Research Article

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Healthcare resources and costs associated with nonvalvular atrial fibrillation in Spain: apixaban versus acenocoumarol

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Aim: Healthcare resources usage and costs associated to nonvalvular atrial fibrillation (NVAF) were analyzed in Spain. **Methods:** This is an observational and retrospective study on patients with NVAF who started their treatment with apixaban or acenocoumarol between 1 January 2015 and 31 December 2017. **Results:** 2160 patients treated with apixaban were paired (1:1) with patients treated with acenocoumarol (propensity score matching). Apixaban reduced the incidence of strokes and systemic embolisms, minor and major bleedings and deaths, versus acenocoumarol. Apixaban led to reductions of 80, 55 and 43% in costs related to nursing visits, hospitalizations, and emergency visits, respectively, leading to annual cost savings of €274/patient, from the perspective of society. **Conclusion:** Our results suggested that apixaban is a cost-effective alternative for patients with NVAF.

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Keywords: acenocoumarol • apixaban • cardiovascular events • cost–effectiveness • healthcare resources

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia with uncoordinated atrial electrical activation that leads to ineffective atrial contraction [1]. It is the most common cardiac arrhythmia, and its prevalence increases with age, affecting 4.4% of the population aged >40 years in Spain [2,3]. It is estimated that around 80% of AF patients have nonvalvular AF (NVAF), which is defined as AF without moderate or severe mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair [4,5]. NVAF is associated with increased morbidity, as it may raise the risk of strokes up to five-times, which usually have more severity than those not related to AF [3,6,7]. Therefore, the prevention of systemic embolisms, even after the first episode of AF, is the cornerstone of treatment [7].

Oral anticoagulation with traditional vitamin K antagonists (VKA; acenocoumarol and warfarin) reduces the incidence of stroke and has an acceptable risk of bleeding compared with aspirin in patients at moderate/high risk of thromboembolic episodes [5]. However, new direct-acting oral anticoagulants (DOACs), such as non-vitamin K antagonist oral anticoagulants (including dabigatran, apixaban, rivaroxaban), showed better risk–benefit profiles than VKA in patients with NVAF in conventional clinical trials [8–10]. In addition, observational real-life studies confirmed the effectiveness and safety of DOAC in patients with NVAF, with generally favorable results for DOAC versus VKA [11–18]. DOAC were mainly associated with a lower incidence of stroke or systemic embolism and intracranial and other major bleedings in comparison to warfarin [12,13,18]. In this sense, the study carried out by Ramagopalan *et al.* in a Spanish population of 4,320 patients with NVAF who started anticoagulant treatment with apixaban or acenocoumarol estimated that apixaban reduced the risk of stroke and systemic embolism, and minor and major bleedings, compared with acenocoumarol [17]. In fact, the European Society of Cardiology recommends in their guidelines DOAC as the first-line treatment for NVAF [19].

DOAC and VKA have been compared in economic analyses in patients with NVAF [20,21]. A simulation study developed by Barrios *et al.*, reported that poor coagulation control in patients treated with VKA would lead to an increase in ischemic strokes, major bleeding events and deaths in comparison to DOAC. The improvement

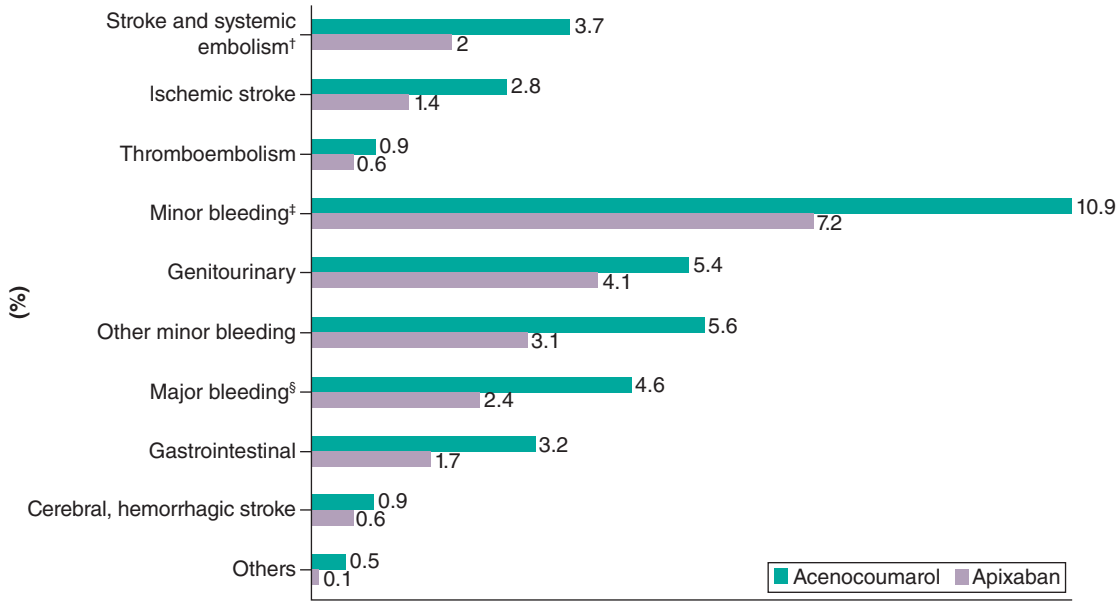

Figure 1. Clinical events per study group after propensity score matching. Results expressed as percentage of equivalent events per 100-person-year (n for each study group = 2160). *Stroke and systemic embolism: n = 124 (44 vs 80); HR = 0.54 (95% CI: 0.38–0.78; p = 0.001, **Minor bleeding: n = 392 (156 vs 236); HR = 0.64 (95% CI: 0.52–0.79); p < 0.001; ***Major bleeding: n = 152 (52 vs 100); HR = 0,51 (95% CI: 0.37–0.72); p < 0.001.
DOAC: Direct-acting oral anticoagulant; HR: Hazard ratio; p: Statistical significance.
Figure created using data from Ramagopalan *et al.* [17]

in the prevention of cardiovascular events and deaths was associated to cost savings of around €30 million for the Spanish National Health System (SNHS) and €76 million for society [20]. In addition, a systematic review of cost–effectiveness analyses carried out by Pinyol *et al.*, reported that according to the evaluations conducted in different countries, apixaban is generally a cost-effective alternative in comparison to VKA. However, the economic evaluations mainly considered the efficacy results of clinical trials in patients with NVAF [21].

Despite these clinical and economic results, in Spain, VKA are used in first line, and the prescription of DOAC is restricted to NVAF patients with indication of anticoagulant treatment (and no counterindications for anticoagulant treatment), able to adhere to the medication and to have a regular follow-up, and within these patients, those: a) with known hypersensitivity or with specific contraindication to the use of acenocoumarol or warfarin; b) with a history of intracranial bleeding (except during acute phase) where anticoagulation benefits surpass hemorrhagic risk; c) with ischemic stroke and high risk of cerebral hemorrhage; d) treated with VKA but suffer thromboembolic events despite having a controlled normalized international ratio (NIR); e) treated with VKA and who have good compliance with the treatment but cannot reach a good NIR control or; f) unable to access standard NIR control, according to the Therapeutic Positioning Report from the Ministry of Health, Social Services and Equality of Spain [22]. Therefore, there is a need to estimate the cost–effectiveness value of apixaban versus VKA in clinical practice to improve the care of these patients. As a consequence, our study aims to compare the use of healthcare resources and costs associated with the management of patients with NVAF treated with apixaban versus VKA, based on the results provided by Ramagopalan *et al.* [17] in Spain.

Materials & methods

Study design

The methods followed in this study were already published [17]. This is an observational and retrospective study based on the electronic medical records (EMRs) from the BIG-PAC® [23] database. It gathers a population of 1.8 million patients [24] from seven public health areas (primary care centers and hospitals) in seven Spanish autonomous communities. EMRs are anonymized in the centers/hospitals of origin, in compliance with the Spanish Organic Law 3/2018 of December 5 on the Protection of Personal Data and guarantee of digital rights [25]. The BIG-PAC® database demonstrated its representativeness of the Spanish population in previous studies [23,26].

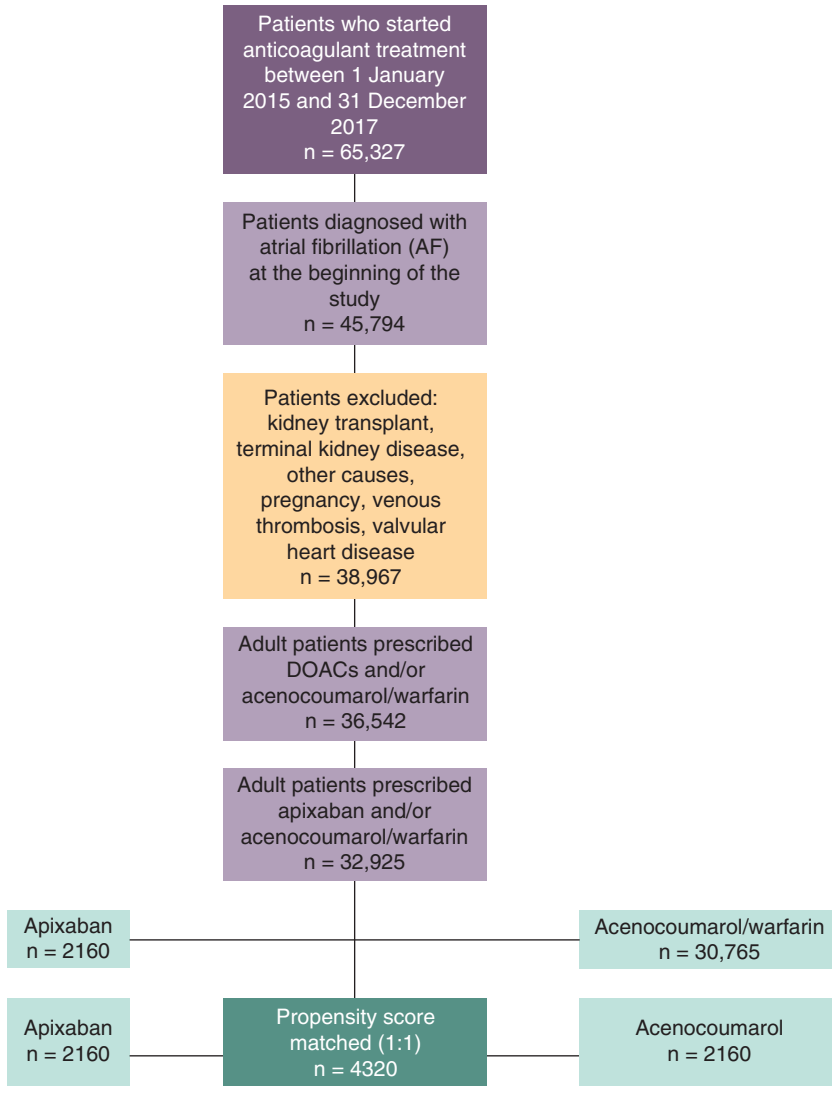

Figure 2. Patient flow diagram.

Study population

The study population was patients with AF (International Classification of Diseases, 10th edition, Clinical Modification [ICD-10-CM] code: I48.91), without mitral valve heart disease (ICD-10-CM codes: I05.x, I08.0, I08.8, I08.9, I34.0, I34.8, Q20.0–Q20.5, Q20.8, Q21.0–Q21.3, Q21.8, Q21.9, I27.83, Z95.2, Z95.3), receiving new anticoagulant treatment with apixaban or VKA between 1 January 2015 and 31 December 2017 (patient recruitment period). These patients are the same from Ramagopalan *et al.*, who compared the risk of stroke, systemic thromboembolism and bleeding after apixaban or acenocoumarol treatment after matching patients using propensity score matching [17]. Figure 1 shows the main findings of their study. The index date was defined as the date when patients started the new anticoagulant treatment for the treatment of NVAF during the recruitment period. Patients who initiated apixaban and who had had a previous switch with acenocoumarol were also included (or *vice versa*). The follow-up period covered from the index date until treatment interruption, the first event (hemorrhagic/ischemic stroke, thromboembolism, or major/minor bleeding), 12 months (end of study period), or death, whichever occurred first. This methodology is similar to that used in previous studies [17,18]. In Spain, the prescription of DOAC (e.g., apixaban) requires a specific authorization before starting the treatment. Patients were classified into two cohorts: apixaban and VKA.

Inclusion criteria were age ≥18 years, diagnosis of AF (ICD-10-CM code: I48.91) starting a new anticoagulant treatment between 1 January 2015 and 31 December 2017, patients in the database for ≥12 months before the

index date, inclusion in the chronic prescription program (≥2 prescriptions during the follow-up period), and regular patient monitoring (≥2 health records in the database). Exclusion criteria were patients diagnosed with AF (ICD-10-CM code: I48.91) with mitral valve heart disease (ICD-10-CM codes: I05.x, I08.0, I08.8, I08.9, I34.0, I34.8, Q20.0–Q20.5, Q20.8, Q21.0–Q21.3, Q21.8, Q21.9, I27.83, Z95.2, Z95.3), subjects transferred to other centers, displaced or out-of-area; residents of nursing homes, patients with a history of AF secondary to reversible causes (thyrotoxicosis, pericarditis), heart surgery, venous thromboembolism, hip or knee surgery in the 6 weeks before the index date, valvular heart disease and/or pregnancy, subjects with valvular AF (with mechanical heart valve or moderate-severe mitral stenosis) and end-stage kidney disease, dialysis or kidney transplantation.

Patients who initiated their treatment with VKA and switched to a DOAC other than apixaban during the follow-up period were excluded.

Variables

Demographic variables & comorbidities

The sociodemographic characteristics such as age (continuous and by range) and sex were recorded [17], along with the comorbidities of patients. As a summary variable of general comorbidity, the Charlson [27] comorbidity index were used as an approximation to severity (Supplementary Table 1). These variables and the CHA2DS2-VASc and HAS-BLED [28] (range: 0–8) scores were obtained at the index date (Supplementary Tables 2 & 3) [29].

Medication administered & treatment persistence/duration

The medication was collected from dispensing records. The prescription of medications was carried out at physicians' discretion. Medications were obtained using the Anatomical Therapeutic Chemical (ATC) classification system [30]: warfarin (code: B01AA03), acenocoumarol (code: B01AA07) and apixaban (code: B01AF02). The time from the diagnosis of NVAF to the first prescription and the dosages prescribed in the record of the first prescription were estimated. Treatment persistence/duration was calculated from the index date up to 1 year, or up to the development of a new event (hemorrhagic/ischemic strokes, bleedings), the switch to another anti-platelet/anticoagulant treatment other than that which motivated inclusion (in the succeeding 30 days), or interruption/discontinuation of medication (≥60 days without renewing the medication) or death, whichever occurs first. Treatment persistence was estimated at 6 and 12 months of follow-up. The date of interruption was 30 days from the date of the last prescription.

Effectiveness

The study considered episodes of ischemic stroke and systemic thromboembolism, and major and minor bleedings (genitourinary, and other minor bleedings). Major bleedings included intracranial, gastrointestinal, and other locations (liver, eye, spleen) requiring hospital admission, defined as acute or subacute manifest bleedings accompanied by ≥1 of the following criteria [31]: a) reduction in hemoglobin levels of ≥2 g/dl; b) transfusion of ≥2 red blood cell concentrates, and/or; c) fatal bleeding. These events were identified as early as 30 days after the initiation of anticoagulant medication (apixaban vs VKA) until the date of treatment discontinuation (described above; treatment period). Episodes were classified according to the ICD-10-CM coding system. The mortality rate was calculated using the number of deaths divided by the number of patients.

Use of healthcare resources, costs, & incremental cost–effectiveness ratio

The use of healthcare resources and costs were estimated during the follow-up period. Healthcare resources included medical visits (primary care, nursing, specialist care [neurology, vascular, cardiology, internal medicine, geriatrics, endocrinology, and hematology services], emergency medical visits), hospitalizations (number and percentage of hospitalized patients, annual rates of hospitalization and length of stay), diagnostic/therapeutic tests (laboratory tests, radiology, computed tomography, nuclear magnetic resonance, catheterization, angioplasty, endarterectomy/thrombectomy, echocardiogram and Doppler echocardiography) and cardiovascular medication.

Costs were estimated based on the use of healthcare resources and the unit costs (Supplementary Table 4). Medical prescriptions were quantified according to the retail price per pack at the time of prescription. Indirect costs were estimated according to the productivity loss (non-healthcare costs), the number of days of work disability and the mean salary for the Spanish population, estimated by the National Institute of Statistics (INE) [32]. The study did not include direct non-health costs, i.e., out of pocket costs or those paid for by the patient/family, as they are not registered in the database. Costs were expressed as average annual cost per patient in euros (2021).

The incremental cost–effectiveness ratio (ICER) per ischemic stroke/thromboembolism avoided and per surviving patient was estimated as $(C_1-C_0)/(E_1-E_0)$, being C_1 the cost in the intervention group (DOAC), C_0 the cost in the control group (VKA), E_1 the effectiveness in the intervention group (DOAC) and E_0 the effectiveness in the control group (VKA). Costs were those estimated according to the social perspective. The survival rate (defined as the time between the index date and the patient's death, which is notified by the general practitioner in the EMR) was also estimated.

Statistical analysis

The search criteria in the database were based on computer statements (SQL script). Data were reviewed, looking for possible coding or recording errors. Data were validated to ensure the quality of the results.

Descriptive-univariate statistical analyses were carried out to describe the variables in each group. Qualitative variables were described using absolute and relative frequencies (n, %), while means and standard deviations (SDs) were used for quantitative variables with symmetric distributions and medians and interquartile ranges (IQR; P25-P75) were used for those with asymmetric distributions. In addition, 95% confidence interval (CI) were estimated for population parameters.

Propensity score matching (PSM) was used to maximize the comparability of study cohorts. Each case in cohort 1 (apixaban) was matched with one patient in cohort 2 (VKA) (1:1). The procedure was the greedy nearest neighbor algorithm, with substitution and accepting a tolerance of 0.20 (caliper width). Priority was given to exact matches randomly. Group homogeneity was assessed using a logistic regression model. Once PSM was carried out, standardized coefficients (standardized differences) were provided in subsequent comparisons. The variables (estimators; covariates) included were age, sex, Charlson comorbidity index [27], CHA2DS2-VASc scores and HAS-BLED scores [28].

Bivariate analyses were conducted (ANOVA and Chi-square tests) to compare the demographic variables, comorbidities and medication in the groups of the study. In addition, these tests were used to compare the incidence rates of thromboembolic and bleeding events between both study groups. A covariance analysis (ANCOVA; generalized linear model; estimate of marginal means; Bonferroni adjustment) was used to correct costs. Covariates were age, sex, Charlson comorbidity index [27] and CHA2DS2-VASc and HAS-BLED score [28]. The 95% CI were calculated by non-parametric resampling (1000 bootstrap iterations).

The treatment persistence/duration was analyzed using a Kaplan–Meier survival analysis (procedure: log-rank test). Cox proportional risk regression was used to determine the treatment persistence and events during follow-up (hazard ratio [HR]; censored data). Percentage results were obtained, equivalent to one per 100 persons-year (incidence rate; accumulated risk). Data were censored in case of absence of the event.

The SPSSWIN version 27 statistical program was used, and values of two-sided $p < 0.05$ were considered statistically significant.

Ethics approval & consent to participate

This study was approved by the Ethics Committee of the Hospital of Terrassa (Barcelona) (code: 02-21-399-094) on 27 September 2021. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement guidelines for reporting observational studies were followed. The individual consent was not necessary, according to Article 5 of Royal Decree 957/2020, of November 3rd, which regulates observational studies with medicines for human use [33].

Results

Study population

The study estimated that 36,542 patients with NVAF started an anticoagulation treatment (DOAC or VKA) between 1 January 2015 and 31 December 2017. Most of them (n = 32,925) were treated with apixaban and/or acenocoumarol/warfarin and were divided into those treated with acenocoumarol/warfarin (n = 30,765) and those who received apixaban (n = 2160). PSM paired 2160 patients in the apixaban group with 2160 patients treated with acenocoumarol (Figure 2). The characteristics of the population before carrying out the PSM can be seen in Supplementary Table 1.

No differences were observed in sociodemographic characteristics, comorbidities and Charlson comorbidity index of patients treated with apixaban or acenocoumarol, highlighting the high degree of comparability between both groups after the PSM (Table 1).

Table 1. Baseline characteristics after propensity score matching.

Study groups PSM Patients	Apixaban (n = 2160)	Acenocoumarol (n = 2160)	p-value	Standardized difference
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
Sex (male)	47.6%	47.8%	0.903	-0.003
Associated comorbidities				
Arterial hypertension	70.9%	71.1%	0.893	-0.021
Mellitus diabetes	31.7%	30.6%	0.430	0.012
Dyslipidaemia	45.0%	45.6%	0.714	-0.006
Ischemic heart disease	23.0%	22.2%	0.561	0.009
Heart failure	20.2%	19.8%	0.761	0.004
COPD	15.0%	15.2%	0.865	-0.023
Cerebrovascular accident	14.8%	15.2%	0.733	-0.005
Previous bleeding	14.6%	14.5%	0.887	0.058
Renal failure	10.9%	10.7%	0.845	0.013
Anemia	10.3%	9.7%	0.222	0.022
Scales				
Charlson comorbidity index (SD)	2.5 (2.0)	2.6 (1.9)	0.758	0.016
CHA_2-DS_2-VASc (SD)	3.3 (1.9)	3.4 (1.7)	0.009	-0.015
HAS-BLED (SD)	2 (1.3)	2.1 (1.1)	<0.001	-0.017

Values expressed as a percentage or mean (SD).
COPD: Chronic obstructive pulmonary disease; p: Statistical significance; PSM: Propensity score matching; SD: Standard deviation.

Effectiveness

Mortality rate was lower in patients who received apixaban (3.7%) in comparison to those treated with acenocoumarol (8.3%, $p < 0.001$) (Table 2).

Duration & persistence to treatments

The time from diagnosis was similar in both groups ($p = 0.611$), but the treatment lasted longer in patients on treatment with apixaban in comparison to those treated with acenocoumarol (300 days vs 266.4 days, $p < 0.001$). Therefore, the persistence to treatment was higher in patients treated with apixaban (79.8% and 71.1% at 6 and 12 months, respectively), in comparison to patients on treatment with acenocoumarol (70.4% and 60.6% at 6 and 12 months, respectively).

Use of resources

Apixaban patients required a lower use of healthcare resources compared with those needed by the acenocoumarol group. The highest differences between both groups were reported in the number of nursing visits (14.7 [SD: 9.8] vs 3 [SD: 2.3], respectively; $p < 0.001$), and primary care visits (10.9 [SD: 7.0] vs 6.3 [SD: 4.3], respectively; $p < 0.001$). Patients on treatment with apixaban had fewer specialist visits in comparison to acenocoumarol patients ($p < 0.001$), mostly to cardiologists and neurologists (Table 3).

It was observed that 6.6% of patients treated with apixaban were hospitalized during the follow-up period, with an average length of hospital stay of 0.6 days (SD: 2.5), whereas in patients with acenocoumarol, these results were 10.8% and 1.37 days (SD: 4.2) (Table 3).

In general, patients treated with apixaban required fewer clinical tests and procedures during the follow-up period. The healthcare resources most frequently used were laboratory tests (apixaban: 2.2 [SD: 1.6] and acenocoumarol: 3.2 [SD: 2.3]), followed by other tests (apixaban: 1.2 [SD: 1.0] and acenocoumarol: 2.4 [SD: 1.7]), which included echocardiogram and Doppler echocardiography. However, there were no differences in the use of catheterization ($p = 0.154$) and angioplasty ($p = 0.709$) (Table 3).

Table 2. Duration and persistence of treatments per study group after propensity score matching.

Study groups PSM Patients	Apixaban (n = 2160)	Acenocoumarol (n = 2160)	p-value
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)	
Treatment duration, days			
Mean (SD)	300.3 (104.0)	266.4 (121.1)	<0.001
Median (P25–P75)	330 (216–365)	304 (136–365)	
Previous use of antithrombotic medication			
Acenocoumarol initial	28.2%	100.0%	0.001
Apixaban	71.8%	0.0%	0.001
Not treatment persistence 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
12 months	71.1%	60.6%‡	<0.001
Mortality	3.7%	8.3%	<0.001

Values expressed as a percentage or mean (SD).
†HR: 1.2 (95% CI: 1.0–1.3) p = 0.006.
‡HR: 1.3 (95% CI: 1.1–1.4) p = 0.012.
CI: Confidence interval; COPD: Chronic obstructive pulmonary disease; HR: Hazard ratio; DOAC: Non-vitamin K antagonist oral anticoagulants; p: statistical significance; P: Percentile; PSM: Propensity score matching; SD: Standard deviation.

Productivity losses were lower in the apixaban group, in comparison to the acenocoumarol group. It was estimated that 12.4% of patients in the former group required sick leave (average: 1.7 days [SD: 4.7]), whereas 15.6% of patients in the acenocoumarol group had to take days off work because of their disease (2.5 days [SD: 6.3]) (Table 3).

Costs

Annual healthcare costs were lower in apixaban patients, in comparison to those treated with acenocoumarol. The highest annual costs were associated to hospitalizations (apixaban: €293 [SD: 1196] vs acenocoumarol: €658 [SD: 2036]; $p < 0.001$), followed by nursing visits (apixaban: €60 [SD: 45] vs acenocoumarol: €294 [SD: 195]; $p < 0.001$) and specialist visits (apixaban: €193 [SD: 175] vs acenocoumarol: €257 [SD: 185]; $p < 0.001$). Apixaban showed reductions of 80%, 55% and 43% in the annual costs related to nursing visits, hospitalizations and emergency visits, respectively (Table 4).

In general, apixaban patients had lower annual costs in most of clinical tests and procedures, mainly in endarterectomy (apixaban: €2 [SD: 29] vs acenocoumarol: €99 [SD: 195]; $p < 0.001$) and nuclear magnetic resonance (apixaban: €60 [SD: 84] vs acenocoumarol: €148 [SD: 136]; $p < 0.001$). The deepest reductions in annual healthcare costs were recorded in the costs associated to endarterectomy (97%), computed tomography (68%) and nuclear magnetic resonance (59%). However, there were no differences in the costs associated to catheterization ($p = 0.154$) and angioplasty ($p = 0.709$) (Table 4).

The annual cost associated with medicines in patients with apixaban was €899 (SD: 327), whereas in patients treated with acenocoumarol, it amounted to €42 ($p < 0.001$) (Table 4) (Figure 3).

After the adjustments, the annual total healthcare cost amounted to €2046 (95% CI: 1986–2107) in patients with apixaban, whereas it was €2224 (95% CI: 2128–2315) in patients with acenocoumarol ($p = 0.001$). Non-healthcare costs also were lower in patients on apixaban in comparison to those who received acenocoumarol (€162 [95% CI: 145–181] vs €259 [95% CI: 234–286], $p < 0.001$). The annual total costs were lower in patients treated with apixaban versus the acenocoumarol group (€2208 [95% CI: 2146–2271] vs €2482 [95% CI: 2380–2584],

Table 3. Resource consumption per study group after propensity score matching.

Study groups PSM Patients	Apixaban (n = 2160)	Acenocoumarol (n = 2160)	p-value
Healthcare resources			
Visits			
Primary care visits	6.3 (4.3)	10.9 (7)	<0.001
Nursing visits	3 (2.3)	14.7 (9.8)	<0.001
Specialist visit	2.1 (1.9)	2.8 (2)	<0.001
Cardiology	0.4 (0.6)	0.5 (0.6)	<0.001
Intern medicine	0.3 (0.5)	0.4 (0.5)	0.009
Endocrinology	0.3 (0.5)	0.4 (0.5)	0.003
Vascular	0.3 (0.5)	0.4 (0.5)	<0.001
Neurology	0.4 (0.6)	0.5 (0.6)	<0.001
Hematology	0 (0.1)	0.4 (0.5)	<0.001
Geriatrics	0.3 (0.5)	0.4 (0.5)	0.023
Emergency visits	0.2 (0.4)	0.3 (0.5)	<0.001
Hospitalizations			
Hospitalizations (%)	6.6%	10.8%	<0.001
Days, mean (SD)	0.6 (2.5)	1.37 (4.2)	<0.001
Clinical tests and procedures			
Laboratory tests	2.2 (1.6)	3.2 (2.3)	<0.001
Radiology	0.8 (0.8)	1 (0.8)	<0.001
Computerized tomography	0.3 (0.5)	1 (0.8)	<0.001
Nuclear magnetic resonance	0.3 (0.5)	0.8 (0.8)	<0.001
Other tests†	1.2 (1)	2.4 (1.7)	<0.001
Catheterization	0.2 (0.4)	0.2 (0.4)	0.154
Angioplasty	0.2 (0.4)	0.2 (0.4)	0.709
Endarterectomy	0 (0.1)	0.2 (0.4)	<0.001
Indirect resources			
Temporary labor loss			<0.001
Labor loss (%)	12.4%	15.6%	
Days, mean (SD)	1.7 (4.7)	2.5 (6.3)	

Values expressed as a percentage or mean (SD).
†Includes echocardiogram and Doppler echocardiography.
p: Statistical significance; PSM: Propensity score matching; SD: Standard deviation.

$p < 0.001$). Therefore, the use of apixaban led to annual cost savings of €274 (95% CI: €157–€387) from the perspective of the society (Table 4) (Figure 4).

Incremental cost–effectiveness ratios

Based on the effectiveness and costs results, the ICER of apixaban versus acenocoumarol was estimated. Apixaban patients showed a reduction in the incidence of stroke and systemic embolism events, and minor and major bleedings in comparison to acenocoumarol patients. Therefore, for every 27 patients treated with apixaban, 1 minor bleeding would be avoided in patients treated with acenocoumarol, for every 46 patients treated with apixaban, 1 major bleeding would be avoided in patients treated with acenocoumarol, and for every 59 patients treated with apixaban, 1 stroke or systemic embolism would be avoided in patients treated with acenocoumarol (Table 5). In addition, it was observed that the survival rate in patients treated with apixaban was 55.4%, higher than that of acenocoumarol-treated patients during the follow-up period (Table 6).

In addition, apixaban patients required fewer healthcare resources than patients treated with acenocoumarol, leading to lower management and non-healthcare costs from the perspective of society. Therefore, it is considered that apixaban is a dominant alternative from the perspective of the SNHS and society (Tables 5 & 6).

Table 4. Annual cost (€, 2021) per patient by study group after propensity score matching.

Study groups, PSM Patients	Apixaban (n = 2160)	Acenocoumarol (n = 2160)	p-value	
Healthcare cost				
Visits				
Primary care visits	146 (99)	252 (163)	<0.001	
Nursing visits	60 (45)	294 (195)	<0.001	
Specialist visit	193 (175)	257 (185)	<0.001	
Emergency visits	21 (48)	37 (63)	<0.001	
Hospitalizations	293 (1196)	658 (2036)	<0.001	
Clinical tests and procedures				
Laboratory tests	48 (35)	70 (51)	<0.001	
Radiology	15 (14)	18 (15)	<0.001	
Computerized tomography	31 (45)	97 (80)	<0.001	
Nuclear magnetic resonance	60 (84)	148 (136)	<0.001	
Other tests[†]	43 (37)	89 (65)	<0.001	
Catheterization	96 (192)	104 (198)	0.154	
Angioplasty	100 (195)	102 (197)	0.709	
Endarterectomy	2 (29)	99 (194)	<0.001	
Medicines				
Cardiovascular medicines cost	899 (327)	42 (20)	<0.001	
Healthcare cost	2008 (1490)	2268 (2251)	<0.001	
Non-healthcare cost	169 (478)	252 (641)	<0.001	
Total cost	2177 (1488)	2520 (2268)	<0.001	
Cost correction[‡]	**Apixaban**	**Acenocoumarol**	**Difference**	**p**
Healthcare cost	2046	2224	-178	0.001
95% CI	(1986–2107)	(2128–2315)	(-282–[-73])	
Non-healthcare cost	162	259	-97	<0.001
95% CI	(145–181)	(234–286)	(-126–[-67])	
Total cost	2208	2482	-274	<0.001
95% CI	(2146–2271)	(2380–2584)	(-387–[-157])	

Values expressed as a percentage or mean (SD).
[†]Includes echocardiogram and Doppler echocardiography.
[‡]Covariates: age, sex, time from diagnosis and Charlson comorbidity index.
CI: Confidence interval; p: Statistical significance; PSM: Propensity score matching; SD: Standard deviation.

Table 5. Results of the CEA per event avoided.

Event type	Study group	Total cost[†]	Percentage of patients with event	Effect.[‡]	Incremental cost	Incremental effect.	NNT[§]	ICER	Total cost/ event avoided[¶]
Stroke and systemic embolism	Api.	€2208	0.02	0.98					€2253
	Acen.	€2482	0.037	0.963	-€274	0.017	59	- €16,118	€2577
Minor bleeding	Api.	€2208	0.072	0.928					€2379
	Acen.	€2482	0.109	0.891	-€274	0.037	27	- €7,405	€2786
Major bleeding	Api.	€2208	0.024	0.976					€2262
	Acen.	€2482	0.046	0.954	-€274	0.022	46	- €12,455	€2602

[†]Total corrected cost including healthcare and non-healthcare costs.
[‡]Estimated as the percentage of patients without events.
[§]Estimated as the number of patients needed to treat to prevent one additional event.
[¶]Estimated as the total cost divided by the effectiveness.
Acen: Acenocoumarol; Api: Apixaban; CEA: Cost–effectiveness analysis; ICER: Incremental cost–effectiveness ratio; NNT: Number of patients needed to treat.

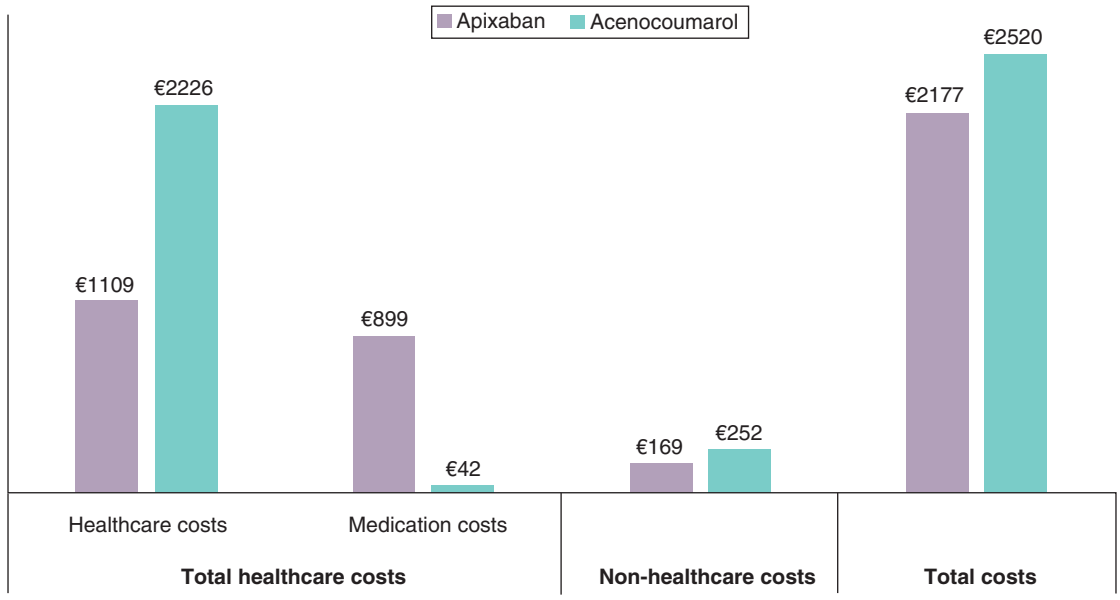

Figure 3. Cost per patient year by type of cost.

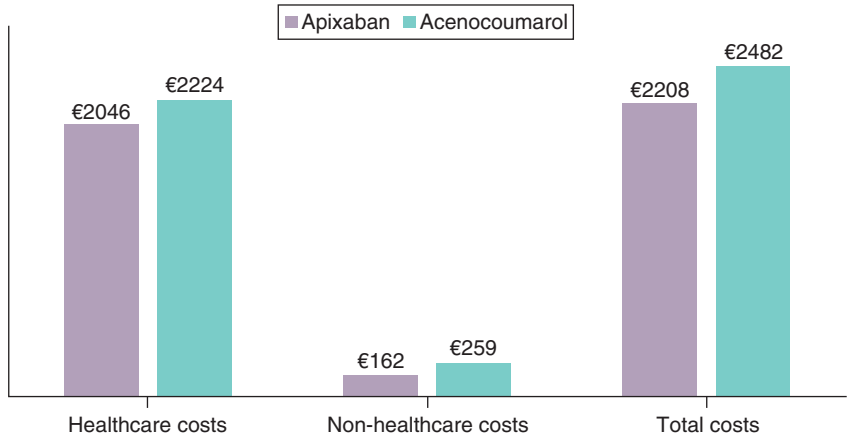

Figure 4. Corrected cost per study group.

Table 6. Results of the CEA per surviving patient.

Study group	Total cost†	Mortality rate	Effectiveness (survival rate)	Incremental cost	Incremental effectiveness	ICER	Total cost per surviving patient‡
Apixaban	€2208	0.037	0.963	–	–	–	€2293
Acenocoumarol	€2482	0.083	0.917	-€274	0.046	-€5957	€2707

†Total corrected cost including healthcare and non-healthcare costs.
‡Estimated as the total cost divided by the effectiveness.
CEA: Cost–effectiveness analysis; ICER: Incremental cost–effectiveness ratio.

Discussion

Our results showed that apixaban reduced the use of healthcare resources, particularly nursing and specialist visits for treatment follow-up, and hospitalizations. In addition, apixaban reduced healthcare costs and productivity loses, leading to annual costs savings of €274 (95% CI: 157–387) per patient with NVAF, in comparison to acenocoumarol. Lastly, the mortality rate in apixaban-treated patients was more than half-fold change lower than that of patients who had been administered acenocoumarol. Ramagopalan *et al.*, whose results served as a basis for

our study, had already observed the benefit of apixaban versus VKA on clinical outcomes (bleedings, stroke and systemic thromboembolisms risk) in patients with NVAF. Apixaban reduced the incidence of strokes and systemic embolisms and minor and major bleedings (Figure 1) ($p \leq 0.001$ in all comparisons) [17], and it is thus a dominant alternative for the SNHS and society in Spain.

The cost–effectiveness of apixaban over acenocoumarol in our country was previously estimated by Barón *et al.* They adapted a simulation model from the UK to the Spanish perspective and showed that the administration of apixaban would avoid 18 strokes, 71 bleeding events, 2 acute myocardial infarctions, 1 systemic embolism and 23 cardiovascular deaths during the lifetime of a cohort of 1000 patients with NVAF. They estimated that apixaban would improve the survival and the quality of life of patients in comparison to acenocoumarol, and the costs per life year gained would be €13,305, whereas the cost per quality-adjusted life year would be €9,765, from the perspectives of the SNHS and society, respectively [34]. Baron *et al.* used a simulation (Markov model) to perform their cost–effectiveness analysis, and patient data was obtained from a randomized trial comparing apixaban versus warfarin, therefore assuming that warfarin and acenocoumarol were therapeutically equivalent. We used real-life data from a bigger group of patients (2160 patients) who started treatment with apixaban or acenocoumarol between 2015 and 2017. Our results are in line with their study, suggesting that apixaban had better clinical results than acenocoumarol, leading to a reduction in the costs of disease management in these patients. Variations with Baron *et al.* are due to differences in the calculation of healthcare and productivity costs, as they considered higher unit costs and various severity grades of stroke. In addition, the use of healthcare resources was collected from clinical trials and registries from other countries. On the other hand, Escobar *et al.* developed a prevalence-based Markov model to estimate the clinical and economic impact associated to an increase in the use of DOAC versus VKA in patients with NVAF in Spain. They considered efficacy, safety, and mortality data from real-life studies and in line with our results, they showed that the use of apixaban reduced healthcare costs from the perspective of the SNHS [35].

To our knowledge, this is the first study that estimates the cost–effectiveness of apixaban versus acenocoumarol in Spanish patients with NVAF, based on data from medical practice. Nevertheless, the protocol of a study based on observational data from patients with NVAF treated with DOAC or VKA in the primary care service of the Institut Català de la Salut was recently published [36]. This study will estimate the cost–effectiveness of DOAC versus VKA from the SNHS and societal perspectives, in a regional setting. However, our results are based on the BIG-PAC® database, which records data from the overall Spanish population. Our results might be of interest to decision makers, as they complement other economic evaluations of apixaban versus acetylsalicylic acid [37], and other studies that recommend the use of DOAC over acenocoumarol and warfarin [20,38,39]. Therefore, the restrictions in the use of apixaban in Spain might be limited, improving the management of patients with NVAF.

Our study also has some limitations. First, since BIG-PAC® is an administrative database, its use in observational studies may have deficiencies, such as missing data of the study population, particularly of those who received medical care in public or private centers outside of its area of influence. Second, there may be limitations on the categorization of the NVAF, as the ICD-10-CM coding system did not allow to differentiate by type of AF (permanent, persistent and/or paroxysmal). Third, although the groups of the study were compared after carrying out a PSM, other factors not considered in this statistical procedure, such as the medication used, may have influenced the results. Fourth, we could not obtain data on the degree of control of anticoagulation in patients on acenocoumarol (time in therapeutic range), which is relevant to estimate the benefits and risks of these drugs. Fifth, primary care and nursing visits might be associated to the results of the same NIR test in the same patient, leading to an increase in the costs associated to these resources. Other limitations are those associated to the possible patient classification and prescription bias since the medication is not randomly prescribed in real-life studies.

Conclusion

Our results suggested that apixaban improves the health status of patients with NVAF, leading to a reduction in the use of healthcare resources and costs. Therefore, apixaban is cost-effective in comparison to acenocoumarol in a real-life setting in Spain. These results are considered of interest to improve clinical outcomes and quality of life for patients, while reducing the economic burden of NVAF for the SNHS and society.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: https://bpl-prod.literatumonline.com/doi/10.57264/cer-2023-0007

Author contributions

The study was conceived by A Sicras Mainar, D Vilanova Larena, A Sicras Mainar, D Vilanova Larena, J Comín Colet and O Delgado Sánchez participated and contributed to the study design. Data collection and the statistical analyses were made by A Sicras Mainar. All authors interpreted the results, and critically reviewed and approved the final version of the manuscript.

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This study was funded by Pfizer and Bristol Myers Squibb. A Sicras Mainar is an employee of Atrys Health SA, who was paid consultant to BMS in connection with this manuscript. D Vilanova Larena, J Salazar-Mendiguchía, MI del Campo Alonso and A Echeto are employees of Bristol Myers Squibb and have BMS stocks. J Comín Colet and O Delgado Sánchez declare to have received fees as coordinator investigators of this study by Bristol Myers Squibb. 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.

Ethical conduct of research

This study was approved by the Ethics Committee of the Hospital of Terrassa, Barcelona, (no. 02-21-399-094) on 27 September 2021. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement guidelines for reporting observational studies were followed. Individual consent was not necessary, according to Article 5 of Royal Decree 957/2020, of November 3rd, which regulates observational studies with medicines for human use.

Data sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Summary points

- Apixaban reduced the incidence of strokes and systemic embolisms and minor and major bleedings, in comparison with acenocoumarol.
- Patients treated with apixaban had a lower mortality rate than those on treatment with acenocoumarol.
- After 6 and 12 months, patients treated with apixaban had higher persistence rates that those on treatment with acenocoumarol.
- Patients on treatment with apixaban required fewer healthcare resources compared with those needed by the acenocoumarol, particularly nursing, primary care, and specialist visits.
- Hospital admissions were less frequent and shorter in the apixaban group than in the acenocoumarol group.
- Apixaban patients required fewer healthcare resources than patients treated with acenocoumarol, leading to lower management and non-healthcare costs from the perspective of society.
- Apixaban reduced healthcare costs and productivity loses, leading to annual costs savings of €274 (95% CI: 157–387) per patient with NVAF, in comparison to acenocoumarol.
- Due to the improvements in the clinical outcomes, and the reduction in healthcare and non-healthcare costs, apixaban is considered a dominant alternative versus acenocoumarol, from the perspective of the Spanish National Health System and society.

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