



ORIGINAL ARTICLE

Edoxaban Treatment in routine clinical practice in patients with non-valvular Atrial Fibrillation (ETNA-AF) in Iberia: Baseline data[☆]



Pedro Monteiro

Cardiology Department, Coimbra University Hospital and Medical School, Coimbra, Portugal

Received 9 September 2019; accepted 23 September 2020

KEYWORDS

Atrial fibrillation;
Edoxaban;
Baseline;
Real-world

Abstract

Introduction and Objectives: Atrial fibrillation (AF) is the most common form of arrhythmia worldwide and a significant health burden. Edoxaban, a recent novel oral anticoagulant (NOAC), is being investigated in the European real-world ETNA-AF study of patients with non-valvular atrial fibrillation (NVAF). The aim of this study was to characterize the Iberian edoxaban-treated cohort of ETNA-AF at baseline and to compare it with previously retrieved Portuguese data.

Methods: Patients with NVAF treated with edoxaban and followed in Portuguese and Spanish centers were consecutively enrolled between June 2017 and January 2018. Only patients with a previous clinical decision to receive edoxaban were included. Patients' baseline demographic and clinical parameters, medical history, and AF-related characteristics were retrieved.

Results: A total of 892 NVAF patients, with a mean age of 73.9 years, were included, 75.3% of whom received high-dose (60 mg) and 24.7% low-dose (30 mg) edoxaban. Most patients (55.9%) were male. Of the patients receiving 30 mg and 60 mg edoxaban, 55.9% and 37.9%, respectively, had an estimated CHA₂DS₂-VASc score ≥ 4 . Previous bleeding event rates were low, with a predominance of clinically relevant non-major bleeding (1.9%). Most patients (47.5%) with NVAF had paroxysmal AF, followed by 26.4% with permanent AF. Median overall CHA₂DS₂-VASc score was 3.0 and median HAS-BLED score was 2.0. Previous treatments mostly included vitamin K antagonists (35.7%). A considerably higher proportion of patients on low-dose edoxaban required dose adjustments (71.4% vs. 8.6%). Overall adherence to label dosing recommendations was 86.5%. **Conclusions:** This study provides valuable data on disease and patient profiles and will provide valuable insights into disease management and progression, as well as the safety, effectiveness, and patterns of cardiovascular events associated with edoxaban.

© 2020 Published by Elsevier España, S.L.U. on behalf of Sociedade Portuguesa de Cardiologia. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

[☆] The author declares that the publication of this article in the *Portuguese Journal of Cardiology* was expressly authorized by all the institutions involved.

E-mail address: pedromonte@gmail.com

PALAVRAS-CHAVE

Fibrilhação auricular;
Edoxabano;
Baseline;
Vida real

Tratamento com edoxabano na prática clínica de rotina em doentes com fibrilhação auricular não valvular (ETNA-AF) na Península Ibérica: dados de base

Resumo

Introdução e objetivos: A fibrilhação auricular (FA) é a arritmia mais comum globalmente e associa-se a um substancial ónus de saúde. O novo anticoagulante oral (NOAC) edoxabano está a ser investigado no estudo europeu de vida real ETNA-AF em doentes com fibrilhação auricular não valvular (FANV). O objetivo deste estudo é caracterizar a coorte ibérica do ETNA-AF na base de dados e compará-la com dados portugueses prévios.

Métodos: Doentes com FANV tratados com edoxabano e seguidos em centros portugueses e espanhóis foram consecutivamente incluídos no estudo entre junho de 2017 e janeiro de 2018. Apenas doentes com indicação prévia para receber edoxabano foram incluídos e os seus dados clínicos e demográficos, história clínica e características relacionadas com a FA foram registados.

Resultados: Fora, incluídos 892 doentes com FANV, com média de 73,9 anos, 75,3% dos quais receberam a dose elevada (60 mg) e 24,7% a dose reduzida (30 mg) de edoxabano. A maioria dos doentes (55,9%) era do sexo masculino. Dos doentes que receberam 30 mg e 60 mg de edoxabano, 55,9% e 37,9%, respetivamente, tinham CHA₂DS₂-VASc estimado ≥ 4 . As taxas de eventos hemorrágicos prévios foram baixas, com predominância de hemorragia não *major* clinicamente relevante (1,9%). A maioria (47,5%) dos doentes com FANV tinha FA paroxística, seguidos de 26,4% com FA permanente. A mediana de CHA₂DS₂-VASc global foi 3,0 e a mediana de HAS-BLED, 2,0. Os tratamentos prévios incluíram sobretudo VKAs (35,7%). Uma proporção consideravelmente maior de doentes a receber dose reduzida de edoxabano necessitou de ajustes de dose (71,4% *versus* 8,6%). A adesão global às recomendações de dose foi de 86,5%.

Conclusões: Este estudo fornece dados importantes sobre a doença e o perfil dos doentes e possibilitará considerações futuras acerca da gestão e progressão da doença, bem como de segurança, efetividade e padrões de eventos cardiovasculares associados a edoxabano.

© 2020 Publicado por Elsevier España, S.L.U. em nome de Sociedade Portuguesa de Cardiologia. Este é um artigo Open Access sob uma licença CC BY-NC-ND (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Atrial fibrillation (AF) is the most common form of arrhythmia worldwide and represents a significant health burden.¹ Its prevalence increases with age and with conditions such as hypertension, valvular heart disease, obesity, diabetes, and chronic kidney disease (CKD).²

AF is associated with an increased risk of ischemic stroke, heart failure, and all-cause mortality,³⁻⁵ as well as hospital admissions, with 10-40% of patients hospitalized annually,⁶ which has been shown to be an independent risk factor for cardiovascular (CV) death in AF patients.⁷ With the aging of populations and a higher incidence of CV disease in the elderly, the number of patients with AF is expected to grow exponentially over the coming decades.⁸ Furthermore, patients with AF have poorer quality of life and may experience vascular dementia and a decline in cognitive function despite anticoagulation for stroke prevention.²

The prevalence of AF is reported to be increasing steadily worldwide, but there is considerable variation between studies and countries.⁶ In Europe, the USA, and Australia, AF has an estimated prevalence of 1-4%, but it is markedly lower in Asia (0.49-1.9%).⁶

In Portugal in 2010, the large-scale cross-sectional observational FAMA study reported a 2.5% prevalence of AF in individuals aged 40 years and over.⁹ No differences were

found between genders, but AF prevalence increased with age, and was significantly higher in the ≥ 70 -year-old group.⁹ Subsequently, two other studies – Primo et al.¹⁰ and the SAFIRA study¹¹ – reported a 12.4% overall prevalence of AF/atrial flutter in a younger population of individuals aged ≥ 40 years¹⁰ and a 9% prevalence of AF in an older population, aged ≥ 65 years,¹¹ respectively.

Differences were also found in antithrombotic treatment use between these studies. SAFIRA reported that 56.3% of patients were non-anticoagulated,¹¹ higher than the 37.8% reported in FAMA.⁹

The significantly higher incidence of stroke and systemic embolism observed in AF patients can be reduced with appropriately adjusted anticoagulant therapy. Although vitamin K antagonists (VKAs) have been recognized to effectively decrease the risk of thromboembolic events in these patients, their effect is influenced by many factors and new options were needed. The development of novel oral anticoagulants (NOACs) in the last few years has offered new treatment opportunities for clinicians.

Edoxaban is the most recent agent of this new class. Its approval was based on a large phase III trial of NOACs for stroke prevention in patients with non-valvular atrial fibrillation (NVAf), ENGAGE AF-TIMI 48, in which edoxaban was associated with similar efficacy for preventing stroke or systemic embolism and a significant reduction in

bleeding events and death from CV causes compared with warfarin.¹²

ETNA-AF¹³ is a large multicenter post-authorization observational study of patients with NVAF treated with edoxaban in routine clinical practice in 10 different European countries and care settings (primary and secondary care and different specialties). Its aim is to investigate the risks and benefits of edoxaban use in patients with NVAF in a real-world clinical setting and to gain insight into the drug's safety (bleeding, liver adverse events, all-cause mortality and other drug-related adverse events). Due to its non-interventional nature, this is a non-randomized study.

The present paper aims to describe and characterize the Iberian (Portuguese and Spanish) edoxaban-treated cohort of ETNA-AF at baseline and to compare it with data previously retrieved on Portuguese patients, mainly from the SAFIRA study.

Methods

ETNA-AF is an ongoing observational prospective cohort study of patients with NVAF in Europe. The Iberian cohort included patients from Portuguese and Spanish centers (see [Appendix](#)).

Patient selection

Patients with NVAF followed in selected Portuguese and Spanish centers, treated with edoxaban according to the Summary of Product Characteristics (SmPC), aged ≥ 18 years, who provided written informed consent to participate, were consecutively enrolled in the study between August 2017 and March 2018.

To avoid treatment choice bias, patients were only included after the attending physician had made the clinical decision to prescribe edoxaban, so the physician's treatment option was not influenced.

Patients were excluded from the study if they (i) were simultaneously participating in an interventional study; (ii) had missing baseline data; (iii) had baseline data retrieved after the cut-off date; (iv) were missing information on edoxaban treatment at baseline; or (v) did not fulfill the regional eligibility criteria defined in the SmPC for each region.

Study protocol

The protocol and statistical analysis plan have been described previously.¹³

A one-year patient recruitment period was planned, with the possibility of extension if patient recruitment numbers were not reached. Patient data were documented at baseline, at one annual data documentation point during the four-year follow up, and at final assessment.

Patients who permanently discontinued edoxaban during the observation period will continue to be followed annually for an additional two-year period, or until the end of the observation period (whichever comes first).

The primary outcome measure of the ETNA-AF study is the percentage of patients experiencing real-world safety

data events within four years, which include bleeding events (including intracranial hemorrhage), drug-related adverse events such as liver adverse events, and cardiovascular and all-cause mortality. The secondary outcome measures are (i) percentage of patients with patient-relevant outcomes within four years, including ischemic and hemorrhagic stroke, systemic embolic events, transient ischemic attack, major adverse cardiovascular events, venous thromboembolism, acute coronary syndrome, and hospitalizations related to a CV condition; and (ii) percentage of patients compliant with edoxaban within four years (compliance categories: always, almost always, most of the time, less than half the time, unknown).

Patient demographic and clinical parameters, as well as medical history, were collected at baseline. Type of NVAF at first diagnosis and at baseline was also retrieved.

Stroke risk assessment was performed using the CHADS₂¹⁴ and CHA₂DS₂-VASc¹⁵⁻¹⁷ scores, and bleeding risk was estimated with the HAS-BLED score.¹⁸ Patients were considered high-risk if they had at least one of the following conditions: prior stroke, prior major bleeding, prior intracranial hemorrhage, or CHA₂DS₂-VASc ≥ 4 .

The ETNA-AF study is registered under ClinicalTrials.gov number NCT02944019.

Statistical analysis

A descriptive analysis of numerical variables was performed, consisting of estimates of the mean and respective standard deviation. Categorical variables were expressed as absolute and relative frequencies. The analysis was performed with IBM SPSS version 25.

Results

A total of 960 patients from Portugal and Spain were prescribed edoxaban by their attending physicians and were initially enrolled in the study. Of these, 68 patients were excluded for not meeting eligibility criteria: two were missing baseline data, 62 were missing information on edoxaban treatment at baseline, six did not fulfill the regional eligibility criteria, and four were excluded for other reasons. A total of 892 patients were included in the study and are currently undergoing follow-up and being analyzed for study outcome measures.

Demographic and clinical characteristics

Baseline demographic and clinical characteristics of patients included in ETNA-AF Iberia are depicted in [Table 1](#). A total of 672 patients (75.3%) received high-dose (60 mg) edoxaban and 220 patients (24.7%) received the lower dose (30 mg).

At baseline, patients had a mean age of 73.9 years, with those receiving low-dose edoxaban being older (mean 79.5 years) than those receiving the higher dose. Overall, more than half of patients included (50.7%) were aged ≥ 75 years, this also being the most prevalent age group in patients prescribed low-dose edoxaban (45.0%). Most patients receiving high-dose edoxaban (36.9%) were in the 65-74 age group.

Table 1 Baseline demographic and clinical characteristics of the study population.

	Total	Low-dose edoxaban (30 mg)	High-dose edoxaban (60 mg)
No. of patients included (%)	892 (100)	220 (24.7)	672 (75.3)
Age, years, mean (SD)	73.9 (9.91)	79.5	72.1
<i>Age categories, %</i>			
<65 years	17.0	5.9	20.7
65-74 years	32.3	18.2	36.9
≥75 years	50.7	45.0	33.9
≥85 years	14.0	30.9	8.5
<i>Gender, %</i>			
Male	55.9	41.8	60.6
Female	44.1	58.2	39.4
Weight, kg, mean (SD)	77.2 (14.80)	70.2	79.7
<i>Weight categories, %</i>			
<60 kg		30.6	3.0
≥60 kg		69.4	97.0
BMI, kg/m ² , mean (SD)	28.5 (4.88)	27.5	28.9
SBP, mmHg, mean (SD)	132.1 (18.81)	133.7 (19.55)	131.6 (18.55)
DBP, mmHg, mean (SD)	75.7 (10.85)	73.5 (10.83)	76.4 (10.78)
Heart rate, bpm, mean (SD)	73.4 (15.85)	70.8 (15.72)	74.3 (15.81)
Current smoking, %	4.9	1.8	5.8
Alcohol use, %	31.3	20.1	34.9
<i>Frailty status, %</i>			
Yes	11.9	26.5	7.0
No	84.4	66.5	89.7
Unknown	3.7	5.0	3.3
High risk, ^a %		55.9	37.9

BMI: body mass index; bpm: beats per minute; DBP: diastolic blood pressure; SBP: systolic blood pressure; SD: standard deviation.

^a With at least one of the following: prior stroke, prior major bleeding, prior intracranial hemorrhage or calculated CHA₂DS₂-VASc score ≥4.

Patients prescribed edoxaban in clinical practice were mostly male (55.9%), but more female patients (58.2%) received low-dose and more male patients (60.6%) received high-dose edoxaban. Patients on high-dose edoxaban had higher mean weight (79.7 kg) and higher body mass index (28.9 kg/m²) than their low-dose counterparts.

This population had a mean systolic blood pressure (BP) of 132.1 mmHg and a mean diastolic BP of 75.7 mmHg, with patients in the low-dose group reporting higher systolic and lower diastolic values than those in the high-dose group. Mean heart rate was 73.4 beats per minute (bpm), which was higher in patients on high-dose treatment (74.3 vs. 70.8 bpm).

A minority of patients were current smokers (4.9%) or alcohol users (31.3%), with more patients in the high-dose group reporting these habits than in the low-dose group.

According to the European Society of Cardiology guidelines for the management of atrial fibrillation, many patients present AF at older ages (e.g. >75 or >80 years) and are considered 'frail' patients, due to the presence of comorbidities such as dementia, tendency to falls, CKD, anemia, hypertension, diabetes, and cognitive dysfunction.² In the ETNA-AF Iberia study, a minority of NVAf patients were considered frail (11.9%), with the proportion of these patients being higher in the low-dose (26.5%) than in the high-dose (7.0%) edoxaban group.

A total of 55.9% and 37.9% patients receiving 30 mg and 60 mg edoxaban, respectively, were considered high-risk according to the estimated CHA₂DS₂-VASc score (≥4).

Medical history

The most prevalent comorbidities at baseline in this cohort of patients with NVAf were hypertension (76.7%), dyslipidemia or hyperlipidemia (50.9%), and diabetes (26.8%), followed by coronary heart disease (11.1%), valvular disease, and hyper- or hypothyroidism (10.9% each) (Table 2). Patients who received low-dose edoxaban were more likely to have more comorbidities, except for chronic obstructive pulmonary disease, sleep apnea, gastrointestinal (GI) disease, ischemic stroke, and pulmonary embolism, which were less prevalent in this group than in the high-dose group.

Overall, the number of bleeding events prior to baseline was low, with a predominance of clinically relevant non-major bleeding (1.9% of patients), followed by minor bleeding (1.7%), thrombocytopenia (1.6%), and major or clinically relevant non-major GI bleeding (1.3%) (Table 3). Rates of previous bleeding events that were higher in the low-dose than in the high-dose edoxaban group included intracranial hemorrhage (0.9% vs. 0.3%), major or clinically relevant non-major GI bleeding (2.7% vs. 0.9%), major

Table 2 Comorbidities in the study population.

Comorbidity, % of patients	Total	Low-dose edoxaban (30 mg)	High-dose edoxaban (60 mg)
Hypertension	76.7	78.6	76.0
Diabetes	26.8	27.3	26.6
Dys- or hyperlipidemia	50.9	50.9	50.9
CHF	8.3	10.0	7.7
MI	3.6	5.5	3.0
Angina	1.5	2.3	1.2
Valvular disease	10.9	14.1	9.8
PAD	2.4	3.2	2.1
COPD	8.1	6.8	8.5
Sleep apnea	7.5	5.0	8.3
GI disease	9.8	9.5	9.8
LV systolic impairment	7.7	9.5	7.1
Cardiomyopathy	7.1	10.0	6.1
CHD	11.1	15.0	9.8
Hyper-/hypothyroidism	10.9	13.6	10.0
Anemia	2.0	3.6	1.5
Previous ischemic stroke	8.6	7.3	9.1
Previous undefined type stroke	0.4	0.5	0.4
Previous TIA	3.9	5.5	3.4
Previous PE ^a	1.1	0.5	1.3
Previous DVT	0.7	0.9	0.6

CHD: coronary heart disease; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; DVT: deep vein thrombosis; GI: gastrointestinal; LV: left ventricular; MI: myocardial infarction; PAD: peripheral arterial disease; PE: pulmonary embolism; TIA: transient ischemic attack.

^a Includes previous pulmonary embolism and previous deep vein thrombosis.

Table 3 Bleeding history.

Previous bleeding events, % of patients	Total	Low-dose edoxaban (30 mg)	High-dose edoxaban (60 mg)
Intracranial hemorrhage	0.4	0.9	0.3
Major or clinically relevant non-major GI bleeding	1.3	2.7	0.9
Major bleeding	0.9	1.4	0.7
Clinically relevant non-major bleeding	1.9	4.1	1.2
Minor bleeding	1.7	1.4	1.8
History of all bleeding	4.5	6.8	3.7
Congenital or acquired disease related to bleeding	-	-	-
Thrombocytopenia	1.6	1.8	1.5

bleeding (1.4% vs. 0.7%), clinically relevant non-major bleeding (4.1% vs. 1.2%), history of all bleeding (6.8% vs. 3.7%), and thrombocytopenia (1.8% vs. 1.5%), while the opposite was true for minor bleeding (1.4% vs. 1.8%, respectively).

Renal dysfunction was observed in 24.4% of patients included in the study, and hepatic dysfunction in only 2.0%, as reported by patients themselves (Table 4). More patients assigned to receive low-dose edoxaban had renal dysfunction (50.5% vs. 15.9%), while more patients assigned to receive high-dose edoxaban had hepatic dysfunction. Mean creatinine clearance (CrCl) was 70.6 ml/min in the overall study cohort, with most patients (45.0%) falling in the 50-80 ml/min category. Patients set to receive high-dose edoxaban had a higher mean CrCl (77.6 ml/min) than those assigned to the low-dose group (50.1 ml/min).

Chronic kidney disease estimated by the Cockcroft-Gault formula indicated a large proportion of patients (70.1%) in the low-dose edoxaban group with stage 3 CKD, followed by a considerably lower proportion (17.3%) with stage 2 CKD (Table 5). In the high-dose group, more patients had stage 2 CKD (45.2%), followed by stage 1 (32.3%) and stage 3 (22.2%).

Atrial fibrillation-related characteristics

Patients were classified according to the current type of NVAF as having paroxysmal (recurrent episodes that self-terminate within seven days, usually within 48 hours), persistent (of more than seven days duration), long-standing persistent (lasting for >1 year when a decision is made to adopt a rhythm control strategy), or permanent AF

Table 4 Renal and hepatic disease, as reported by patients.

Characteristic	Total	Low-dose edoxaban (30 mg)	High-dose edoxaban (60 mg)
Renal disease, including dialysis, % of patients	24.4	50.5	15.9
Hepatic disease, % of patients	2.0	1.4	2.2
CrCl, ml/min, mean (SD)	70.6 (24.43)	50.1 (18.61)	77.6 (22.14)
CrCl categories, % of patients			
<15 ml/min	0.8	-	1.1
15-30 ml/min	2.7	10.1	0.2
30-50 ml/min	16.1	48.9	4.9
50-80 ml/min	45.0	32.4	49.4
≥80 ml/min	35.3	8.5	44.4

CrCl: creatinine clearance; SD: standard deviation.

Table 5 Chronic kidney disease stage estimated by the Cockcroft-Gault equation.

Chronic kidney disease, % of patients	Low-dose edoxaban (30 mg)	High-dose edoxaban (60 mg)
Stage 1 (GFR ≥90)	2.5	32.3
Stage 2 (GFR ≥60-89)	17.3	45.2
Stage 3 (GFR ≥30-59)	70.1	22.2
Stage 4 (GFR ≥15-29)	10.2	0.4
End-stage renal disease (GFR<15)	-	-

GFR: glomerular filtration rate (ml/min/1.73 m²).

Table 6 Baseline atrial fibrillation-related characteristics.

	Total	Low-dose edoxaban (30 mg)	High-dose edoxaban (60 mg)
<i>Current AF type, % of patients</i>			
Paroxysmal	47.5	40.9	49.6
Persistent	21.9	19.5	22.7
Long-standing persistent	4.2	4.5	4.1
Permanent	26.4	35.0	23.6
<i>Type of AF at first diagnosis,^a % of patients</i>			
Symptomatic	53.9	52.7	54.3
Asymptomatic	34.8	29.1	36.7
Unknown	11.3	18.2	9.0
<i>Time since first AF diagnosis</i>			
Days since first AF diagnosis, mean (SD)		1285.6 (1529.8)	999.7 (1485.0)
Months since first AF diagnosis, mean (SD)		42.5 (50.57)	33.0 (49.09)
Months since first AF diagnosis, median (SD)		19.3	11.6

AF: atrial fibrillation; SD: standard deviation.

^a Estimated for n=885 patients in total (n=665 on high-dose edoxaban; 7 with missing data).

(accepted by the patient and physician). Most patients (47.5%) with NVAF had paroxysmal AF at baseline, followed by 26.4% with permanent AF (Table 6). This was also the case for the edoxaban treatment groups individually, with 40.9% and 49.6% of patients in the low- and high-dose groups having paroxysmal AF, and 35.0% and 23.6% of patients having permanent AF, respectively. At first diagnosis, most patients (53.9%) were symptomatic, with a mean time since the first AF diagnosis of 42.5 months for low-dose edoxaban and 33.0 months for high-dose edoxaban patients.

Table 7 shows the risk of stroke and major bleeding for patients with NVAF, as calculated by physicians and reported

by patients. A mean CHADS₂ score of 1.9 was estimated for the entire cohort, ranging between 1.8 for patients on high-dose treatment and 2.2 for patients on low-dose treatment. The median CHADS₂ score was 2.0 for the three study groups, indicating a moderate risk of stroke for this patient population.

The median overall CHA₂DS₂-VASc score was 3.0, higher in the low-dose (4.0) than in the high-dose (3.0) group. When patients were stratified according to stroke risk, no patients in the low-dose group were considered to have low stroke risk (score of 0) as opposed to 1.8% of patients in the high-dose group, 2.3% of patients in the low-dose group were

Table 7 Baseline (reported and calculated) risk of stroke and major bleeding for patients with atrial fibrillation.

Risk score	Total	Low-dose edoxaban (30 mg)	High-dose edoxaban (60 mg)
CHADS₂			
<i>Calculated</i>			
Mean	1.9	2.2	1.8
Median	2.0	2.0	2.0
CHA₂DS₂-VASc			
<i>Reported</i>			
Mean	3.4	4.1	3.1
Median	3.0	4.0	3.0
<i>Calculated</i>			
Mean	3.2	3.8	3.0
Median	3.0	4.0	3.0
Risk classes, % of patients			
<i>Low risk (0)</i>		-	1.8
<i>Low to moderate risk (1)</i>		2.3	10.9
<i>Moderate to high risk (≥2)</i>		97.7	87.4
<i>Score 2</i>		10.5	24.9
<i>Score 3</i>		31.8	27.1
<i>Score 4</i>		30.5	21.0
<i>Score 5</i>		16.4	10.0
<i>Score 6</i>		5.9	4.0
<i>Score ≥7</i>		2.7	0.4
HAS-BLED			
<i>Reported</i>			
Mean	2.0	2.4	1.9
Median	2.0	2.0	2.0
<i>Calculated</i>			
Mean	2.5	2.9	2.4
Median	2.0	3.0	2.0

AF: atrial fibrillation; CHADS₂: atrial fibrillation stroke risk; CHA₂DS₂-VASc: updated atrial fibrillation stroke risk; HAS-BLED: major bleeding risk.

considered to have low to moderate stroke risk (score of 1) compared to 10.9% of patients in the high-dose group, and most patients in both groups had moderate to high stroke risk (scores of 2 or higher; 97.7% of patients in the low-dose group vs. 87.4% of those in the high-dose group). Most patients in both treatment groups scored 3 on CHA₂DS₂-VASc (31.8% and 27.1%, respectively), suggesting a moderate stroke risk.

The median HAS-BLED bleeding score was 2.0 for the overall population and the high-dose edoxaban cohort, indicating moderate bleeding risk, and 3.0 for the low-dose edoxaban cohort, suggesting a high bleeding risk for this group.

Previous and concomitant atrial fibrillation treatment

Previous treatments, suspended at or before the baseline enrollment date, mostly consisted of VKAs (35.7%) and, among these, mostly acenocoumarol (Table 8). NOACs and antiplatelets had been previously used by 9.5% of patients each, apixaban (44.7%) and aspirin (84.7%) being the most frequently used drugs within each class, respectively. Heparin or fondaparinux had been previously used by 6.8% of

patients and antiarrhythmics and rate control drugs by only 4.4%.

Before study entry, patients assigned to low-dose treatment were mostly receiving VKAs (40.0%), followed by NOACs (11.8%), and antiplatelets (9.1%), and patients assigned to high-dose treatment were also mostly receiving VKAs (34.2%), but antiplatelets were the second most frequently used agents in the latter group (9.7%), followed by NOACs (8.8%).

Concurrent use of antiarrhythmics and rate control drugs was reported in 39.3% of patients overall, accounting for 46.4% of patients on low-dose and 37.1% of patients on high-dose edoxaban. Antiplatelets, non-steroidal anti-inflammatory drugs, heparin or fondaparinux, and p-glycoprotein inhibitors were also concurrently reported by smaller proportions of patients.

Edoxaban treatment

A considerably higher proportion of patients in the low-dose group required adjustments to the initial edoxaban dose compared to the high-dose group (71.4% vs. 8.6%, respectively) (Table 9).

Table 8 Previous treatments for atrial fibrillation (suspended at or before baseline date).

Treatment, % of patients	Total	Low-dose edoxaban (30 mg)	High-dose edoxaban (60 mg)
VKAs	35.7	40.0	34.2
Warfarin	13.5	13.6	13.5
Acenocoumarol	86.2	86.4	86.1
Phenprocoumon	0.3	-	0.4
Other	-	-	-
NOACs	9.5	11.8	8.8
Apixaban	44.7	42.3	45.8
Dabigatran	34.1	30.8	35.6
Rivaroxaban	20.0	26.9	16.9
Other	1.2	-	-
Heparin/fondaparinux	6.8	6.8	6.8
Antiarrhythmics/rate control drugs	4.4	4.1	4.5
Antiplatelets	9.5	9.1	9.7
Aspirin	84.7	85.0	84.6
Other	15.3	15.0	15.4

NOACs: novel oral anticoagulants; VKAs: vitamin K antagonists.

Table 9 Edoxaban dosing and number of adjustment criteria.

Dose adjustment criteria, % of patients	Low-dose edoxaban (30 mg)	High-dose edoxaban (60 mg)
≥1	71.4	8.6
1	58.2	7.9
2	13.2	0.7
3	-	-
None	28.6	91.4

Only one dose adjustment criterion was required for most patients in both treatment groups (58.2% and 7.9%, respectively), with 13.2% and 0.7% of patients in both groups requiring two dose adjustment criteria, respectively.

Reasons for dose adjustments in the low-dose treatment group were mainly having CrCl ≤50 ml/min (59.0%) and body weight ≤60 kg (32.5%), while in the high-dose treatment group they were mostly both body weight and CrCl (8.6%) and CrCl ≤50 ml/min (6.2%) (Table 10).

Considering that 28.6% of patients receiving 30 mg (63 out of 220 patients) had no dose reduction criteria (underdosed) and that 8.6% of patients receiving 60 mg (58 out of 672) had at least one reduction criterion (overdosed), 7.1% of all anticoagulated subjects who were underdosed (63 out of 892) and 6.5% were overdosed (58 out of 892). Overall, the data suggest good adherence by the attending physicians to the SmPC recommendations with respect to dose reduction criteria.

Discussion

The present study aimed to describe and characterize the baseline parameters of a cohort of Iberian (Portuguese and Spanish) patients with NVAf treated with edoxaban and

Table 10 Overview of edoxaban dose adjustment criteria.

Dose adjustment criterion	Low-dose edoxaban (30 mg)	High-dose edoxaban (60 mg)
Missing patients, weight	11	75
Missing patients, CrCl	32	123
Missing patients, P-gp inhibitors	-	-
Body weight ≤60 kg, %	32.5	4.5
CrCl ≤50 ml/min, %	59.0	6.2
P-gp inhibitors (mandatory), %	3.2	0.3
Body weight+CrCl, %	17.2	8.6

CrCl: creatinine clearance; P-gp: P-glycoprotein.

included in the large ongoing ETNA-AF study, and to compare it with previously retrieved Portuguese data.

AF is a significant health burden. It accounts for approximately 15% of all ischemic strokes,⁸ which represent a major cause of mortality in Portugal. The SAFIRA study recently reported an 11.2% stroke rate in the Portuguese population with AF, which is not negligible.¹¹ The present study therefore helps to gain insights and deepen current knowledge of the situation in Portugal concerning this condition, on the assumption that the availability of reliable data on AF prevalence and incidence is key for optimal management and stroke prevention.

The FAMA study set a reference value of 2.5% for the prevalence of AF in Portugal, which has since been acknowledged as representative of the Portuguese population over 40 years of age.⁹ No differences were found between genders, but AF prevalence increased with age, and was significantly higher in the ≥70-year-old group.⁹ However, by not considering the frequency of paroxysmal AF, the study may have underestimated the real prevalence of AF in the country. To address this limitation, the study by Primo et al.¹⁰

and the SAFIRA study¹¹ set out to document the prevalence of paroxysmal AF, besides the overall prevalence of AF, using 24-hour electrocardiographic monitoring. However, the use of 24-hour Holter in both studies may have biased population selection and the results to some extent, since this is an expensive and complex test which could therefore not be used in a community setting, but only in specialized health units.

Compared with FAMA, SAFIRA analyzed a more elderly population, of patients aged ≥ 65 years. Although this population was also included in the FAMA study, it was more thoroughly studied in SAFIRA, and revealed a 9% prevalence of AF, which is higher than reported in FAMA.¹¹ Results according to age class were not so disparate between the studies. Both found that AF prevalence increased with age, with FAMA reporting a prevalence of 6.6% in the 70-79 age group and 10.4% in those over 80 years of age,⁹ and SAFIRA reporting prevalences of 6.8% in those aged 65-69 years, 11.1% in those aged 70-79 years, and 15.2% in those aged over 80 years.¹¹ These values are lower than those found by Primo et al., who reported an overall 12.4% prevalence of AF/atrial flutter in a younger population of individuals (aged ≥ 40 years).¹⁰ Bonhorst¹⁹ provides a more thorough comparison between the FAMA and SAFIRA studies.

In the present study, an even older population of patients with AF was included, with an overall mean age of 73.9 years (79.5 and 72.1 years in the low- and high-dose edoxaban groups, respectively) and more than half (50.7%) aged ≥ 75 years. This patient population is closer to that of the ENGAGE AF-TIMI clinical trial, in which a median age of 72 years was reported in both the high- and low-dose edoxaban groups.¹²

In the Iberian cohort of ETNA-AF, most patients (47.5%) had paroxysmal AF, followed by 26.4% with permanent, 21.9% with persistent, and 4.2% with long-standing persistent AF, and most patients (53.9%) were symptomatic at first diagnosis. When the two edoxaban dose groups are analyzed individually, a considerably higher proportion of patients receiving both low- and high-dose edoxaban in ETNA-AF Iberia had paroxysmal AF (40.9% and 49.6%) compared with ENGAGE AF-TIMI (26.1% and 24.9%, respectively).¹²

With regard to antithrombotic treatment, despite the reported evidence of the safety, efficacy, and cost-effectiveness of oral anticoagulants in ischemic stroke prevention, particularly among the elderly,² there is a widespread perception that they are underused by Portuguese clinicians. FAMA reported that 62.2% of patients with AF were anticoagulated⁹ compared to only 43.7% of those in the SAFIRA study.¹¹ In ETNA-AF Iberia, all patients were anticoagulated with edoxaban, as per the inclusion criteria, with previous treatment (suspended at or before baseline enrollment) mostly consisting of VKAs (35.7%), followed by NOACs and antiplatelets (9.5% each), heparin or fondaparinux (6.8%) and antiarrhythmics and rate control drugs (4.4%). In SAFIRA, a considerably higher proportion of anticoagulated patients were receiving VKAs (65.7%) and NOACs (34.3%).¹¹ In the study by Primo et al., only 29.9% of patients with persistent AF and 12.8% of those with paroxysmal AF were anticoagulated, but the type of anticoagulation was not reported.¹⁰ A systematic review and meta-analysis of observational studies found that 60% of patients with AF in

Portugal were not receiving oral anticoagulation therapy.²⁰ Overall, the low prevalence of oral anticoagulation reported in Portuguese clinical practice is worrying and does not meet international guideline recommendations.² This may be partially explained by patients' advanced age and possibly the reluctance of clinicians to prescribe anticoagulants due to the potential for bleeding complications.

The inappropriate dosing rate of the present study was relatively low (7.1% and 6.5% of all anticoagulated subjects were under- and overdosed, respectively) and adherence to the label dosing recommendation was good. In SAFIRA, 24.7% of subjects were incorrectly treated, with only 6.1% of overdosing and no reports of underdosing.¹¹

ETNA-AF Iberia found a median overall CHA₂DS₂-VASC score of 3.0, which was higher in the low-dose (median 4.0) than in the high-dose (median 3.0) edoxaban group. Despite this difference, most patients in both treatment arms (31.8% and 27.1%, respectively) had a CHA₂DS₂-VASC of 3, suggesting a moderate stroke risk. This is consistent with the results of SAFIRA, which reported a median CHA₂DS₂-VASC score of 3.5.¹¹ Regarding the relationship between anticoagulation rate and CHA₂DS₂-VASC score, except for scores of 4 or 5, for which the rates were similar in both studies (46.9% in the low- and 31.0% in the high-dose arm in ETNA-AF Iberia vs. 50.1% in SAFIRA), the results were somewhat different from ETNA-AF Iberia and SAFIRA. The anticoagulation rate in patients with a CHA₂DS₂-VASC score between 1 and 3 was considerably higher in ETNA-AF Iberia (44.6% in low- and 62.9% in high-dose arms) than in SAFIRA (25.3%),¹¹ but both were considerably lower than the CHADS₂ scores in the ENGAGE AF-TIMI trial (77.8% in low- and 77.1% in high-dose arms).¹² The opposite was true for patients with a CHA₂DS₂-VASC score ≥ 6 , for whom considerably lower anticoagulation rates were described in ETNA-AF Iberia (8.6% in low- and 4.4% in high-dose arms) than in SAFIRA (18.6%). ENGAGE AF-TIMI further reported 22.9% and 22.2% of patients in the high- and low-dose treatment groups, respectively, with CHADS₂ scores between 4 and 6 and no patients with CHADS₂ scores ≥ 7 .¹²

Concerning bleeding risk, both the overall and the high-dose edoxaban cohorts in ETNA-AF Iberia were found to have a moderate bleeding risk (median HAS-BLED score of 2.0), while a higher bleeding risk (median HAS-BLED score of 3.0) was reported in the low-dose edoxaban cohort.

The prevalence of CV risk factors was high in this study, as expected in an elderly population. Hypertension (76.7%), dys- or hyperlipidemia (50.9%), and diabetes (26.8%) were the most prevalent comorbidities, in agreement with the findings of SAFIRA (85.3%, 75.4% and 22.7%),¹¹ but this was considerably higher than reported in FAMA (43.5%, 36.8% and 13.1%, respectively).¹⁰ The ENGAGE AF-TIMI population had more patients with hypertension (93.7% in the high-dose and 93.5% in the low-dose group)¹² than in any of the Portuguese studies, and the same was also true for diabetes (36.4% in the high- and 36.2% in the low-dose group).¹² Congestive heart failure was the second most prevalent comorbidity in ENGAGE AF-TIMI (58.2% and 56.6% in the high- and low-dose groups, respectively),¹² rather than the dys- or hyperlipidemia observed in the Portuguese population.

Overall, ETNA-AF Iberia describes a real-world patient population which is not very different from that of the

ENGAGE AF-TIMI clinical trial. Additionally, it confirms the results of the SAFIRA and FAMA Portuguese reference AF studies, in that a significantly high number of patients still fail to receive anticoagulant therapy, highlighting the need to further optimize management of this condition. Lastly, involving both patients and health professionals is crucial to increase health gains in AF.

This study has some limitations, particularly the sample size, which was partially determined by restrictions regarding the end of enrollment, and the limited experience with edoxaban, which may also have reduced sample size. This may be compensated to some extent by the study's longer follow-up, giving the opportunity to study edoxaban in a broad contemporary AF patient population.

Conclusion

These data, although only concerning clinical and epidemiological profiles at admission, offer a snapshot on a contemporary Iberian AF patient population, thus providing a valuable tool to assess disease profile, patients' concomitant medications and comorbidities, and how edoxaban is used in clinical practice.

In the future, these real-world patient data will provide valuable insights into disease management and progression and the safety and effectiveness of edoxaban, as well as patterns of cardiovascular events, which are crucial to appropriately position edoxaban in the constantly changing landscape of stroke prevention in Iberian AF patients.

Funding

Daiichi Sankyo, Inc. provided funding for this study.

Conflicts of interest

Pedro Monteiro is an investigator and Steering Committee member of ETNA-AF Europe, investigator of the RE-LY and Engage-AF trials, and has received research and lecturing fees from Bayer, Boehringer Ingelheim, Daiichi Sankyo and Pfizer-BMS.

Appendix. Portuguese centers participating in ETNA-AF Iberia

Cardiology Department of Centro Hospitalar de Setúbal - Hospital de São Bernardo
 Cardiology Department of Clínica Cuida Mais - Cuidados de Saúde
 Cardiology Department of Vergílio Schneider - Clínica de Cardiologia
 Cardiology Department of Centro Hospitalar do Baixo Vouga - Hospital de Aveiro
 Cardiology Department of Instituto do Coração
 Immunotherapy Department of Centro Hospitalar Cova da Beira
 Internal Medicine Department of Centro Hospitalar de Vila Nova de Gaia
 Cardiology Department of Hospital do Divino Espírito Santo

Internal Medicine Department of Centro Hospitalar de Lisboa Norte - Hospital de Santa Maria
 Cardiology Department of Hospital Lusíadas Lisboa
 Internal Medicine Department of ULSM - Hospital Pedro Hispano
 Cardiology Department of Centro Hospitalar de Lisboa Norte - Hospital de Santa Maria
 Cardiology Department of Hospital de Braga

Appendix B. Spanish centers participating in ETNA-AF Iberia

Cardiology Department of Hospital Virgen Macarena
 Cardiology Department of Clínica Cardiología DR. Anguita
 Neurology Department of Hospital Universitario Virgen del Rocío (HUVR)
 Cardiology Department of Hospital Universitario Virgen del Rocío (HUVR) - National coordinator
 Cardiology Department of Hospital Virgen de la Victoria
 Cardiology Department of Hospital Costa del Sol
 Internal Medicine Department of Hospital Costa del Sol
 Internal Medicine Department of Hospital Virgen del Camino
 Cardiology Department of Fundación Hospital de Jove
 Internal Medicine Department of Hospital Carmen y Severo Ochoa (Centro de Cangas)
 Cardiology Department of Hospital Universitario Central de Asturias
 Cardiology Department of Hospital Son Llàtzer
 Cardiology Department of Hospital de Gran Canaria Dr. Negrin
 Cardiology Department of Clinica Vida
 Internal Medicine Department of Hospital Universitario de Canarias
 Internal Medicine Department of Hospital Insular Las Palmas
 Cardiology Department of Clinica Cardiorreal (H. General La Mancha Centro)
 Cardiology Department of Hospital General de Albacete
 Internal Medicine Department of Hospital Virgen de la Luz
 Geriatrics Department of Hospital Perpetuo Socorro
 Internal Medicine Department of Hospital Universitario de Burgos
 Cardiology Department of Complejo Asistencial Universitario de Salamanca
 Internal Medicine Department of Hospital Clínico de Valladolid
 Internal Medicine Department of Complejo Asistencial Universitario de Salamanca
 Cardiology Department of Hospital Nuestra Sra. de Sonsóles
 Hematology Department of Hospital Río Carrión
 Hematology Department of Complejo Asistencial Universitario de Salamanca
 Internal Medicine Department of Hospital El Bierzo
 Cardiology Department of Hospital El Bierzo
 Cardiology Department of Consulta Privada
 Cardiology Department of Hospital Comarcal Medina del Campo
 Internal Medicine Department of Complejo Asistencial Universitario de León
 Cardiology Department of Complejo Asistencial Universitario de León

Hematology Department of Hospital Universitario de La Vall D'Hebron
 Neurology department of Hospital Universitario de La Vall D'Hebron
 Neurology Department of Hospital Del Mar
 Cardiology Department of Hospital Del Mar
 Hematology Department of Hospital Universitari de Bellvitge
 Hematology Department of Hospital Clinic de Barcelona
 Cardiology Department of Hospital del Vendrell
 Hematology Department of Hospital de la Santa Creu I Sant Pau
 Hematology Department of Hospital l'Hospitalet
 Cardiology Department of Hospital Moises Broggi
 Neurology Department of Hospital Clinico Universitario de Valencia
 Cardiology Department of Hospital Clinico Universitario de Valencia
 Cardiology Department of Hospital General Universitario de Valencia
 Internal Medicine Department of Hospital Vega Baja
 Cardiology Department of Hospital San Juan de Alicante
 Cardiology Department of Hospital General Universitario de Alicante
 Cardiology Department of Hospital Universitario de Torre- vieja
 Cardiology Department of Hospital de la Vega Baja (Ori- huela)
 Cardiology Department of Hospital General Universitario de Elche
 Cardiology Department of Hospital General de Castellon
 Internal Medicine Department of Hospital de Sagunto
 Hematology Department of Hospital de Sagunto
 Internal Medicine Department of Hospital General Universi- tario Valencia
 Cardiology Department of Hospital General Universitario ELDA
 Cardiology Department of Hospital Virgen de los Lirios
 Cardiology Department of Hospital San Pedro de Alcántara
 Cardiology Department of Hospital Clinico Universitario de Santiago (CHUS)
 Internal Medicine Department of Complejo Hospitalario Uni- versitario A Coruña (CHUAC)
 Hematology Department of Complejo Hospitalario de Pon- tevedra
 Internal Medicine Department of Hospital Clinico San Carlos
 Cardiology Department of Hospital La Paz
 Cardiology Department of Hospital Ramón y Cajal
 Internal Medicine Department of Hospital Puerta de Hierro
 Neurology Department of Hospital Puerta de Hierro
 Internal Medicine Department of Hospital Universitario de la Princesa
 Cardiology Department of Hospital General Universitario Gregorio Marañón
 Cardiology Department of Hospital Universitario Madrid Montepíncipe – Centro Integral Enfermedades Cardiovas- culares (CIEC)
 Hematology Department of Hospital Universitario de la Princesa
 Internal Medicine Department of Hospital San Rafael
 Cardiology Department of Hospital Universitario 12 de Octubre
 Cardiology Department of Hospital HM Madrid

Cardiology Department of Hospital Sanchinaro
 Cardiology Department of Hospital Madrid Montepíncipe
 Cardiology Department of HM Policlínico
 Cardiology Department of HM Vallés
 Cardiology Department of HM Torrelodones
 Cardiology Department of HM Puerta del Sur
 Cardiology Department of Hospital Clinico Universitario Vir- gen de la Arriaxaca
 Hematology Department of Hospital Clinico Universitario Virgen de la Arriaxaca
 Cardiology Department of Hospital General Universitario Morales Meseguer
 Internal Medicine Department of Hospital Universitario Santa Lucía
 Cardiology Department of Hospital General Universitario Santa Lucia (Cartagena)
 Cardiology Department of Complejo Hospitalario de Navarra
 Cardiology Department of Clinica Universitaria de Navarra
 Cardiology Department of Hospital Universitario de Cruces
 Cardiology Department of Hospital Universitario de Álava
 Cardiology Department of Hospital de Galdakao-Usansolo

References

1. Rahman F, Kwan GF, Benjamin EJ. Global epidemiology of atrial fibrillation. *Nat Rev Cardiol.* 2014;11:639–54.
2. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Europace.* 2016;18:1609–78.
3. Björck S, Palaszewski B, Friberg L, et al. Atrial fibrillation, stroke risk, and warfarin therapy revisited: a population-based study. *Stroke.* 2013;44:3103–8.
4. Stroke Risk in Atrial Fibrillation Working Group. Independent predictors of stroke in patients with atrial fibrillation: a systematic review. *Neurology.* 2007;69:546–54.
5. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke.* 1991;22:983–8.
6. Zulkifly H, Lip GYH, Lane DA. Epidemiology of atrial fibrillation. *Int J Clin Pract.* 2018;72:e13070.
7. Pedersen OD, Abildstrøm SZ, Ottesen MM, et al. Increased risk of sudden and non-sudden cardiovascular death in patients with atrial fibrillation/flutter following acute myocardial infarction. *Eur Heart J.* 2006;27:290–5.
8. Fuster V, Rydén LE, Cannom DS, et al. ACC/AHA/ESC 2006 Guide- lines for the management of patients with atrial fibrillation. *Circulation.* 2006;114.
9. Bonhorst D, Mendes M, Adragão P, et al. Prevalência de fibrilhação auricular na população portuguesa com 40 ou mais anos. *Estudo FAMA. Rev Port Cardiol.* 2010;29:331–50.
10. Primo J, Gonçalves H, Macedo A, et al. Prevalência da fibrilhação auricular paroxística numa população avaliada por monitorização contínua de 24 horas. *Rev Port Cardiol.* 2017;36:535–46.
11. Monteiro P. Estudo Safira: reflexões sobre a prevalência e os padrões de tratamento de fibrilhação auricular e risco cardio- vascular em 7500 indivíduos com 65 ou mais anos. *Rev Port Cardiol.* 2018;37:307–13.
12. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus Warfarin in patients with atrial fibrillation. *N Engl J Med.* 2013;369:2093–104.
13. De Caterina R, Kelly P, Monteiro P, et al. ETNA-AF-Europe inves- tigators. Design and rationale of the Edoxaban Treatment in routiNe clinical prActice for patients with Atrial Fibrillation

- in Europe (ETNA-AF-Europe) study. *J Cardiovasc Med (Hagerstown)*. 2019;20:97–104.
14. Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001;285:2864–70.
 15. van Walraven C, Hart RG, Connolly S, et al. Effect of age on stroke prevention therapy in patients with atrial fibrillation: the atrial fibrillation investigators. *Stroke*. 2009;40:1410–6.
 16. Friberg L, Rosenqvist M, Lip GYH. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. *Eur Heart J*. 2012;33:1500–10.
 17. Olesen JB, Lip GYH, Lane DA, et al. Vascular disease and stroke risk in atrial fibrillation: a nationwide cohort study. *Am J Med*. 2012;125, 826.e13–23.
 18. Pisters R, Lane DA, Nieuwlaat R, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation. *Chest*. 2010;138:1093–100.
 19. Bonhorst D. A new look at the prevalence of atrial fibrillation in Portugal: the Safira study. *Rev Port Cardiol*. 2018;37:315–7.
 20. Caldeira D, Barra M, David C, et al. Prevalência da anticoagulação oral em doentes com fibrilhação auricular em Portugal: revisão sistemática e meta-análise de estudos observacionais. *Rev Port Cardiol*. 2014;33:555–60.