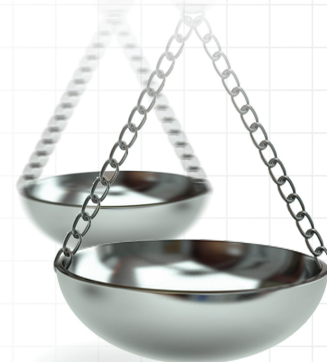




Patient characteristics and stroke and bleeding events in nonvalvular atrial fibrillation patients treated with apixaban and vitamin K antagonists: a Spanish real-world study

Journal of **Comparative Effectiveness Research**

Sreeram V Ramagopalan^{*1}, Antoni Sicras-Mainar², Carlos Polanco-Sanchez³, Robert Carroll¹ & Jaime F de Bobadilla⁴

¹Centre for Observational Research & Data Sciences, Bristol-Myers Squibb, Uxbridge, UK

²Scientific Direction, HEOR, Real Life Data, Badalona, Barcelona, Spain

³Bristol-Myers Squibb, Madrid, Spain

⁴Cardiology Service, Hospital Universitario La paz, Madrid, Spain

*Author for correspondence: Tel.: +44 189 552 3382; Sreeram.ramagopalan@bms.com

Aim: To compare the risk of stroke, systemic thromboembolism and bleeding, in patients initiating apixaban or acenocoumarol for the treatment of nonvalvular atrial fibrillation. **Methods:** An observational, retrospective study was performed using medical records of patients who initiated apixaban or acenocoumarol between 2015 and 2017. Propensity score matching was used to match patients; stroke, systemic thromboembolism, major and minor bleeding events were compared between the matched patients. **Results:** Patients who were prescribed apixaban had a lower rate of systemic embolism/stroke (hazard ratio [HR] = 0.54; 95% CI: 0.38–0.78; $p = 0.001$), minor bleeding (HR = 0.64; 95% CI: 0.52–0.79; $p < 0.001$) and major bleeding (HR = 0.51; 95% CI: 0.37–0.72; $p < 0.001$). **Conclusion:** Patients prescribed apixaban for the treatment of nonvalvular atrial fibrillation had lower rates of thromboembolic events and minor/major bleeding than patients on acenocoumarol.

First draft submitted: 20 June 2019; Accepted for publication: 5 July 2019; Published online: 23 July 2019

Keywords: acenocoumarol • apixaban • bleeding • nonvalvular atrial fibrillation • stroke • systemic embolism

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation and ineffective atrial contraction [1]. The prevalence of AF was 0.05% in Spanish individuals aged 18–45 years in 2018 and 4.4% in the general Spanish population aged >40 years [2–4]. Patients with AF may have valvular heart disease or not. AF without valvular heart disease is known as nonvalvular atrial fibrillation (NVAF) [1,5].

NVAF has long been identified as a significant risk factor for disabling or fatal ischemic stroke and systemic embolism [1]. Specifically, NVAF is associated with a fivefold increase in stroke risk, which is considered as more severe than non-AF-associated stroke [6]. Prevention of systemic embolization, even after the first episode of AF, is the cornerstone of treatment. Anticoagulant treatments have been evaluated in clinical trials [6–9]. Anticoagulation with vitamin K antagonists (VKA), acenocoumarol and warfarin has demonstrated a reduction in the incidence of clinical stroke, with an acceptable risk of bleeding compared with aspirin, in patients with AF at moderate and high risk of thromboembolic events [1,7]. In patients with NVAF, novel oral anticoagulants (NOACs) have demonstrated a better risk–benefit profile than VKA in clinical trials [10]. Available NOACs include dabigatran, rivaroxaban, apixaban and edoxaban [11–15]. No head-to-head clinical trials have compared NOACs, although observational studies suggest differences in the risk–benefit profile between them [11].

Real-world studies have been performed in different populations to clarify whether clinical trial results are also observed in clinical practice [11,12,16–18]. To our knowledge, no real-world study has assessed this issue in a representative Spanish population. The aim of this study was to describe NVAF patients treated with apixaban

Table 1. International Classification of Disease, 9th Revision, Clinical Modification coding used to define the results (effectiveness, safety).

Outcomes/others	ICD-9-CM codes
Stroke or systemic embolism	
Ischemic stroke, TIA	433.x1, 434.x1, 436, 435.x
Systemic embolism	444.x, 445.x
Minor bleeding	
Other sites	285.1, 360.43, 362.43, 362.81, 363.61, 363.62, 363.72, 364.41, 372.72, 374.81, 376.32, 377.42, 379.23, 423.0x, 719.1x, 782.7, 784.7, 784.8, 786.3x, 958.2, 997.02, 998.11, 99.04
Genito-urinary	596.7x, 599.7x, 602.1x, 620.1, 621.4, 626.2, 626.5, 626.7, 626.8, 626.9
Major bleeding	
Intracranial bleeding, hemorrhagic stroke	430, 431, 432.x, 852.x, 853.x
Gastrointestinal bleeding	456.0, 456.20, 530.21, 530.7, 530.82, 531.0x, 531.2x, 531.4x, 531.6x, 532.0x, 532.2x, 532.4x, 532.6x, 533.0x, 533.2x, 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 535.71, 537.83, 537.84, 562.02, 562.03, 562.12, 562.13, 568.81, 569.3, 569.85, 578.x
Bleeding from other sites	423.0, 459.0, 596.7, 599.71, 719.1x, 784.8, 786.3
Others	
Atrial fibrillation	427.31
Valvular heart disease	394.x, 396.0, 396.1, 396.8, 396.9, 424.0, 745.x, V42.2, V43.3

ICD-9-CM: International Classification of Disease, 9th Revision, Clinical Modification; TIA: Transient ischemic attack.

Table 2. Baseline patient characteristics by study group.

Study groups	Apixaban	Acenocoumarol/warfarin	p-value
Number of patients	N = 2160	N = 30,765	
Sociodemographic characteristics			
Mean age (SD), years	71.2 (12.8)	73.8 (13.1)	<0.001
Gender (male)	47.6%	50.2%	<0.001
General comorbidity			
Mean number of diagnoses (SD)	10.1 (6.3)	12.1 (6.7)	<0.001
Charlson index (SD)	2.5 (2.0)	2.8 (2.2)	<0.001
Scales			
CHA ₂ -DS ₂ -VASc	3.3 (1.9)	3.8 (1.9)	<0.001
HAS-BLED	2.0 (1.3)	2.5 (1.1)	<0.001

N = 32,925. Values expressed as a percentage or mean. p-value represents the statistical significance.
SD: standard deviation.

compared with conventional VKA in terms of bleeding, stroke and systemic embolic events in daily clinical practice in Spain.

Material & methods

Design & study population

An observational, multicenter, retrospective longitudinal study was carried out through review of medical records (computerized databases, with dissociated data). The study population was obtained from the records of health providers from various primary and hospital centers in Spain (unified in the dissociated, anonymized BIG-PAC[®] database, 2017 Real Life Data) [19]. Data came from computerized medical records and other supplementary databases of financing/provision of public services from nine Spanish autonomous communities (2.9 million potential patients).

Study periods, inclusion & exclusion criteria

Patients who requested care and began new anticoagulant treatment with apixaban or VKA (acenocoumarol or warfarin) between 1 January 2015 and 31 December 2017 (inclusion period) for the treatment of NVAF were included. Date of treatment initiation in the inclusion period was the index date. Patients prescribed apixaban who

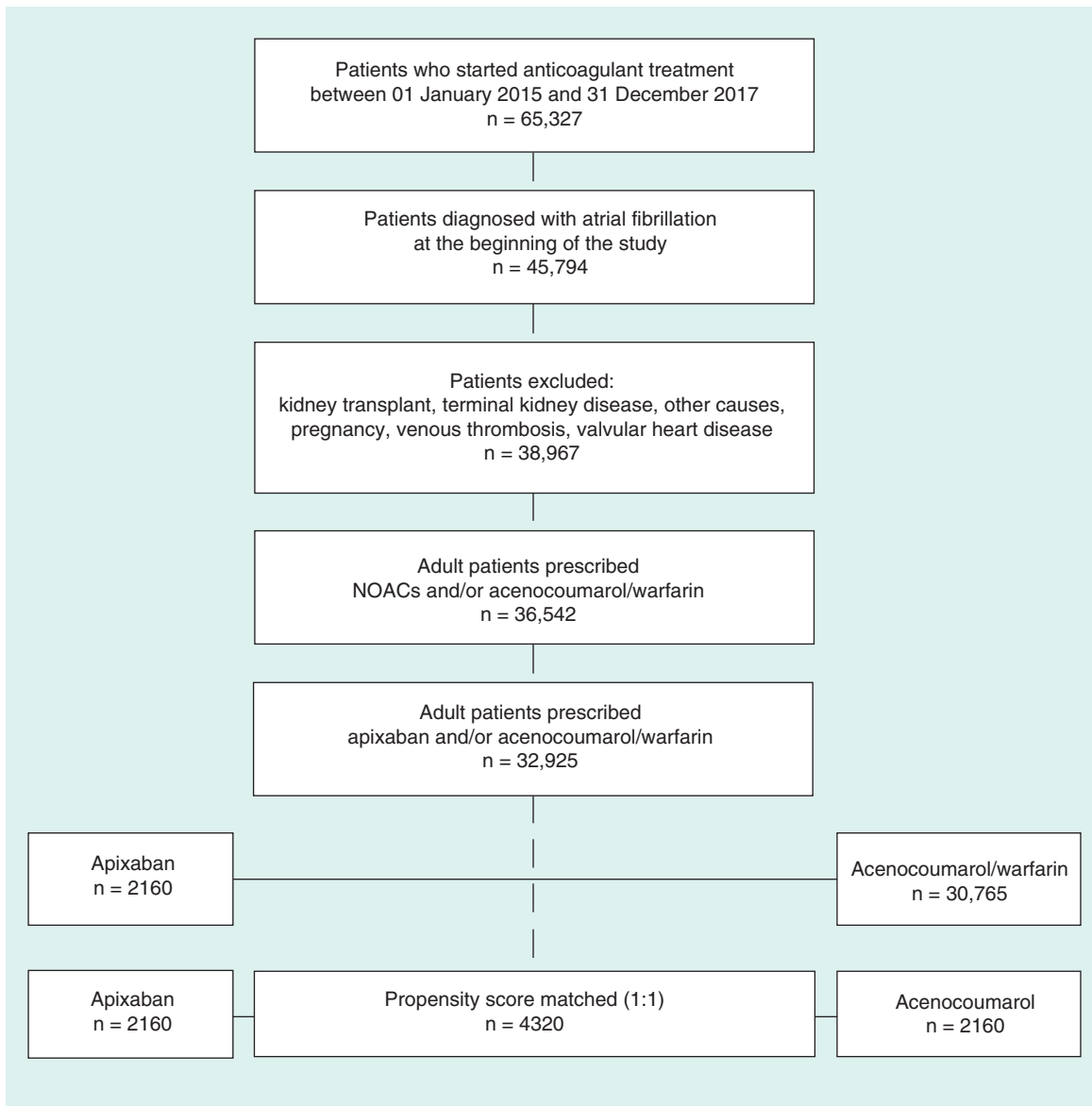


Figure 1. Study flow diagram. A retrospective observational study was carried out based on review of medical records (computerized databases with anonymized and dissociated data) of patients diagnosed with non-valvular atrial fibrillation prescribed apixaban and acenocoumarol/warfarin.
NOAC: Novel oral anticoagulant.

had switched from VKA and vice versa were eligible for inclusion. In Spain, authorization for prescription of a NOAC is required before starting treatment.

Inclusion criteria were as follows: age ≥ 18 years; patients active in the database for ≥ 12 months before study initiation (baseline period); inclusion in the program of chronic prescriptions (with a record of the daily dose, the time interval and the duration of each treatment administered, and ≥ 2 prescriptions during the follow-up period); regular patient monitoring (≥ 2 health records in the computer system). Exclusion criteria were as follows: subjects being transferred to other centers, displaced or out of area; permanently institutionalized patients; a history of transient AF (thyrotoxicosis, pericarditis), heart surgery, venous thromboembolism, hip or knee surgery in the previous 6 weeks, valvular heart disease and/or pregnancy; subjects with valvular AF (with prosthetic valves); and end-stage renal disease, dialysis or kidney transplant. Patients who started treatment with VKA and were switched to a NOAC other than apixaban during the follow-up period were also excluded. Depending on the analysis, patients were followed from index date until death, treatment interruption, the end of the study period (31 December

Table 3. Baseline patient characteristics by study group.

Study groups, PSM	Apixaban	Acenocoumarol	p-value	Standardized difference
Number of patients	N = 2160	N = 2160		
Sociodemographic characteristics				
Mean age (SD), years	71.2 (12.8)	71.6 (10.1)	0.271	-0.041
Ranges: 40–64 years	20.2%	21.6%	0.552	-0.014
65–74 years	38.6%	37.8%	0.391	0.009
≥75 years	41.2%	40.6%	0.475	0.005
Gender (male)	47.6%	47.8%	0.903	-0.003
General comorbidity				
Mean number of diagnoses (SD)	10.1 (6.3)	10.4 (5.3)	0.163	0.024
Charlson Index (SD)	2.5 (2.0)	2.6 (1.9)	0.758	0.016
– 0	15.5%	15.1%	0.874	0.010
– 1	24.1%	24.2%	0.557	-0.003
– 2	38.3%	38.5%	0.673	-0.007
– 3+	22.1%	22.2%	0.675	-0.002
Associated comorbidities				
Arterial hypertension	70.9%	71.1%	0.893	-0.021
Mellitus diabetes	31.7%	30.6%	0.430	0.012
Dyslipidemia	45.0%	45.6%	0.714	-0.006
Obesity	22.8%	22.2%	0.662	0.007
Active smoking	6.5%	5.2%	0.080	0.028
Alcohol ingestion	2.6%	2.8%	0.707	-0.006
Ischemic heart disease	23.0%	22.2%	0.560	0.009
Cerebrovascular accident	14.8%	15.2%	0.733	-0.005
Heart failure	20.2%	19.8%	0.761	0.004
Renal failure	10.9%	10.7%	0.845	0.013
Asthma	8.9%	8.8%	0.998	0.017
COPD	15.0%	15.2%	0.865	-0.023
Depressive syndrome	13.7%	13.3%	0.722	0.025
Malignant neoplasms	10.7%	10.4%	0.692	0.006
Liver decompensation	5.0%	5.2%	0.782	-0.014
Previous bleeding	14.6%	14.5%	0.887	0.058
Anemia	10.3%	9.7%	0.222	0.022
Scales				
CHA ₂ -DS ₂ -VASc	3.3 (1.9)	3.4 (1.7)	0.148	-0.015
HAS-BLED	2.0 (1.3)	2.1 (1.1)	0.221	-0.017

Values expressed as a percentage or mean. p-value represents the statistical significance.

COPD: Chronic obstructive pulmonary disease; PSM: Propensity score matched; SD: Standard deviation.

2018), 12 months or an event the first (stroke, thromboembolism or major/minor bleeding), whichever occurred first. Patients were classified into two cohorts depending on treatment initiated in inclusion period: apixaban and VKA.

Definition of diagnosis, demographic variables & comorbidities

Patients with a diagnosis of AF (International Classification of Disease, 9th Revision, Clinical Modification [ICD-9-CM]: 427.31) with no valvular heart disease (ICD-9-CM: 394.x, 396.0, 396.1, 396.8, 396.9, 424.0, 745.x, V42.2, V43.3) prior to the index date were included (Table 1). The sociodemographic and comorbidity variables collected are detailed in Table 3. The Charlson Comorbidity Index [20] was used as a summary variable of general comorbidity. These variables were obtained at baseline. For each patient, the CHA₂DS₂ -VASc and HAS-BLED [10] scores were obtained at baseline. The operational definition of these scales in this dataset is detailed in Supplementary Table 1.

Table 4. Medication administered & treatment persistence by study groups.

Study groups, PSM	Apixaban	Acenocoumarol	p-value
Number of patients	N = 2160	N = 2160	
Time since diagnosis, years			
– Mean (SD)	0.9 (1.4)	0.9 (1.5)	0.611
– Median (P25–P75)	0.1 (0.0–1.8)	0.1 (0.0–1.9)	
BMI, kg/m ²			
– Mean (SD)	27.7 (3.2)	27.9 (4)	0.189
– Median (P25–P75)	27.3 (26.3–28.4)	27.2 (26.0–28.4)	
Previous use of antithrombotic medication			
– Acenocoumarol initial	28.2%	100.0%	<0.001
– Apixaban	71.8%	0.0%	<0.001
Daily dose			
– 5 mg	22.5%	–	
– 10 mg	77.5%	–	
– Mean (SD)	8.6 (2.2)	3.4 (0.7)	<0.001
– Median (P25–P75)	10.0 (5.0–10.0)	3.0 (2.8–4.0)	
Weekly dose			
– Mean (SD)	60.2 (2.2)	22.3 (4.3)	<0.001
– Median (P25–P75)	10.0 (5.0–10.0)	20.0 (18.0–22.0)	
Use of concomitant medication			
– Antiplatelet	13.2%	11.3%	0.065
Nonsteroidal anti-inflammatory drugs	9.5%	10.1%	0.284
Treatment duration, days			
– Mean (SD)	300.3 (104.0)	266.4 (121.1)	<0.001
– Median (P25–P75)	330 (216–365)	304 (136–365)	
– Not treatment persistent at 1 year	28.9%	39.4%	<0.001
– Treatment abandonment	5.6%	5.2%	0.570
– Dose reduction	2.2%	7.2%	<0.001
– Switch to heparin	6.5%	5.5%	0.421
– Switch to antiplatelet	11.3%	4.3%	<0.001
– Switch to other NOAC	3.3%	17.2%	<0.001
Treatment persistence			
– 6 months	79.8%	70.4%	<0.001
– Hazard ratio (95% CI)		1.2 (1.0–1.3)	0.006
– 12 months	71.1%	60.6%	<0.001
– Hazard ratio (95% CI)		1.3 (1.1–1.4)	0.012

† Cox proportional hazards regression.
Values expressed as a percentage or mean. Reference medicine: apixaban. p-value represents the statistical significance as a percentile.
PSM: Propensity score matched; SD: Standard deviation.

Medication administered & treatment persistence/duration

Data were obtained from records of the pharmacological dispensation of medicines. The choice of medication for a specific patient was at the physician's discretion (clinical practice). Drugs were coded according to the Anatomical Therapeutic Chemical Classification System [21]: VKA (B01AA) and NOAC (apixaban, B01AF02), anticoagulant treatment (B01A) including heparin (B01AB) and platelet aggregation inhibitors (B01AC). The time from diagnosis of NVAf until the first prescription and the doses prescribed in the record of the first prescription issued were also collected.

Treatment persistence or duration was calculated from the start date until the discontinuation date (in days). The start date was the start of treatment (apixaban or acenocoumarol/warfarin), and the discontinuation date was the first between: the end date of the follow-up period (1 year), death, switch to an antiplatelet/anticoagulant treatment other than the inclusion medication and medication interruption/abandonment (≥ 60 days without renewing the

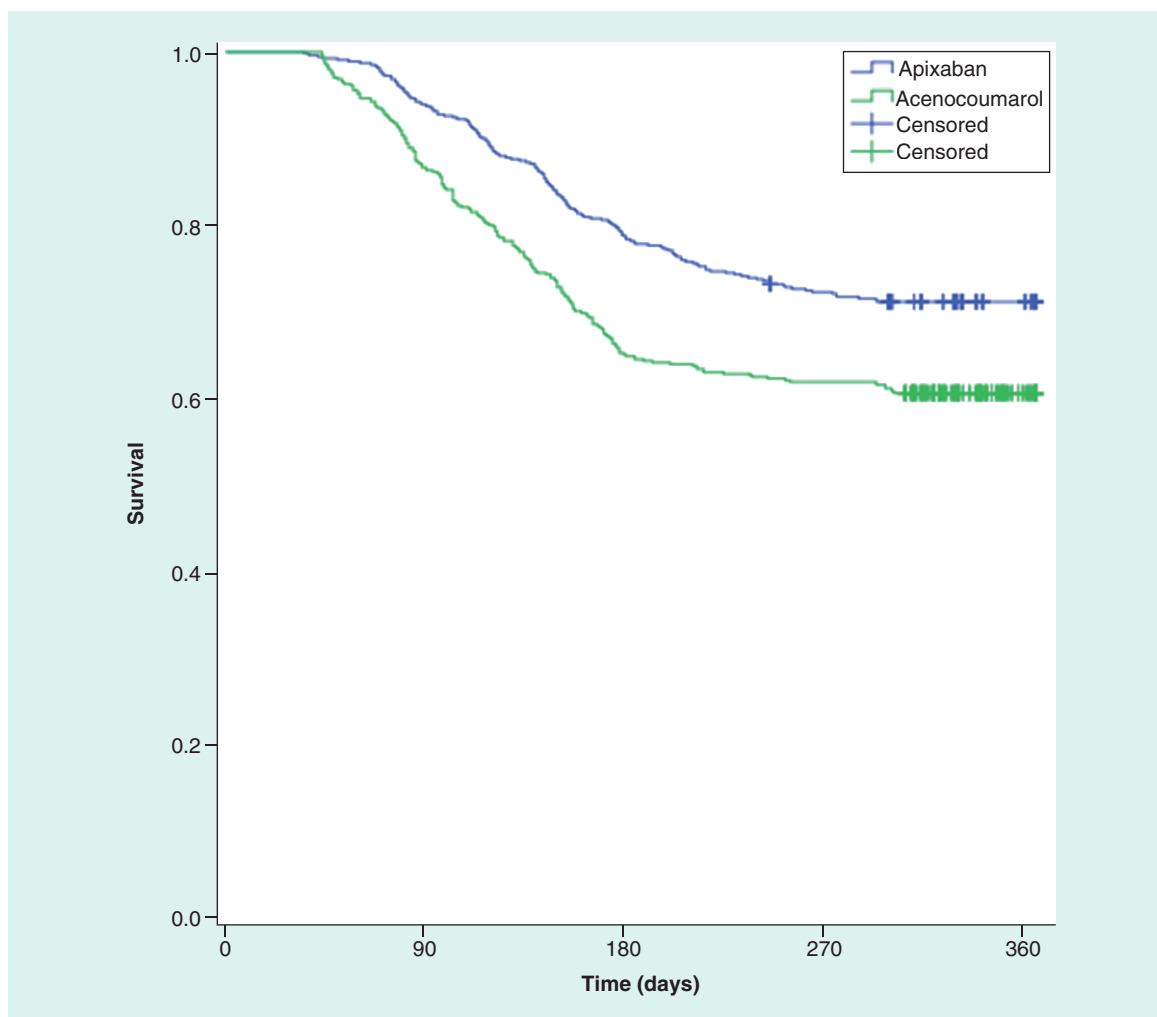


Figure 2. Kaplan–Meier curves of treatment persistence at 12 months of follow-up by study groups. Kaplan–Meier curves: Log Rank procedure (Mantel–Cox). Pairwise comparison: Chi-square = 65.858, $p < 0.001$. Treatment persistence: apixaban 71.1% vs acenocoumarol 60.6%.

medication). Treatment persistence was assessed at 6 and 12 months of follow-up. The date of interruption was 30 days from the last prescription end date.

Outcomes: effectiveness/safety

Clinical effectiveness was assessed according to episodes of ischemic stroke and systemic thromboembolism and safety according to major and minor bleeding. Major bleeding included intracranial, gastrointestinal and other sites (liver, ocular, splenic) and was defined as bleeding that required hospital admission for acute or subacute clinically manifest bleeding. These events were identified from 30 days after the initiation of anticoagulant medication (until the date of treatment discontinuation). Episodes were obtained using the ICD-9-CM codes shown in [Table 1](#).

Confidentiality of information/ethical aspects

The confidentiality of records (anonymous and dissociated) was respected according to the Law of Protection of Personal Data, Regulation (EU) 2016/679 of the European Parliament and the Council of 27 April 2016 on Data Protection and Organic Law 3/2018, of 5th December, on the Protection of Personal Data and Guarantee of Digital Rights. The study was classified by the Spanish Agency for Medicines and Health Products (EPA-OD) and approved by the Research Ethics Committee of the Hospital de Terrassa (Barcelona).

Table 5. Description of events (stroke/embolism, minor/major bleeding) by study groups.

Study groups, PSM	Percentage of events [†]		Hazard ratio (95% CI) [‡]	p-value
	Apixaban	Acenocoumarol		
Stroke and systemic embolism	2.0%	3.7%	0.54 (0.38–0.78)	0.001
N = 124; 44 vs 80				
– Ischemic stroke	1.4%	2.8%		
– Thromboembolism	0.6%	0.9%		
Minor bleeding	7.2%	10.9%	0.64 (0.52–0.79)	<0.001
N = 392; 156 vs 236				
– Genitourinary	4.1%	5.4%		
– Other minor bleeding	3.1%	5.6%		
Major bleeding	2.4%	4.6%	0.51 (0.37–0.72)	<0.001
N = 152; 52 vs 100				
– Gastrointestinal	1.7%	3.2%		
– Others	0.1%	0.5%		
– Cerebral, hemorrhagic stroke	0.6%	0.9%		

[†]Percentage of equivalent events per 100 person-years.

[‡]Cox proportional hazards regression.

Reference medicine: apixaban. p-value represents the statistical significance.

PSM: Propensity score matched.

Statistical analysis

Data were subject to exploratory analysis and preparation, inspecting the frequency distributions and searching for possible registration or coding errors in the data sources and the BIG-PAC database to guarantee data quality. A descriptive-univariate analysis was carried out. Categorical data were described using absolute and relative frequencies and continuous data using means, standard deviation, medians and percentiles 25 and 75 of the distribution (interquartile range). The 95% CI for the estimate of parameters were based on the total number of subjects with nonmissing values. The normality of distributions was checked using the Kolmogorov–Smirnov test. Propensity score matching (PSM) was used to pair patients (apixaban/VKA) on baseline variables that were significantly different between groups (analyzed age, gender, Charlson index [20], CHA₂DS₂-VASc [10] score and HAS-BLED score [10]). There was no multicollinearity between these variables. The tolerance of the model (PSM) was 1, with sampling with substitution and giving priority to exact matches (randomly). To measure treatment persistence/duration, a Kaplan–Meier survival analysis was performed, testing for differences using log-rank tests. Cox proportional hazards regression was used to compare events occurring during follow-up (hazard ratio [HR], with censored data). The rate of events of interest were expressed as percentages, equivalent to a rate per 100 persons–year (incidence rate, accumulated risk). The data were censored in the absence of the event. Characteristics were compared between matched apixaban and warfarin patients using standardized differences. The analysis was made using SPSSWIN, version 23 software. Statistical significance was set at $p < 0.05$.

Results

Of the initial population of 2.9 million, 65,327 received anticoagulant treatment between 1 January 2015 and 31 December 2017 and, of these, 45,794 were diagnosed with AF. In total, 32,925 patients met the inclusion/exclusion criteria and could be followed during the study period (apixaban: N = 2160 vs acenocoumarol/warfarin: N = 30,765). Table 2 shows the general characteristics of these patients overall showing significant differences. PSM yielded 2160 patients paired in each group (Figure 1). No patient was paired with warfarin, since it only accounted for 5.8% of the total VKA population.

Table 3 shows general patient characteristics according to the matched study groups. The mean age was 71.4 years and 47.7% were male. High blood pressure, dyslipidemia and diabetes were the most frequent comorbidities. There was a high degree of comparability between the matched apixaban and acenocoumarol groups: Charlson index (2.5 vs 2.6; $p = 0.758$), CHA₂DS₂-VASc (3.3 vs 3.4; $p = 0.148$) and HAS-BLED (2.0 vs 2.1; $p = 0.221$).

The medication administered and treatment persistence by study groups is shown in Table 4. Totally, 28.2% of patients who began treatment with apixaban had previously received acenocoumarol and 71.8% were ‘*de novo*.’ Totally, 77.5% of apixaban patients initiated a dose of 10 mg/day. The mean dose/day of acenocoumarol users

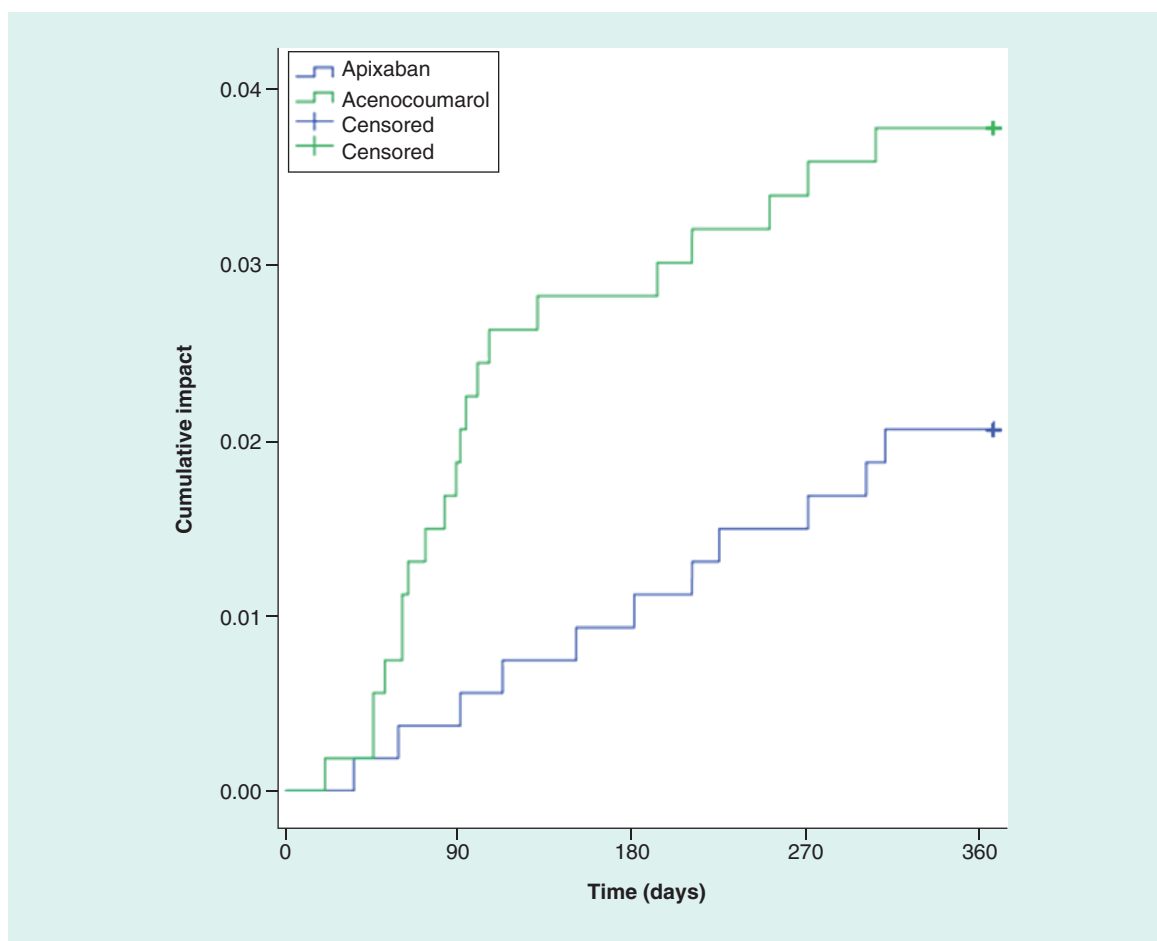


Figure 3. Kaplan–Meier curves (Log Rank procedure: Mantel–Cox) of embolic events (stroke/systemic embolism) at 12 months of follow-up by study groups. Pairwise comparison: Chi-square = 10.937, $p = 0.001$.

was 3.4 mg/day. There were no significant differences in the use of concomitant medication between apixaban and acenocoumarol patients: platelet aggregation inhibitors (13.2 vs 11.3%; $p = 0.065$) and nonsteroidal anti-inflammatory drugs (9.5 vs 10.1%; $p = 0.284$). Treatment persistence with apixaban was 71.1% compared with 60.6% with acenocoumarol at 12 months of follow-up ($p < 0.001$). The hazard ratio (HR) of apixaban relative to acenocoumarol was 1.3 (1.1–1.4), $p = 0.012$. Figure 2 shows the Kaplan–Meier curves of treatment persistence. Of the patients who discontinued treatment with apixaban, 11.3% changed to a platelet aggregation inhibitor and 6.5% to heparin. In contrast, 17.2% of patients on acenocoumarol changed to another NOAC.

Table 5 shows strokes/embolisms and minor/major bleeding, during the follow-up by study groups. Patients prescribed apixaban had a lower rate of events compared with acenocoumarol, both in systemic embolism and stroke (2.0 vs 3.7%; HR = 0.54; $p = 0.001$), minor bleeding (7.2 vs 10.9%; HR = 0.64; $p < 0.001$) and major bleeding (2.4 vs 4.6%; HR = 0.51; $p < 0.001$). Figures 3 & 4 show the Kaplan–Meier curves of embolic events (stroke or embolism), and major and minor bleeding at the end of the study in the two study groups. Patients who were prescribed apixaban *de novo* versus apixaban with previous acenocoumarol use showed a similar event rate: major bleeding, 2.3 vs 2.4% ($p = 0.832$); systemic embolism and stroke, 1.9 vs 2.0% ($p = 0.811$); apixaban *de novo* vs apixaban with previous acenocoumarol, respectively. Some of the characteristics of these patients (*de novo*) were: mean age 70.3 years, male 47.7%, Charlson index 2.3, CHA₂DS₂ -VASc 3.2 and HAS-BLED 2.1.

Discussion

This study found that patients who were prescribed apixaban for the treatment of NVAF had lower rates of thromboembolic events (clinical effectiveness) and minor/major bleeding (safety) than patients receiving acenocoumarol.

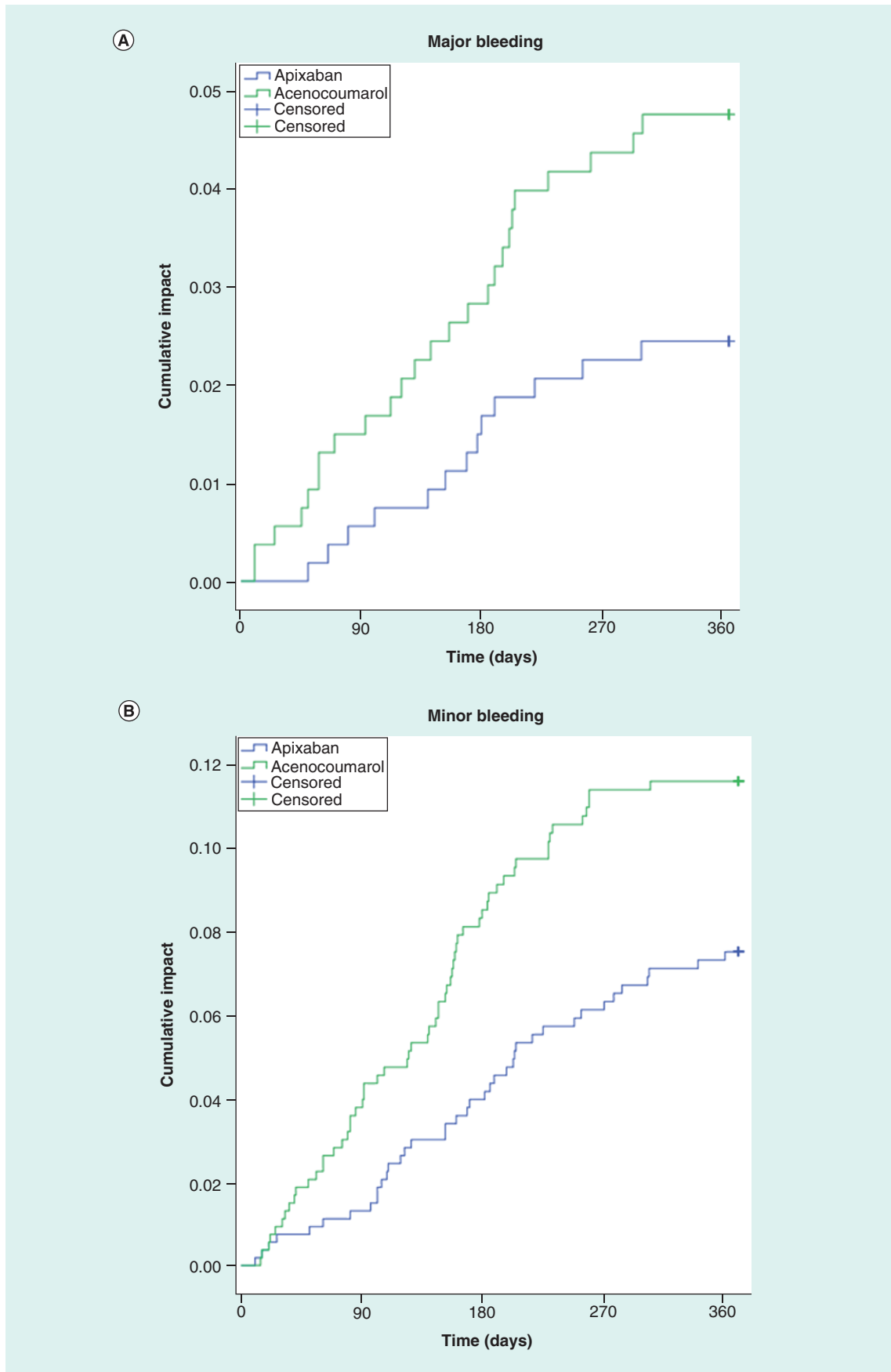


Figure 4. Kaplan–Meier curves (Log Rank procedure: Mantel–Cox) of major and minor bleeding at 12 months of follow-up by study groups. Pairwise comparison **(A)** Chi-square = 15.793, $p < 0.001$. **(B)** Chi-square = 18.819; $p < 0.001$.

The lack of Spanish real-life observational studies makes it difficult to compare the results but enhances the value of the present study [3,4,22,23]. The representativeness of the results is, likewise, enhanced by the inclusion of patients from various centers throughout Spain. Other studies carried out in routine clinical practice with a similar methodology to ours have found similar effectiveness and safety results [11,12,24–29]. In general, possible differences in the results could be related to differences in study populations, time periods and, especially, the number of patients included. These results in usual clinical practice are also consistent with those of randomized clinical trials [22].

Only 28.2% of patients who began treatment with apixaban had previously received acenocoumarol. This finding is similar to another Spanish study (23.2%) [22], but also may be due to an unexpected random effect or to the fact that, as it is a very recent study, there may be greater awareness by physicians of the benefits of apixaban, especially in complex chronic patients and elderly or polymedicated patients. Intracranial bleeding is considered the most prominent and potentially fatal complication in patients on oral anticoagulants [1,10]. As apixaban may have greater clinical benefits than acenocoumarol, this may have been accepted by physicians when selecting anticoagulant treatment [13–15]. Likewise, 77.5% of patients initiated apixaban at a dose of 10 mg/day, consistent with other studies [11,12].

The possible limitations of the study are those inherent to retrospective studies, such as under recording (missing data) or the possible intrinsic variations in physicians and patients due to the observational design, the methods of measurement used, the main study variables or possible classification/selection bias. Therefore, given the observational nature of the study, associations and not causal relationships can be identified. In this regard, the possible inaccuracy of the diagnostic coding of NVAF and the lack of some variables that could influence the final results (socioeconomic level, evolution of the prescribed pharmacological dose, concomitant medication, left ventricle ejection fraction values, renal filtration levels, etc.) should also be considered as limitations [30]. Using the ICD-9-CM codes did not allow differentiation of the type of permanent, persistent and/or paroxysmal AF, which may be considered a limitation of the database used. In addition, PSM minimizes potential bias between the variables analyzed, other, unmeasured factors, such as the use of aspirin, glucocorticoids, etc., either over the counter or by private prescription might have affected the between-group comparisons. We were unable to obtain data on the degree of anticoagulation control in patients on acenocoumarol (time in therapeutic range), an important factor given the relationship between this parameter and the efficacy/safety of this medication. However, the main limitation was indication bias by the attending physician at the initiation of treatment with apixaban or acenocoumarol, since, as usual in real-life situations, it was not random. Another limitation was that disaggregated results were not obtained from the study centers due to the high degree of confidentiality and anonymization of all study data; however, without this condition the study would not have been possible. In conclusion, patients prescribed apixaban for the treatment of NVAF had lower rates of thromboembolic events and minor/major bleeding than those receiving acenocoumarol, although further studies are required to validate our results.

Summary points

- Patients with atrial fibrillation (AF) have up to a fivefold increased risk of stroke.
- Anticoagulation therapy is offered to patients for stroke prevention; however, these treatments can lead to an increased risk of bleeding.
- Vitamin K antagonists (VKA) have up until recently been the main anticoagulation agent available. Recent advances in AF treatment have led to the availability of novel or direct oral anticoagulants, such as apixaban.
- Given the availability of newer treatments, it is unclear how patients are currently treated in the 'real-world' in Spain.
- In this investigation, we sought to describe AF patients receiving either VKAs or apixaban and to compare the risk of major bleeding and stroke in these groups of patients.
- After controlling for differences in patient characteristics, the risk of major bleeding and stroke was significantly less in patients taking apixaban as compared with patients taking VKAs.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/full/10.2217/cer-2019-0079

Author contributions

SV Ramagopalan and C Polanco-Sanchez conceived the study. The study was designed by A Sicras-Mainar and JF de Bobadilla. Data collection and statistical analysis was led by A Sicras-Mainar and the interpretation of the data, writing, review and approval of the submitted manuscript was undertaken by all authors.

Financial & competing interests disclosure

The study was sponsored by Bristol-Myers Squibb and Pfizer. S Ramagopalan, C Polanco-Sanchez and R Carroll are employees of Bristol-Myers Squibb. A Sicras is an independent consultant in relation to the development of this manuscript. J Fernández de Bobadilla is an independent author in relation to the development of this manuscript. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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