD.

[‡] Events/100 patients/year.

[§] Ischemic stroke and/or systemic embolism and/or transient ischemic attack and/or myocardial infarction; MACE: Non-fatal myocardial infarction and/or revascularization and/or cardiovascular death.

AF: Atrial fibrillation; CAD: Coronary artery disease; PAD: Peripheral artery disease; SE: Systemic embolism; TIA: Transient ischemic attack.

Table 3. Predictors of MACE, thromboembolic events and major bleeding in patients with previous coronary artery disease or vascular disease.**3.1. Previous coronary artery disease.**

Independent variables	Univariate analysis			Multivariate analysis		
	p-value	OR	95% CI	p-value	OR	95% CI
Dependent variable 'MACE events'						
Antiplatelet agents	0.003	5.71	1.83–17.77	0.001	7.07	2.16–23.11
Hyperlipidemia	0.112	5.30	0.68–41.36			
Cancer	0.130	3.52	0.69–17.87			
Chronic kidney disease	0.045	3.11	1.02–9.42			
HAS-BLED (discrete quantitative)	0.098	1.54	0.92–2.57			
Age (continuous variable)	0.072	1.06	1.00–1.13	0.032	1.08	1.01–1.17
Dependent variable 'thromboembolic events'						
Type of AF (permanent vs paroxysmal)	0.045	8.87	1.05–74.90	0.038	9.85	1.14–84.95
Previous stroke	0.047	4.77	1.02–22.32	0.035	5.56	1.13–27.43
Diabetes	0.099	4.05	0.77–21.34			
HAS-BLED (discrete quantitative)	0.063	1.97	0.97–4.02			
CHA ₂ DS ₂ -VASC (discrete quantitative)	0.082	1.50	0.95–2.36			
BMI (continuous variable)	0.114	0.84	0.68–1.04			
Arterial hypertension	0.134	0.31	0.07–1.44			
Dependent variable 'Major bleeding'						
Chronic kidney disease	0.006	10.46	1.96–55.67	0.006	10.46	1.96–55.67
Cancer	0.016	8.72	1.50–50.59			
Patient autonomy (dependent vs autonomous)	0.047	4.78	1.02–22.40			
HAS-BLED (discrete quantitative)	0.005	3.01	1.39–6.52			
CHA ₂ DS ₂ -VASC (discrete quantitative)	0.130	1.42	0.90–2.23			
Age (continuous variable)	0.027	1.13	1.014–1.26			

3.2. Vascular disease[†].

Independent variables	Univariate analysis			Multivariate analysis		
	p-value	OR	95% CI	p-value	OR	95% CI
Dependent variable 'MACE events'						
Antiplatelet agents	<0.001	8.23	2.84–24.10	<0.001	7.98	2.71–23.51
Ischemic heart disease	0.037	4.95	1.10–22.22			
Coronary revascularization	0.025	3.77	1.18–12.04			
Heart failure	0.021	3.47	1.21–9.97	0.032	3.28	1.11–9.70
Hyperlipidemia	0.141	3.09	0.69–13.90			
Chronic kidney disease	0.084	2.55	0.88–7.38			
Sex (female vs male)	0.058	0.14	0.02–1.07			
Previous stroke	0.023	0.09	0.01–0.72			
Dependent variable 'thromboembolic events'						
Type of AF (permanent vs paroxysmal)	0.026	5.90	1.24–28.15	0.026	5.90	1.24–28.15
Heart failure	0.061	3.41	0.95–12.30			
Diabetes	0.123	2.74	0.76–9.88			
HAS-BLED (discrete quantitative)	0.145	1.52	0.87–2.66			
CHA ₂ DS ₂ -VASC (discrete quantitative)	0.052	1.50	0.99–2.25			
Age (continuous variable)	0.072	1.08	0.99–1.17			
BMI (continuous variable)	0.095	0.87	0.73–1.03			

[†]Vascular disease was defined as the presence of either previous CAD and/or previous cerebrovascular disease and/or PAD.

Vascular disease: previous coronary artery disease and/or previous cerebrovascular disease and/or peripheral artery disease; MACE: Non-fatal myocardial infarction and/or revascularization and/or cardiovascular death; thromboembolic events: ischemic stroke and/or systemic embolism and/or transient ischemic attack and/or myocardial infarction. AF: Atrial fibrillation; CAD: Coronary artery disease; OR: Odds ratio; PAD: Peripheral artery disease.

Table 3. Predictors of MACE, thromboembolic events and major bleeding in patients with previous coronary artery disease or vascular disease (cont.).**3.2. Vascular disease[†].**

Independent variables	Univariate analysis			Multivariate analysis		
	p-value	OR	95% CI	p-value	OR	95% CI
Dependent variable 'Major bleeding'						
2MACE ≥ 3	0.062	6.97	0.91–53.61			
Chronic kidney disease	0.001	6.02	2.08–17.42	0.001	6.02	2.08–17.42
Previous bleeding	0.146	3.19	0.67–15.20			
Patient autonomy (dependent vs autonomous)	0.064	2.91	0.94–8.97			
CHA ₂ DS ₂ -VASC (discrete quantitative)	0.108	1.31	0.94–1.81			
Age (continuous variable)	0.016	1.09	1.02–1.17			
HAS-BLED (discrete quantitative)	0.001	2.13	1.34–3.40			
Heart failure	0.146	0.33	0.07–1.47			

[†] Vascular disease was defined as the presence of either previous CAD and/or previous cerebrovascular disease and/or PAD.

Vascular disease: previous coronary artery disease and/or previous cerebrovascular disease and/or peripheral artery disease; MACE: Non-fatal myocardial infarction and/or revascularization and/or cardiovascular death; thromboembolic events: ischemic stroke and/or systemic embolism and/or transient ischemic attack and/or myocardial infarction. AF: Atrial fibrillation; CAD: Coronary artery disease; OR: Odds ratio; PAD: Peripheral artery disease.

events, MACE and death. Therefore, it is necessary to consider not only the risk of stroke, but also that of other cardiovascular outcomes. In ROCKET AF, compared with warfarin, rivaroxaban exhibited a favorable net clinical benefit in terms of death, stroke, systemic embolism, myocardial infarction and major bleeding [24]. Our data would confirm the effectiveness and safety of rivaroxaban in clinical practice among patients with vascular disease.

Despite bleeding risk or cancer could be associated with more events [25,26], the multivariate analysis showed that concomitant use of antiplatelet agents was associated with a higher risk of MACE, both in patients with previous CAD and in those with vascular disease. This observation was also reported by other authors [27] and could have been associated with the possibility that these patients may have had recent acute coronary syndrome or undergone a myocardial revascularization procedure. It is well known that such patients are at particularly high risk for heart failure, repeated urgent revascularization and cardiovascular death [28]. Another explanation for the adverse outcomes affecting patients taking concomitant antiplatelet and anticoagulation medication is the possible increasing risk of embolic or atherosclerotic complications immediately after bleeding events. Accordingly, patients in the AFIRE trial who experienced major bleeding also had a higher risk of thrombotic complications, especially during the first 30 days after the bleeding event, likely associated with withdrawal of antithrombotic therapy [29]. Remarkably, in real-life patients, the combination of antiplatelet agents and oral anticoagulants among patients with AF does not prevent ischemic events, but rather significantly increases the frequency of major bleeding [30]. As a result, except for the first 12 months after an acute event coronary syndrome or coronary revascularization, antiplatelets agents should be withdrawn and anticoagulation should be considered the only antithrombotic therapy in AF patients with stable CAD (7).

Permanent AF was associated with a higher risk of thromboembolic events in affected patients. Although the type of AF is not included in the CHA₂DS₂-VASC score, it is important to remember that patients with a higher AF burden may have a higher risk of stroke [31]. Finally, chronic kidney disease was associated with a higher risk of major bleeding. Of note, as chronic kidney disease also markedly increases the risk of stroke, affected patients should be anticoagulated in most cases [32]. In addition, in a previous analysis of the EMIR study, renal function was preserved among patients chronically anticoagulated with rivaroxaban [13]. However, to obtain the maximum benefit, it is important that the dosage of all direct oral anticoagulants be adjusted according to renal function [8].

This study is subject to a series of limitations. Its observational design precluded the inclusion of a control group. Therefore, despite the high number of patients included, the consecutive recruitment, and the high quality of data recorded, confounding factors could be present. In addition, as the presence of coronary heart disease, vascular disease and aortic plaque were recorded from the electronic clinical history of patients, according to physicians' criteria, some of these conditions could be underdiagnosed. On the other hand, patients with some of these conditions could be included in the other groups, limiting the analysis for each conditions separately. As a result, this was an exploratory analysis and the results should be confirmed in future studies. On the other hand,

patients were recruited after at least 6 months of treatment with rivaroxaban in Spain. Consequently, the results of the EMIR study can only be applied to patients with similar clinical characteristics.

Conclusion

Among AF patients anticoagulated with rivaroxaban in clinical practice, approximately 16% have CAD and 28% vascular disease. Overall, rates of thromboembolic events, MACE, cardiovascular death and major bleeding are low. However, patients with atherosclerotic vascular disease exhibit a worse clinical profile and a higher risk of MACE, thromboembolic events and cardiovascular mortality than those without. The management of patients with AF and vascular disease requires a comprehensive approach, with the aim of reducing not only the risk of stroke, but also that of cardiovascular related complications. In this context, rivaroxaban should be considered for the treatment of affected patients in clinical practice.

Summary points

- Atherosclerotic cardiovascular disease and atrial fibrillation (AF) are common conditions that frequently co-occur.
- This study analyzed the impact of the presence of atherosclerotic cardiovascular disease in AF patients anticoagulated with rivaroxaban.
- This observational, multicenter and prospective study included 1433 AF adults anticoagulated with rivaroxaban ≥ 6 months.
- Out of 1433 patients, 235 (16.4%) had coronary artery disease (CAD), 96 (6.7%) peripheral artery disease/aortic plaque and 406 (28.3%) vascular disease. Patients with any of these conditions exhibited a higher-risk clinical profile.
- Patients with CAD had higher rates of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction or coronary revascularization), coronary revascularization, cardiovascular death and death from any cause.
- Patients with vascular disease had higher rates of thromboembolic events, major adverse cardiovascular events, coronary revascularization, cardiovascular death, death from any cause and major bleeding.
- CAD and vascular disease are common in patients with AF. Patients with AF have a worse clinical profile and a higher risk of outcomes.

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Ethical conduct of research

The study was approved by each Ethical Committee of the participating centers.

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