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Clinical profile and outcomes in very elderly patients with atrial fibrillation anticoagulated with rivaroxaban: data from the EMIR study

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ABSTRACT

Objectives To analyze the clinical profile, adequacy of treatment with rivaroxaban and outcomes in octogenarians with atrial fibrillation (AF), taking rivaroxaban in clinical practice.

Methods Observational and non-interventional study that included AF adults recruited from 79 Spanish centers, anticoagulated with rivaroxaban ≥ 6 months before being included. Data were analyzed according to age (≥ 80 *vs.* < 80 years) at baseline.

Results Out of 1433 patients, 453 (31.6%) were octogenarians at baseline. Compared to younger patients, octogenarians had more comorbidities, higher CHA_2DS_2-VASc (4.5 ± 1.3 *vs.* 3.0 ± 1.4; $P < 0.001$) and HAS-BLED scores (2.0 ± 1.0 *vs.* 1.4 ± 1.0; $P < 0.001$). Overall, the dose of rivaroxaban was adequately prescribed in 83.4% of patients, but more frequently in the younger population (71.1% *vs.* 89.1%; $P = 0.039$). After a mean follow-up of 2.2 ± 0.6 years, annual rates of stroke + systemic embolism + transient ischemic attack, MACE, cardiovascular death and major bleeding were 1.03%, 1.24%, 1.03% and 1.75%, respectively, in octogenarian patients. Except for progressive heart failure death and major bleeding, rates of outcomes in octogenarians were similar compared to younger patients. In octogenarians, the concomitant use of antiplatelet agents and non-severe dementia were independently associated with the development of ischemic stroke, whereas previous coronary revascularization and heart failure with MACE, and higher HAS-BLED score with major bleeding.

Conclusions In clinical practice, around one third of patients taking rivaroxaban are octogenarians. These patients have many comorbidities and a high thromboembolic risk. Despite that, rates of adverse events remain low. Rivaroxaban is adequately prescribed in the majority of octogenarians.

The current prevalence of atrial fibrillation (AF) in adult population is around 2%-4%, reaching 15%-20% in very elderly population.[1-3] In addition, the prevalence of AF will raise in the next decades, mainly due to a higher longevity of population.[4] Patients with AF have a four to

five-fold increased risk of developing thromboembolic complications, particularly stroke.[2] Despite chronic oral anticoagulation markedly decreases this risk, patients with AF remain at high risk for further cardiovascular events beyond stroke, including major cardiovascular events (MACE), myocardial infarction, heart failure and cardiovascular death.[5-8] As a result, all these complications should also be considered in addition to stroke prevention in the holistic management of patients with AF.[2]

On the other hand, despite vitamin K antagonists (VKA) have demonstrated to effectively reduce the risk of stroke, they have many limitations, particularly attainting an adequate time in therapeutic range, thus, reducing their proper use in clinical practice.[9,10] This is important, since poor anticoagulation control has been associated with an increased risk of MACE, stroke, major bleeding and death.[11,12] By contrast, direct oral anticoagulants (DOACs) provide a linear and predictable anticoagulant effect, overcoming the majority of limitations of VKA. In addition, the pooled analysis of the phase 3 clinical trials with DOACs have demonstrated the better efficacy and safety profile compared with warfarin.[13]

Elderly patients have a high risk of both, stroke and bleeding.[14,15] Despite that, anticoagulation should also be recommended in these patients due to the favorable net clinical benefit.[16] Substudies of RE-LY, ROCKET-AF, ARISTOTLE and ENGAGE AF TIMI-48 trials have specifically analyzed the population aged 75 years or older, with consistent results regarding the relative benefits of DOACs *vs.* warfarin.[17-20] However, although some studies have suggested a favourable benefit risk profile of DOACs over VKA in octogenarian patients with AF,[21-24] little information is still currently available about the impact of DOACs on the development of cardiovascular complications, beyond stroke prevention, in this population in routine practice.

The EMIR[7,8] (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 non-valvular atrial fibrillation treated with a direct oral anticoagulant [rivaroxaban]") study was aimed to evaluate the performance of the cardiovascular risk 2MACE score in AF patients treated with rivaroxaban. In this study, the clinical characteristics, adequacy of treatment with rivaroxaban and outcomes according to age (≥ 80 *vs.* < 80 years) were analyzed.

METHODS

EMIR was a post-authorization and observational study, performed in 79 public and private centers throughout Spain.[7,8] Patients aged 18 years or older, of both sexes, with an established diagnosis of nonvalvular AF according to European guidelines,[2] treated with rivaroxaban ≥ 6 months before inclusion and that had provided written informed consent were included. Patients were followed up for 2.5 years according to routine clinical practice. By contrast, patients participating in a clinical trial, with prosthetic heart valves, severe valvopathy, severe cognitive impairment (based on clinical criteria), chronic infections or systemic autoimmune diseases, active cancer or severe liver insufficiency were excluded. Patients were recruited from December 5th 2026 to June 15th 2017. The study was approved by each participating Institutional Review Board.

The study consisted of four routine visits (baseline, 12 months, 24 months and study end -after 2 years and 6 months, or early termination-), with a total follow-up of up to 2.5 years. All the study visits coincided with the patients' routine visits to monitor their disease. No specific diagnostic or therapeutic interventions were performed for being included in the study. All data were recorded using an electronic case report form specifically created for the EMIR study.

At baseline, biodemographic data (age, sex, body mass index, permanent AF), cardiovascular risk factors (hypertension, diabetes mellitus), vascular disease (renal insufficiency, heart failure, previous cerebrovascular disease, peripheral artery disease) and scores (CHA_2DS_2-VASc, HAS-BLED, and 2MACE),[25-27] were collected. Data were recorded from the electronic clinical history of the patients and also in the interview with the patient during

the patients' routine visit. Renal insufficiency was defined as an estimated glomerular filtration rate < 60 mL/min per 1.73 m^2 by the MDRD-4 formula.[28] Dependency was classified as autonomous (no dependency) and partial or complete dependency to daily activities. Adequacy of dosage of rivaroxaban (20 mg if creatinine clearance ≥ 50 mL/min; 15 mg if 15-50 mL/min) was determined during the follow-up.[29] Data were analyzed according to age (≥ 80 *vs.* < 80 years).

Events during the follow-up, including stroke/transient ischemic attack/systemic embolism, thromboembolic events, MACE, myocardial infarction, heart failure, major bleeding, cardiovascular death and all-cause death were investigated. Thromboembolic events were defined as the presence of any of the following events during the follow-up ischemic stroke, systemic embolism, transient ischemic attack or myocardial infarction. MACE was defined as a combination of non-fatal myocardial infarction, revascularization and cardiovascular death (death for coronary events, progressive heart failure death and sudden cardiac death). Major bleeding was defined according to the International Society of Thrombosis and Hemostasis definition.[30] Annual event rates were calculated for the combined and individual events in the overall study population and according to age (≥ 80 *vs.* < 80 years). A scientific committee independently evaluated and classified the events. In addition, independent factors associated with ischemic stroke, MACE and major bleeding were determined in those patients ≥ 80 years.

Statistical Methods

Qualitative variables were presented as absolute (*n*) and relative (%) frequencies and quantitative variables were described with measures of central tendency (mean) and dispersion (standard deviation). Annual event rates were calculated and presented as event/100 patients per year. Qualitative variables were compared using the chi-square test or the Fisher exact test, as required. When two means were compared, the *t* test or the Mann-Whitney test was used, as applicable. Correlation between two continuous variables was performed using the Pearson or Spearman test, as appropriate. To assess predictors of MACE, ischemic stroke and major bleeding (dependent variables) in those patients ≥ 80 years, multivariate analyses were performed. The following independent variables were considered: age (continuous variable), sex (female *vs.* male), body mass index (continuous variable), previous bleeding, diabetes, permanent AF, ischemic heart disease, coronary revascularization, antiplatelet agents, previous cerebrovascular disease (stroke, transient ischemic attack, or previous non-cerebral embolisms), dependence level (autonomous or dependency for daily activities), arterial hypertension, hyperlipidaemia, smoking, pulmonary disease, renal insufficiency, liver dysfunction, cancer, peripheral artery disease, alcohol use, non-severe dementia, heart failure, CHA_2DS_2-VASc (continuous variable), HAS-BLED (continuous variable) and 2MACE ≥ 3. The multivariate models begun to be constructed by introducing those factors with a significance of $P < 0.150$ in the bivariates by the automatic variable selection method by steps forward. Only the significant factors were finally considered to build the model. A level of statistical significance of 0.05 was applied in all the statistical tests. The data were analyzed using the statistical package SPSS (v20.0).

RESULTS

A total of 1,503 patients were initially enrolled from the 79 Spanish centers (median number of patients included per center of 19). After the exclusion of 70 patients, 1433 (93.7%) patients were included for the final analysis, of whom 453 (31.6%) were 80 years or older at baseline (Figure 1).

The baseline clinical characteristics of the overall study population and according to age are presen-

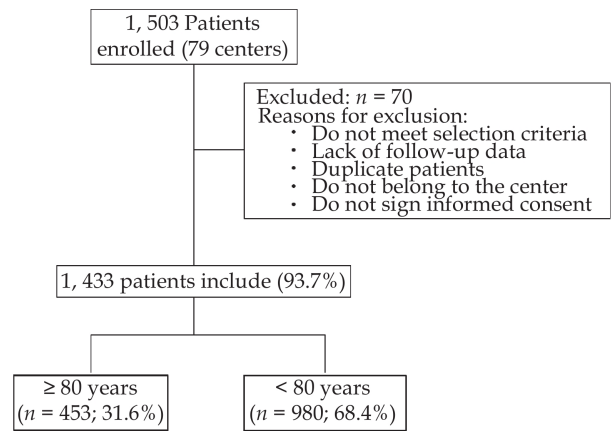

Figure 1 Flow chart of the study population.

Table 1 Baseline clinical characteristics by age.

	Total (n = 1433; 100%)	< 80 years (n = 980; 68.4%)	≥ 80 years (n = 453; 31.6%)	P
Biodemographic data				
Sex (Female)	638 (44.5%)	372 (38.0%)	266 (58.7%)	< 0.001
Body mass index, kg/m^2	29.1 ± 4.9	29.5 ± 4.9	28.2 ± 4.7	< 0.001
Permanent atrial fibrillation	535 (37.3%)	321 (32.8%)	214 (47.2%)	< 0.001
Cardiovascular risk factors				
Hypertension	1137 (79.3%)	758 (77.3%)	379 (83.7%)	0.006
Diabetes mellitus	388 (27.1%)	268 (27.3%)	120 (26.5%)	0.734
Vascular disease				
Renal insufficiency*	350 (24.4%)	174 (17.8%)	176 (38.9%)	< 0.001
Severe renal insufficiency**	18 (1.3%)	7 (0.7%)	12 (2.6%)	0.001
Heart failure	326 (22.7%)	201 (20.5%)	125 (27.6%)	0.003
Prior stroke	179 (12.5%)	99 (10.1%)	80 (17.7%)	< 0.001
Peripheral artery disease	58 (4.0%)	38 (3.9%)	20 (4.4%)	0.631
SCORES				
CHA_2DS_2-VASc	3.5 ± 1.5	3.0 ± 1.4	4.5 ± 1.3	< 0.001
HAS-BLED	1.6 ± 1.0	1.4 ± 1.0	2.0 ± 1.0	< 0.001
2MACE Score ≥ 3	385 (26.9%)	189 (19.3%)	196 (43.3%)	< 0.001

*eGFR < 60 mL/min (MDRD-4); **eGFR < 30 mL/ min (MDRD-4). eGFR: estimated glomerular filtration rate.

ted in Table 1. Overall, mean age was 74.2 ± 9.7 years, 44.5% of patients were women, 37.3% had permanent AF, mean CHA_2DS_2-VASc score was 3.5 ± 1.5, mean HAS-BLED was 1.6 ± 1.0 and 26.9% had a 2MACE score ≥ 3. In addition, 79.3% of patients had hypertension, 27.1% diabetes, 24.4% renal insufficiency, 22.7% heart failure, and 12.5% prior cerebrovascular disease. Compared to patients < 80 years, those patients aged 80 years or older were more frequently women (58.7% *vs.* 38.0%; P < 0.001), had more permanent AF (47.2% *vs.* 32.8%; P < 0.001), hypertension (83.7% *vs.* 77.3%; P = 0.006), renal insufficiency (38.9% *vs.* 17.8%; P < 0.001), heart failure (27.6% *vs.* 20.5%; P = 0.003) and previous cerebrovascular disease (17.7% *vs.* 10.1%; P < 0.001). In addition, CHA_2DS_2-VASc (4.5 ± 1.3 *vs.* 3.0 ± 1.4; P < 0.001), HAS-BLED (2.0 ± 1.0 *vs.* 1.4 ± 1.0; P < 0.001) and the proportion of patients with 2MACE Score ≥ 3 (43.3% *vs.* 19.3%; P < 001) were higher in patients ≥ 80 years. By contrast, body mass index was lower in this population (28.2 ± 4.7 kg/m^2 *vs.* 29.5 ± 4.9 kg/m^2; P < 0.001). Overall, the dose of rivaroxaban was adequately prescribed in 83.4% of patients, but more frequently in the younger population (71.1% *vs.* 89.1%; P = 0.039). In patients ≥ 80 years, 14.8% of patients were underdosed and 14.1% overdosed (Figure 2).

The mean follow-up was 2.2 ± 0.6 years (median 2.5 years, interquartile range 2.2-2.6 years). Clinical events during the follow-up stratified according to age are presented in Table 2. Overall, 87 (6.1%) patients died during the study period, of whom 20 (1.4%) had a cardiovascular origin. In the total population, annual rates of stroke + systemic embolism + transient ischemic attack, MACE, major bleeding, and cardiovascular death were 0.72%, 1.07%, 1.04%, and 0.63%, respectively. Annual rates of progressive heart failure death (0.93% *vs.* 0.18%; P = 0.009),

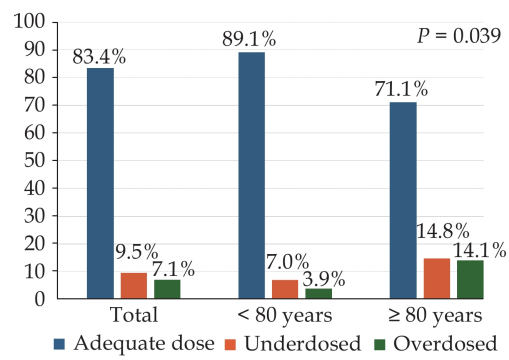

Figure 2 Adequacy of dosage of rivaroxaban during the follow-up.

Table 2 Clinical events during the follow-up by age.

	Total (n = 1433; 100%)	< 80 years (n = 980; 68.4%)	≥ 80 years (n = 453; 31.6%)	P
Combined endpoints				
Stroke/TIA/SE	23 (1.6%)	13 (1.3%)	10 (2.2%)	0.217
Annual rates^	0.72	0.59	1.03	0.262
Ischemic stroke/TIA/SE	16 (1.1%)	8 (0.8%)	8 (1.8%)	0.112
Annual rates^	0.5	0.36	0.82	0.162
Thromboembolic events*	21 (1.5%)	12 (1.2%)	9 (2.0%)	0.264
Annual rates^	0.66	0.54	0.93	0.319
MACE**	30 (2.1%)	19 (1.9%)	11 (2.4%)	0.547
Annual rates^	1.07	0.99	1.24	0.659
Individual endpoints				
Ischemic stroke	11 (0.8%)	7 (0.7%)	4 (0.9%)	0.75
Annual rates^	0.35	0.32	0.41	0.89
Myocardial infarction	5 (0.3%)	4 (0.4%)	1 (0.2%)	0.999
Annual rates^	0.16	0.18	0.1	0.999
Progressive HF death	13 (0.9%)	4 (0.4%)	9 (2.0%)	0.006
Annual rates^	0.41	0.18	0.93	0.009
Major Bleeding	29 (2.0%)	14 (1.4%)	15 (3.3%)	0.019
Annual rates^	1.04	0.72	1.75	0.019
Death				
Cardiovascular death	20 (1.4%)	10 (1.0)	10 (2.2%)	0.075
Annual rates^	0.63	0.45	1.03	0.106
All-cause death	87 (6.1%)	33 (3.4%)	54 (11.9%)	< 0.001
Annual rates^	2.73	1.49	5.56	< 0.001

Data are presented as n (%). *Ischemic stroke + SE + TIA + Myocardial infarction; **MACE: non-fatal myocardial infarction, revascularization and cardiovascular death (death for coronary events, progressive heart failure death and sudden cardiac death); ^Event/100 patients/year. MACE: major adverse cardiovascular events; SE: systemic embolism; TIA: transient ischemic attack

major bleeding (1.75% *vs.* 0.72%; P = 0.019), and all-cause death (5.56% *vs.* 1.49%; P < 0.001) were higher in patients aged 80 years or older, compared to younger patients. By contrast, rates of stroke + transient ischemic attack + systemic embolism, thromboembolic events, MACE, ischemic stroke, myocardial infarction and cardiovascular death, were similar between both groups.

Multivariate logistic regression analyses were performed to study the potential predictors of ischemic stroke, MACE and major bleeding in patients aged 80 years or older (Table 3). The concomitant use of antiplatelet agents (OR = 73.84; 95% CI: 5.35-1018.81; P = 0.001) and non-severe dementia (OR = 32.15; 95% CI: 2.37-435.99; P = 0.009) were independently associated with the development of ischemic stroke, whereas previous coronary revascularization (OR = 5.31; 95% CI: 1.50-18.77; P = 0.001) and heart failure (OR = 5.87; 95% CI: 1.49-

Table 3 Independent factors associated with ischemic stroke, MACE and major bleeding in patients aged 80 years or older.

	OR	95% CI	P
Ischemic stroke			
Antiplatelet agents	73.84	5.35-1018.81	0.001
Non-severe dementia	32.15	2.37-435.99	0.009
MACE			
Coronary revascularization	5.31	1.50-18.77	0.001
Heart failure	5.87	1.49-23.12	0.011
Major bleeding			
HAS-BLED	2.37	1.45-3.87	0.001

CI: confidence interval; MACE: non-fatal myocardial infarction, revascularization and cardiovascular death (death for coronary events, progressive heart failure death and sudden cardiac death); OR: Odds ratio.

23.12; $P = 0.011$) with MACE, and higher HAS-BLED score (OR = 2.37; 95% CI: 1.45-3.87; $P = 0.001$) with major bleeding.

DISCUSSION

Our study showed in a wide sample of patients with AF anticoagulated with rivaroxaban in clinical practice that despite exhibiting a worse clinical profile, with a higher thromboembolic and bleeding risk, rates of outcomes were low in octogenarians, with similar rates of thromboembolic events, MACE, ischemic stroke, myocardial infarction and cardiovascular death as in younger patients. In addition, rivaroxaban was adequately prescribed in the majority of octogenarians.

The prevalence of AF markedly increases with age.[1-3] In our study, 453 patients were 80 years or older at baseline that accounted for around one third of the total population. This is important, as it has been observed that despite the benefits of anticoagulation in very elderly patients, a significant proportion of them are not taking the appropriate treatment.[31-33] Different reasons have been proposed to explain why some physicians have decided not to anticoagulate octogenarians, such as cognitive impairment, perceived high bleeding risk, difficult access to INR monitoring, or perceived low thromboembolic risk, among others.[34] In this context, due to the advantages of DOACs over VKA, including lower risk of intracranial bleeding and no requirement for anticoagulation monitoring (in these patients it is more difficult to reach an adequate time in therapeutic range), DOACs should be considered of choice in this population.[2,13] As a result, our data provide relevant information, as our study has been focused on octogenarians with AF anticoagulated with DOACs, in particular with rivaroxaban.

In our study, octogenarians had many comorbidities (hypertension 84%, renal insufficiency 39%, heart failure 28%, previous cerebrovascular disease 18%), and a high thromboembolic risk (CHA_2DS_2-VASc 4.5). These results are in line with previous observational studies performed in anticoagulated octogenarians with AF,[21-24,33,35] and also with clinical trials that included patients aged 75 years or older.[17-20] In addition, although some previous studies have analyzed the clinical profile, effectiveness and safety of patients taking rivaroxaban, showing that these patients were old and had a high thromboembolic risk, they did not focus on very elderly patients, as we did, thus providing additional information to available evidence.[36-39] Therefore, our sample may be considered representative of octogenarians with AF anticoagulated with DOACs in clinical practice and our results could potentially be extended to this population. This is important, since the management of octogenarians is challenging and requires a comprehensive approach, not limited to only stroke prevention, but to all AF-related complications.[2]

On the other hand, inappropriate DOAC dosage prescription is a relevant problem in clinical practice. In fact, it may affect up to 15% of AF patients, increasing this number to nearly one-third of octogenarians with AF, particularly with underdosing.[40,41] Of note, octogenarians with inappropriate DOAC underdosing may exhibit lower survival rates.[41] In our study, 71% of octogenarians received the proper dosage and only 15% of patients were underdosed. In another study performed in patients taking rivaroxaban in clinical practice (mean age 76 years), around one quarter of patients received an inadequate dose.[42] Therefore, although there is room for improvement, dosing of rivaroxaban is properly performed in many octogenarians with AF, potentially related to its simplicity of use, as it is adjusted only according to renal function.[29]

In our study, annual rates of stroke + systemic embolism + transient ischemic attack, myocardial infarction, and cardiovascular death were 1.03%, 0.10%, and 1.03%, respectively, in octogenarian patients, without significant differences compared to younger patients. By contrast, annual rates of major bleeding were higher in octogenarian patients (1.75% *vs.* 0.72%; $P < 0.001$). Among patients aged 75 years or older from the ROCKET-AF trial, in the rivaroxaban arm, these numbers were 2.29%, 0.80%, 3.6% and 4.86%, respectively.[18] Of note, in the ROCKET-AF trial, although elderly patients had higher stroke and major bleeding rates, the relative efficacy and safety of rivaroxaban compared to warfarin was independent of age.[18] In FANTASIIA, among patients aged 80 years or older taking DOACs, these

figures were 1.8%, 1.12%, 2.72% and 3.45%, respectively.[24] Therefore, our data showed that in octogenarians with AF taking rivaroxaban, rates of adverse events, including thromboembolic and bleeding complications, were much lower than those reported not only in clinical trials, such as the ROCKET-AF trial, but also in observational studies, including among those patients taking DOACs.[18,21-24] Although the differences in the clinical profile of patients could explain these numbers, the fact is that in clinical practice, event rates were low in octogenarians taking rivaroxaban in our study.

The concomitant use of antiplatelet agents was independently associated with the development of ischemic stroke. Many reasons have been proposed to explain this point. Thus, in some cases, some of these patients may have had recent acute coronary syndrome or undergone a percutaneous coronary revascularization and these patients have a higher risk of adverse cardiovascular outcomes.[43] In other cases, it has been described a higher risk of embolic or atherosclerotic complications immediately after major bleeding that is already increased in patients taking concomitantly antiplatelets and oral anticoagulants.[44] Therefore, the concomitant use of antiplatelets and anticoagulants should be limited to patients with recent coronary revascularization or acute coronary syndrome.[2]

Non-severe dementia was also associated with a higher risk of ischemic stroke. Of note, patients with AF have a higher risk of dementia and anticoagulation may reduce this risk. Despite that, it has been described a lower use of oral anticoagulants in these patients.[45] Importantly, dementia by itself should not contraindicate the use oral anticoagulants in these patients.[2] Our data showed that even in octogenarians taking rivaroxaban, the risk of adverse events was low and it could be used also in patients with dementia.

As expected, a higher HAS-BLED score was independently related with major bleeding. As guidelines recommend, the assessment of HAS-BLED score should be used not to contraindicate anticoagulation, but rather to modify those factors that increase the risk of bleeding.[2] Despite the higher risk of bleeding, octogenarians should be anticoagulated, even in patients with a high HAS-BLED score.[46,47]

LIMITATIONS

As this was an observational study, no control group was available and the presence of some confounding factors could have had an impact on the results. However, the high number of patients included, as well as the consecutive recruitment could reduce possible selection bias. On the other hand, patients were recruited after at least 6 months of treatment with rivaroxaban in Spain. Therefore, the results of our study can only be extended to a similar population.

CONCLUSIONS

In clinical practice, around one third of patients taking rivaroxaban were octogenarians. These patients had many comorbidities and a high thromboembolic risk. Despite that, rates of adverse events were low. Thus, annual rates of stroke + systemic embolism + transient ischemic attack, MACE, cardiovascular death and major bleeding were 1.03%, 1.24%, 1.03% and 1.75%, respectively, in octogenarian patients in our study. Except for progressive heart failure death and major bleeding, rates of outcomes in octogenarians were similar compared to younger patients. In addition, rivaroxaban was adequately prescribed in more than 70% of octogenarians. Therefore, all these data indicate that rivaroxaban could be a safe alternative in octogenarians with AF in clinical practice and should be strongly considered in this population.

DISCLOSURE

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Conflict of Interests

Francisco Marín has received consultancy/lecturing fees from Bayer, Boehringer Ingelheim, Pfizer, Bristol Myers Squibb, Daiichi Sankyo and AFNET. Manuel Anguita Sánchez has received funding for

consulting and conference services from Bayer, Daiichi-Sankyo and Pfizer. Iñaki Lekuona has received honoraria for presentations from Bayer, Boehringer-Ingelheim, Daiichi Sankyo and Pfizer-BMS. Marcelo Sanmartin Fernández has received speaker and advisory fees from the following companies in the past 3 years: Bayer, Boehringer Ingelheim, BMS and Pfizer. Vivencio Barrios has received consultancy/lecture fees from Bayer, BMS/Pfizer, Boehringer Ingelheim and Daiichi Sankyo. Juan Cosín-Sales has received consultancy/lecture fees from Bayer, BMS/Pfizer, Boehringer Ingelheim and Daiichi Sankyo. Alejandro I. Pérez Cabeza has received personal fees for educational activities or participation on boards from Daiichi Sankyo, Bayer, Boehringer Ingelheim and Bristol Myers Squibb. Vanesa Roldán Schilling has received honoraria for presentations from Bayer, Boehringer-Ingelheim, Daiichi Sankyo and Pfizer-BMS. Carles Rafols Priu is an employee Bayer Hispania SL. Carlos Pérez Muñoz, Esteban Orenes-Piñero and María Asunción Esteve Pastor declared no personal conflict of interest or financial fees related with the manuscript.

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