

# Outcomes and predictive value of the 2MACE score in patients with atrial fibrillation treated with rivaroxaban in a prospective, multicenter observational study: The EMIR study

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## Abstract

**Background:** The aim of the study was to evaluate the performance of the 2MACE in patients with atrial fibrillation (AF) treated with rivaroxaban and to improve the accuracy of 2MACE.

**Methods:** This was a post-authorization and observational study of AF adults treated with rivaroxaban for  $\geq 6$  months. The primary endpoint was any of the major adverse cardiac events (MACE), namely, cardiovascular death, non-fatal myocardial infarction, and myocardial revascularization. The area under the curve (AUC) was calculated to evaluate the performance of 2MACE, and a new score, 2MACER to predict MACE.

**Results:** A total of 1433 patients were included ( $74.2 \pm 9.7$  years,  $CHA_2DS_2-VASc$   $3.5 \pm 1.5$ , 26.9% 2MACE  $\geq 3$ ). The annual event rates (follow-up 2.5 years) were 1.07% for MACE, 0.66% for thromboembolic events and 1.04% for major bleeding. Patients with 2MACE  $\geq 3$  (vs.  $< 3$ ) had higher risk of stroke/systemic embolism/transient ischemic attack (odds ratio [OR] 5.270; 95% confidence interval [CI] 2.216–12.532), major bleeding (OR 4.624; 95% CI 2.163–9.882), MACE (OR 3.202; 95% CI 1.548–6.626) and cardiovascular death (OR 3.395; 95% CI 1.396–8.259). 2MACE was recalculated giving 1 more point to patients with baseline a glomerular filtration rate  $< 50$  mL/min/1.73 m<sup>2</sup> (2MACER); (2MACER vs. 2MACE: IDI 0.1%,  $p = 0.126$ ; NRI 23.9%,  $p = 0.125$ ; AUC: 0.651 [95% CI 0.547–0.755] vs. 0.638 [95% CI 0.534–0.742], respectively;  $p = 0.361$ ).

**Conclusions:** In clinical practice, AF patients anticoagulated with rivaroxaban exhibit a low risk of events. 2MACE score acts as a modest predictor of a higher risk of adverse outcomes in this population. 2MACER did not significantly increase the ability of 2MACE to predict MACE. (Cardiol J 2022; 29, 4: 601–609)

**Key words:** atrial fibrillation, bleeding, major adverse cardiac events (MACE), stroke, rivaroxaban

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## Introduction

Patients with atrial fibrillation (AF) have a 4- to 5-fold increased risk of stroke. However, this risk can be substantially reduced with long-term anticoagulation therapy [1, 2]. In addition, AF is an important predictor of other important cardiovascular (CV) events, including myocardial infarction (MI) and an independent predictor of CV death [3, 4]. Thus, 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 MI and heart failure (HF) [2].

Although a higher CHA<sub>2</sub>DS<sub>2</sub>-VASc score has been associated with a greater risk of CV events, this scale has been designed to assess thromboembolic risk in the AF population, but not the risk of CV events. By contrast, the 2MACE score (2 points for metabolic syndrome and age ≥ 75 years, and 1 point for MI/revascularization, congestive HF/ejection fraction ≤ 40%, and thromboembolism-stroke/transient ischemic attack [TIA]) has been specifically developed to predict the risk of major adverse cardiac events (MACE) in patients with AF. A 2MACE score ≥ 3 has the best combination of specificity and sensitivity for predicting MACE [5]. Nevertheless, the 2MACE score is affected by limitations (i.e., the original cohort was Caucasian, and all patients were treated with vitamin K antagonists [VKAs]), thus potentially restricting its use in clinical practice [5]. As a result, an improved score for such events is desirable.

In patients taking VKA, the risk of MACE increases as control of anticoagulation worsens [6]. Direct oral anticoagulants (DOACs) overcome the main limitations of VKAs and are now widely prescribed [7]. Results from pivotal studies show that DOACs have a better efficacy and safety profile than warfarin in patients with AF [8]. Although the information provided by clinical trials is of great interest, studies performed in clinical practice assess the efficacy and safety of a drug for treatment of AF under real-world conditions. However, few real-world data are available on the role of rivaroxaban in comprehensive CV protection (i.e., against thromboembolic events and MI or HF) [9–11].

In summary, the dearth of information about the 2MACE score in patients treated with DOACs makes it necessary to assess the performance of the score in a population receiving DOACs and to determine whether 2MACE can be improved by including additional risk factors or by removing some of the existing ones. 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]”] [12] was designed to evaluate the performance of 2MACE for assessing CV risk in AF patients treated with rivaroxaban. The primary endpoint was any of the MACE: CV death, non-fatal MI, or myocardial revascularization. In addition, the study also evaluated the potential for increasing the accuracy of the 2MACE score either by incorporating additional risk factors or by replacing some of the existing ones.

## Methods

EMIR was a post-authorization, observational, and non-interventional study, conducted in 79 centers (hospitals and private clinics) throughout Spain. The study population comprised adult patients with AF treated with rivaroxaban for at least 6 months before inclusion. All patients had to give written informed consent before being enrolled in the study. The exclusion criteria were participation in an investigational program with interventions outside routine clinical practice, initiation of treatment with rivaroxaban after the start of the inclusion period, presence of prosthetic heart valves or severe valve disease, severe cognitive impairment, chronic infections, systemic autoimmune diseases, active cancer, or severe liver failure. The study was approved by the local Institutional Review Boards.

Data were collected at 4 study visits over 2 years and 6 months: baseline visit, follow-up 1 (at year 1), follow-up 2 (at year 2), and final visit (after 2 years and 6 months or early termination). All the study visits coincided with the patients' routine visits to monitor their disease. Only data available from daily clinical practice were collected, and there were no requests for additional visits, laboratory tests, or diagnostic tests.

Baseline data were recorded using an electronic case report form specially designed for this study. The data recorded included biodemographic data, physical examination findings, risk stratification (CHADS<sub>2</sub>, CHA<sub>2</sub>DS<sub>2</sub>-VASc, HAS-BLED, and 2MACE score), CV risk factors, concomitant vascular disease, and other comorbidities. In addition, conditions that increased the risk of bleed-

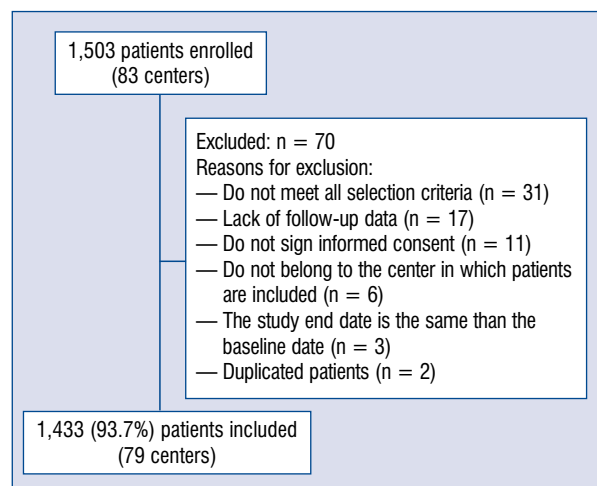
ing, non-severe dementia, laboratory data (most recent hemoglobin, platelet, renal function values within the prior 3 months), and rivaroxaban dose were documented. Dependency was classified as autonomous (no dependency), partial dependency for daily activities, or complete dependency for daily activities. Baseline clinical characteristics were also analyzed according to age, diabetes, hypertension, and renal function (MDRD-4 formula).

MACE (primary endpoint), defined as a combination of non-fatal MI, revascularization, and CV death, were recorded during follow-up. In addition, thromboembolic events (ischemic stroke, TIA, systemic embolism, and MI), death (all-cause and CV), pulmonary embolism, major bleeding (following the International Society of Thrombosis and Hemostasis definition) [13], and fatal bleeding were reported. Annual event rates were calculated. Incidence and annual rate (patient/year) of events (stroke + systemic embolism + TIA, major bleeding, and MACE) were analyzed. A scientific committee independently evaluated and classified the events.

### Statistical methods

The aim of the present study was to assess the performance of the 2MACE score in a population treated with rivaroxaban. The sample size was planned that would enable us to obtain a minimum number of MACE comparable with the events of the study carried out by Pastori et al. [5], which included an original cohort of 1,019 patients with 111 MACE and a validation cohort including 1,089 patients, 68 with MACE. A sample size of 1,500 patients was proposed for this study, assuming a maximum loss to follow-up of 10% and considering two extreme scenarios. In the minimum scenario, it was assumed a loss to follow-up of 10% and a MACE rate of 2%; in the maximum scenario, a loss to follow-up of 5% was considered and a MACE rate of 2.5%. These assumptions yielded 1,350 patients in the minimum scenario and 1,425 patients in the maximum scenario. Given that the overall follow-up period was 2.5 years, we estimated 89 events in the maximum scenario and 68 events in the minimum scenario.

Qualitative variables are expressed as absolute and relative frequencies; quantitative variables are expressed as measures of central tendency and dispersion (mean and standard deviation). Categorical variables were compared using the  $\chi^2$  test or the Fisher exact test, when appropriate. When 2 means were compared, the t test or the Mann-Whitney test was used, as applicable.



**Figure 1.** Study flow chart.

To assess the potential for increasing the accuracy of the 2MACE score either by incorporating additional risk to the 2MACE or replacing some of the existing factors, the feasibility of these factors was initially explored using bivariate models. The multivariate models started to be constructed by introducing those factors with  $p < 0.150$  in the bivariate by the automatic variable selection method by steps forward. Only the significant factors were finally considered to build the model. A logistic regression analysis was used to evaluate the association between specific variables and events during follow-up, and the odds ratio (OR) along with the 95% confidence interval (CI) were calculated. The receiver operating characteristic (ROC) curves were then plotted the sensitivity, specificity, cutoff points for 2MACE were calculated and the new score, if necessary, as well as integrated discrimination index (IDI) and net reclassification index (NRI). Statistical significance was set at 0.05. The data were analyzed using the statistical package SPSS (v18.0 or superior).

### Results

A total of 1,503 patients were enrolled from 79 participating centers. After exclusion of 70 patients for various reasons (i.e., not fulfilling selection criteria, lack of follow-up data, duplicate patients, not belonging to the center, not signing informed consent), 1,433 (93.7%) patients were eventually included in the analysis (Fig. 1).

The clinical characteristics of the study population at baseline are presented in Table 1. Mean age was  $74.2 \pm 9.7$  years, 55.5% of patients were

**Table 1.** Clinical characteristics of the study population at baseline.

	<b>Total (N = 1,433; 100%)</b>
<b>Biodemographic data</b>	
Age [years]:	74.2 ± 9.7
≥ 75	691 (48.2%)
≥ 85	453 (31.6%)
Sex (male)	795 (55.5%)
Level of dependency:	
No dependency	1,251 (89.9%)
Partial dependency	126 (9.1%)
Total dependency	14 (1.0%)
Type of AF:	
Paroxysmal	578 (40.6%)
Persistent	259 (18.2%)
Long-standing persistent	53 (3.7%)
Permanent	535 (37.5%)
<b>Physical examination</b>	
Systolic blood pressure [mmHg]	131.6 ± 16.4
Diastolic blood pressure [mmHg]	76.3 ± 10.5
Heart rate [bpm]	71.9 ± 14.8
Body mass index [kg/m <sup>2</sup> ], median (IQR)	28.4 (25.7–31.9)
<b>Risk stratification</b>	
CHADS <sub>2</sub> score	2.0 ± 1.2
CHA <sub>2</sub> DS <sub>2</sub> -VASc score	3.5 ± 1.5
2MACE score:	1.8 ± 1.4
≥ 3	385 (26.9%)
HAS-BLED score	1.6 ± 1.0
<b>Cardiovascular risk factors</b>	
Hypertension	1,137 (79.3%)
SBP > 160 mmHg	53 (4.7%)
Hyperlipidemia	790 (55.1%)
Diabetes	388 (27.1%)
Smoking:	121 (8.4%)
Current	75 (5.2%)
Ex-smoker < 1 year	23 (1.6%)
Ex-smoker > 1 year	23 (1.6%)
<b>Vascular disease</b>	
Heart failure	326 (22.7%)
Ischemic heart disease	235 (16.4%)
Revascularization	183 (12.8%)
Prior cerebrovascular disease	179 (12.5%)
Peripheral artery disease	58 (4.0%)
Aortic plaque	45 (3.1%)
Venous thromboembolic disease	31 (2.2%)
Prior systemic embolism	14 (1.0%)



**Table 1 (cont.).** Clinical characteristics of the study population at baseline.

	<b>Total (N = 1,433; 100%)</b>
<b>Other conditions/comorbidities</b>	
Kidney failure*	350 (24.7%)
Labile INR	374 (26.1%)
Drug or alcohol use	130 (9.1%)
Medication usage predisposing to bleeding**	123 (8.6%)
Cancer	80 (5.6%)
Falls in the previous 2 years	88 (6.1%)
Previous major bleeding:	46 (3.2%)
Gastrointestinal	17 (1.2%)
Intracranial	8 (0.6%)
Hematuria	8 (0.6%)
Gingival	3 (0.2%)
Joint-muscular	3 (0.2%)
No severe cognitive impairment	33 (2.3%)
Liver failure	10 (0.7%)
<b>Biochemical parameters</b>	
Hemoglobin [g/dL]	14.1 ± 1.6
Platelets [× 10 <sup>12</sup> /L]	17.8 ± 58.7
Creatinine [mg/dL]	1.0 ± 0.4
Glomerular filtration rate (MDRD-4) [mL/min/1.73 m <sup>2</sup> ]	74.9 ± 21.7
Glomerular filtration rate (CKD-EPI) [mL/min/1.73 m <sup>2</sup> ]	69.7 ± 18.4
Creatinine clearance (Cockcroft-Gault) [mL/min]	74.6 ± 30.5

\*Glomerular filtration rate < 60 mL/min/1.73 m<sup>2</sup>; by MDRD-4;  
 \*\*Nonsteroidal anti-inflammatory drugs or antiplatelet agents  
 at least once a week; AF — atrial fibrillation; IQR — interquartile  
 range; INR — international normalized ratio; SBP — systolic blood  
 pressure

men, 40.6% had paroxysmal AF, 37.5% permanent AF, mean CHA<sub>2</sub>DS<sub>2</sub>-VASc score was 3.5 ± 1.5, mean HAS-BLED 1.6 ± 1.0, and 26.9% had a 2MACE score ≥ 3. Cardiovascular risk factors were very common (79.3% hypertension, 27.1% diabetes), as was vascular disease (24.7% kidney failure, 22.7% HF, 16.4% ischemic heart disease [IHD]). Baseline clinical characteristics were analyzed according to age, diabetes, HF, renal function, and 2MACE score (Table 2, **Suppl. Table 1**). Compared with younger patients, those aged 75 years or older were more commonly women, more frequently had HF and permanent AF. They also had higher CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED scores and more frequently had a 2MACE score ≥ 3. Patients with diabetes were more commonly men and more frequently had hypertension, HF, and peripheral



artery disease. In addition, their CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED scores were higher and they more frequently had a 2MACE score  $\geq 3$ . Patients with HF were older, more frequently had diabetes, peripheral artery disease, and permanent AF, as well as higher CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED scores and a 2MACE score  $\geq 3$ . Patients with kidney failure were older and more commonly women. They also had hypertension, HF, and permanent AF more frequently, with higher CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED scores. In addition, their 2MACE score was mostly  $\geq 3$ , although they less frequently had diabetes. Patients with a 2MACE score  $\geq 3$  (vs.  $< 3$ ) were older, had more hypertension, diabetes, HF, prior cerebrovascular disease, peripheral artery disease and kidney failure, with higher CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED scores.

Overall, 1,105 (77.1%) patients were taking rivaroxaban 20 mg once daily, and the remaining 328 (22.9%) were taking rivaroxaban 15 mg. After a median follow-up of 2.5 (2.2–2.6) years, 234 patients discontinued the study prematurely. Eighty-seven (6.1%) patients died during the study, 23.0% (20/87) from CV causes, including progressive chronic HF (13/87, 14.9%). The annual rates of relevant events were calculated based on 1,425 patients and were as follows: death, 2.73%; thromboembolic events, 0.66%; MACE, 1.07%; major bleeding, 1.04%; and fatal bleeding, 0.06%. The annual rates of relevant events were analyzed according to age, diabetes, HF, renal function, and 2MACE score. Annual rates of stroke + systemic embolism + TIA were higher in elderly and diabetic patients and also in those with a 2MACE score  $\geq 3$ . Major bleeding was more common in elderly patients and patients with kidney failure and a 2MACE score  $\geq 3$ . Overall, the risk of stroke, systemic embolism or TIA (OR 5.270; 95% CI 2.216–12.532), major bleeding (OR 4.624; 95% CI 2.163–9.882), MACE (OR 3.202; 95% CI 1.548–6.626) and CV death (OR 3.395; 95% CI 1.396–8.259) was higher in those patients with 2MACE  $\geq 3$  compared to those patients with 2MACE  $< 3$  (Table 3, **Suppl. Fig. 1A–D, Suppl. Table 2**).

Multivariate logistic regression analysis was performed to study the potential association between new CV risk factors and MACE. Ischemic heart disease (OR 3.411; 95% CI 1.599–7.275;  $p = 0.002$ ), kidney failure (OR 2.530; 95% CI 1.165–5.492;  $p = 0.019$ ), and HF (OR 3.402; 95% CI 1.593–7.266;  $p = 0.002$ ) were independently associated with MACE in the overall population. A second multivariate model developed by replacing IHD for IHD and antiplatelet treatment

(the rest of the variables were included as in the first analysis) revealed that combined IHD and antiplatelet treatment (OR 9.067; 95% CI 3.842–21.397;  $p < 0.001$ ), kidney failure (OR 2.561; 95% CI 1.163–5.640;  $p = 0.020$ ), and HF (OR 3.842; 95% CI 1.807–8.170;  $p < 0.001$ ) were independent predictive factors (**Suppl. Table 3**).

The area under the curve (AUC) of 2MACE was 0.638 (95% CI 0.534–0.742;  $p = 0.01$ ). Considering a cut-off = 3 for 2MACE score, sensitivity was 0.533 and specificity 0.737. As IHD and HF are already included in 2MACE score, 2MACE score was recalculated giving 1 more point to the patients with baseline estimated glomerular filtration rate  $< 50$  mL/min/1.73 m<sup>2</sup> by MDRD-4. The new score was called 2MACER (R due to renal impairment). The mean 2MACER score was  $1.9 \pm 1.5$  and (vs.  $1.8 \pm 1.4$  of 2MACE score) and 32.2% had a 2MACER score  $\geq 3$  (vs. 26.9% with 2MACE score  $\geq 3$ ).

The ROC curves for 2MACE and 2MACER scores to predict MACE outcomes are presented in **Supplementary Figure 2**. Both scales were also compared, and the IDI and NRI are in **Supplementary Table 4**. The AUC for 2MACE was 0.638 (95% CI 0.534–0.742) and for 2MACER was 0.651 (95% CI 0.547–0.755),  $p = 0.361$  between the global areas under the two ROC curves. IDI was 0.1%;  $p = 0.126$  and NRI was 23.9%;  $p = 0.125$ .

## Discussion

This study shows that in a stable AF population treated with rivaroxaban, 2MACE score may be helpful in detecting those patients at high risk of adverse outcomes. The prediction of important CV events is modestly improved if the 2MACE score is modified by the addition of 1 point for the estimated glomerular filtration rate  $< 50$  ml/min. The most important message for the clinician is that patients with AF that are already optimally protected from embolic/stroke events by stable treatment with rivaroxaban are still at risk for HF and MI. This risk can be better characterized by considering the past history of IHD, HF and renal insufficiency, with no need for more complex risk calculators.

Despite anticoagulation, patients with AF have a significant residual risk of CV events [14]. The CHA<sub>2</sub>DS<sub>2</sub>-VASc score has been specifically developed to determine stroke risk, but not the risk of CV events. In this context, the 2MACE score could help to identify AF patients at risk for CV events [5]. Both scales provide complementary

**Table 2.** Baseline clinical characteristics according to the 2MACE score.

	Total (n = 1,433; 100%)	2MACE < 3 (n = 1,048; 73.1%)	2MACE ≥ 3 (n = 385; 26.9%)	P
<b>Biodemographic data</b>				
Age [years]	74.2 ± 9.7	72.3 ± 9.6	79.2 ± 7.9	< 0.001
Sex (male)	795 (55.5%)	573 (54.7%)	222 (57.7%)	0.313
Permanent AF	535 (37.5%)	363 (34.6%)	172 (44.7%)	< 0.001
<b>Risk stratification</b>				
CHA <sub>2</sub> DS <sub>2</sub> -VASc score	3.5 ± 1.5	3.0 ± 1.2	4.9 ± 1.4	< 0.001
HAS-BLED score	1.6 ± 1.0	1.4 ± 0.9	2.1 ± 1.0	< 0.001
<b>Cardiovascular risk factors</b>				
Hypertension	1,137 (79.3%)	808 (77.1%)	329 (85.5%)	< 0.001
Diabetes	388 (27.1%)	231 (22.0%)	157 (40.8%)	< 0.001
<b>Vascular disease</b>				
Heart failure	326 (22.7%)	176 (16.8%)	150 (38.9%)	< 0.001
Prior cerebrovascular disease	179 (12.5%)	42 (4.0%)	137 (35.6%)	< 0.001
Peripheral artery disease	58 (4.0%)	26 (2.5%)	32 (8.3%)	< 0.001
<b>Other conditions/comorbidities</b>				
Kidney failure*	350 (24.7%)	222 (21.4%)	128 (33.5%)	< 0.001

\*Glomerular filtration rate < 60 mL/min/1.73 m<sup>2</sup> by MDRD-4; AF — atrial fibrillation

**Table 3.** Incidence and annual rates of events categorized by 2MACE score.

	Patients with 2MACE < 3 (n = 1,048) Annual rate of events (n = 1,042; accumulated time = 2359.90 years)	Patients with 2MACE ≥ 3 (n = 385) Annual rate of events (n = 383; accumulated time = 824.47 years)	P	Odds ratio (95% CI)
<b>Stroke + SE + TIA</b>				
N events [N patients (%)]	8 [8 (0.8)]	15 [15 (3.9)]	< 0.001	<b>5.270</b>
Annual rate of events	0.34	1.82	< 0.001	<b>(2.216–12.532)</b>
<b>Major bleeding</b>				
N events [N patients (%)]	12 [11 (1.0)]	21 [18 (4.7)]	< 0.001	<b>4.624</b>
Annual rate of events	0.51	2.55	< 0.001	<b>(2.163–9.882)</b>
<b>MACE</b>				
N events [N patients (%)]	16 [14 (1.3)]	18 [16 (4.2)]	< 0.001	<b>3.202</b>
Annual rate of events	0.68	2.18	0.001	<b>(1.548–6.626)</b>
<b>Myocardial infarction</b>				
N events [N patients (%)]	3 [3 (0.3)]	2 [2 (0.5)]	0.615	1.819
Annual rate of events	0.13	0.24	0.771	(0.303–10.928)
<b>Revascularization</b>				
N events [N patients (%)]	4 [4 (0.4)]	5 [5 (1.3)]	0.064	3.434
Annual rate of events	0.17	0.61	0.112	(0.917–12.856)
<b>Cardiovascular (cardiac) death</b>				
N events [N patients (%)]	9 [9 (0.9)]	11 [11 (2.9)]	0.004	<b>3.395</b>
Annual rate of events	0.38	1.33	0.011	<b>(1.396–8.259)</b>

CI — confidence interval; MACE — major adverse cardiovascular events; SE — systemic embolism; TIA — transient ischemic attack

information. In the present study, patients with a 2MACE score  $\geq 3$  (vs.  $< 3$ ) had higher annual rates of MACE, CV mortality, fatal HF, stroke + systemic embolism + TIA, and major bleeding. This finding is in line with those of previous studies, which have shown that AF patients with a high 2MACE score have a greater risk of all-cause mortality, CV mortality, MACE, coronary artery disease, and severe coronary artery disease [5, 15–19]. The majority of studies [5, 15–17], but not all [20], have shown a relatively high capacity of 2MACE score to predict CV events in AF patients, that was slightly superior to that found in the current study. This small difference between this study and previous data may be because patients in previous studies were mainly anticoagulated with VKA but not with DOACs, which have a better risk-benefit profile [5, 8, 15–17]. Moreover, low rates of adverse events were recorded herein, despite the high thromboembolic risk of the study patients. These data strongly suggest that adapting the 2MACE score to patients taking DOACs may be of interest, and the addition of renal failure to 2MACE score (2MACER), could slightly improve the accuracy to predict MACE. In the original Pastori cohort, the c-index was 0.79 in the internal derivation cohort and 0.66 in the external validation cohort [5]. In the present study, c-index was 0.638 for 2MACE and 0.651 for 2MACER, very close to the external validation cohort.

Data herein, showed that patients with IHD and concomitant treatment with antiplatelet agents were at especially high risk of CV events. There are at least three possible explanations for this observation. First, baseline characteristics reflect the increased risk of patients with recent acute coronary syndrome or myocardial revascularization. These patients clearly have a higher risk of MACE, such as death, non-fatal MI, new revascularizations or HF. Accordingly, the higher MACE rates would be related to the CV condition itself, rather than the combination of acetylsalicylic acid or P2Y12 inhibitors with rivaroxaban [21]. Second, the combined antithrombotic regimen could lead to additional major bleeding and indirectly higher rates of death or non-fatal HF admissions [22]. Third, there may be polivascular patients, with a known higher risk for additional events [21]. Although some of these findings are not new, this should be further explored.

In the present study, the clinical profile was similar to that found in other real-life studies [11, 23–28], indicating that the current data were representative of patients with AF taking rivaroxaban

in clinical practice, and, consequently, that these results can be extended to this population. With regard to outcomes, annual event rates were low (MACE, 1.07%; thromboembolic events, 0.66%; major bleeding, 1.04%). In a study of patients taking VKAs, annual rates of stroke/TIA and MACE were 1.1% and 2.9%, respectively, after a median follow-up of 30.8 months. Of note, rates of MACE increased as control of the international normalized ratio worsened [6]. In a German registry of patients taking DOACs, the annual incidence of MACE (not including revascularization) was 2% in a population with a mean CHADS<sub>2</sub> of 2 [10]. In the rivaroxaban arm of the ROCKET-AF trial, rates for thromboembolic events, and major bleeding were 1.7, and 3.6 per 100 patient-years, respectively [29]; in the XANTUS study, these values were 1.8 and 2.1 per 100 patient-years, respectively [11]. Therefore, in clinical practice, thromboembolic and bleeding events are less common than in the pivotal clinical trial, and even less frequent in the Spanish population. Although these numbers could be explained by differences in clinical profile, the fact is that in routine practice, event rates are lower with DOACs than with VKAs.

### Limitations of the study

This study is subject to the limitations associated with the population selected. The patients may have differed from those of Pastori's cohort in that they were recruited after at least 6 months of receiving rivaroxaban. In addition, their potentially higher CV risk could prevent the results of this uncontrolled study from being extrapolated to other populations. Clinical evidence indicates that the use of rivaroxaban may also be a limitation in that the number of expected events may be lower than with VKAs, although according to our calculation it was sufficient to assess the performance of the primary and secondary objectives. Another limitation was that the objective of improving the accuracy of the 2MACE score was not validated (internally or externally), because it was an exploratory objective that should be confirmed in further investigations. As this was an observational study, no control group was available, and the presence of residual confounding factors could not be excluded. However, patients were recruited consecutively after an office consultation, thus reducing the possibility of selection bias.

### Conclusions

Although a 2MACE score  $\geq 3$  predicts a higher risk of adverse CV outcomes in AF patients treated

with rivaroxaban, the capacity of 2MACE to estimate major thrombotic outcomes, such as CV death, MI, and myocardial revascularization, is modest in this setting. The new 2MACER score slightly increases the ability to predict MACE in this population. On the other hand, whereas rivaroxaban is used in elderly patients with a high thromboembolic risk and many comorbidities, the rate of adverse events, including death, MACE, thromboembolic complications, and bleeding (major and fatal) is low.

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