

Original article

Cost-effectiveness Analysis Comparing Apixaban and Acenocoumarol in the Prevention of Stroke in Patients With Nonvalvular Atrial Fibrillation in Spain



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ABSTRACT

Introduction and objectives: Cost-effectiveness analysis of apixaban (5 mg twice daily) vs acenocoumarol (5 mg/day) in the prevention of stroke in patients with nonvalvular atrial fibrillation in Spain.

Methods: Markov model covering the patient's entire lifespan with 10 health states. Data on the efficacy and safety of the drugs were provided by the ARISTOTLE trial. Warfarin and acenocoumarol were assumed to have therapeutic equivalence. Perspectives: The Spanish National Health System and society. Information on the cost of the drugs, complications, and the management of the disease was obtained from Spanish sources.

Results: In a cohort of 1000 patients with nonvalvular atrial fibrillation, administration of apixaban rather than acenocoumarol would avoid 18 strokes, 71 hemorrhages (28 intracranial or major), 2 myocardial infarctions, 1 systemic embolism, and 23 related deaths. Apixaban would prolong life (by 0.187 years) and result in more quality-adjusted life years (by 0.194 years) per patient. With apixaban, the incremental costs for the Spanish National Health System and for society would be € 2488 and € 1826 per patient, respectively. Consequently, the costs per life year gained would be € 13 305 and € 9765 and the costs per quality-adjusted life year gained would be € 12 825 and € 9412 for the Spanish National Health System and for society, respectively. The stability of the baseline case was confirmed by sensitivity analyses.

Conclusions: According to this analysis, apixaban may be cost-effective in the prevention of stroke in patients with nonvalvular atrial fibrillation compared with acenocoumarol.

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Análisis coste-efectividad de apixabán frente a acenocoumarol en la prevención del ictus en pacientes con fibrilación auricular no valvular en España

RESUMEN

Introducción y objetivos: Análisis de coste-efectividad de apixabán (5 mg dos veces al día) frente a acenocoumarol (5 mg/día) en la prevención del ictus en pacientes con fibrilación auricular no valvular en España.

Métodos: Modelo de Markov durante toda la vida del paciente con 10 estados de salud. Los datos de eficacia y seguridad de los fármacos proceden del ensayo clínico ARISTOTLE. Se asumió la equivalencia terapéutica de warfarina y acenocoumarol. Perspectivas: Sistema Nacional de Salud y la sociedad. El coste de los medicamentos, las complicaciones y el manejo de la enfermedad se obtuvieron de fuentes españolas.

Resultados: En una cohorte de 1.000 pacientes con fibrilación auricular no valvular, con apixabán se evitarían frente a acenocoumarol: 18 ictus, 71 hemorragias (28 intracraneales o mayores), 2 infartos de miocardio, 1 embolia sistémica y 23 muertes relacionadas. Con apixabán se obtendrían más años de vida (0,187) y más años de vida ajustados por calidad (0,194) por paciente. Los costes incrementales con apixabán para el Sistema Nacional de Salud y la sociedad serían de 2.488 y 1.826 euros por paciente. En

Palabras clave:

Apixabán

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consecuencia, se obtendría unos costes por año de vida ganado de 13.305 y 9.765 euros, y unos costes por año de vida ajustado por calidad ganado de 12.825 y 9.412 euros para el Sistema Nacional de Salud y la sociedad respectivamente. Los análisis de sensibilidad confirmaron la estabilidad del caso base.

Conclusiones: Según este análisis, apixabán puede ser coste-efectivo en la prevención del ictus en pacientes con fibrilación auricular no valvular frente a acenocumarol.

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Abbreviations

AF: atrial fibrillation
 NVAf: nonvalvular atrial fibrillation
 QALY: quality-adjusted life years
 TTR: time in therapeutic range
 VKA: vitamin K antagonists

INTRODUCTION

Atrial fibrillation (AF) is a cardiac arrhythmia associated with aging, hypertension, valve diseases, and other heart diseases.¹ Nonvalvular AF (NVAf) refers to those cases with a change in rhythm in the absence of rheumatic mitral valve disease, artificial heart valve, or mitral valve repair. Atrial fibrillation is associated with a higher risk of death (twice that of patients without AF), cerebrovascular disease (5-fold higher), and systemic embolism.¹

The prevalence of AF is estimated to be 2% in the general Spanish population,¹ 4.4% in the population aged ≥ 40 years,² and up to 10.9% and 11.1% in individuals older than 60 years and 79 years, respectively.^{3,4}

The average annual cost of a patient with AF in Spain is estimated to be € 2365; of this sum, € 1008 would correspond to hospital stays, € 723 to surgical interventions, and € 247 lost productivity at work.⁵ The cost of cardioembolic stroke during the first 38 days after onset has been estimated to be € 13 353.⁶ The direct nonhealth care costs of stroke, corresponding to informal care of patients with sequels, are calculated to range, depending on severity, from € 252 to € 1031 during the acute phase (2 weeks) and from € 1367 to € 1942 a month during subsequent patient follow-up.⁷

Vitamin K antagonists (VKA) (acenocoumarol and warfarin) are currently the standard treatment for stroke prevention in patients with AF.⁸ It is estimated that 84% of the AF patients⁹ in Spain are taking oral anticoagulation therapy, and that 66% are being treated with VKA as monotherapy.¹⁰ However, the use of VKA is limited by the risk of bleeding, its narrow therapeutic margin, and the inconvenience to the patient due to the need for monitoring and drug-drug and food-drug interactions. When VKA doses are adjusted, these agents reduce the risk of stroke by 64% vs placebo but they also double the risk of the development of additional and intracranial hemorrhages.¹¹ In Spain, the most widely used agent for oral anticoagulant therapy is acenocoumarol, whereas warfarin is administered in Anglo-Saxon countries.¹² According to the available data, the effectiveness of the 2 drugs is assumed to be similar in clinical practice.^{12,13}

According to the recommendations of the European Society of Cardiology,¹⁴ direct oral anticoagulants, such as apixaban, are preferable to VKA for the treatment of most cases of NVAf, since they are not inferior in terms of efficacy and reduce the number of intracranial hemorrhages.

Apixaban is a new drug for oral administration that exerts a potent, direct and highly selective inhibition of factor Xa to reduce the conversion of prothrombin to thrombin.¹⁵ A randomized, double-blind trial¹⁶ compared apixaban and warfarin in 18 201 patients with NVAf. The results of that study indicate that apixaban (5 mg twice daily) was significantly superior to warfarin in the prevention of stroke and systemic embolism, produced fewer episodes of major bleeding, and reduced death from any cause.¹⁶

The differences observed between apixaban and acenocoumarol/warfarin may have a health care-related and economic impact. Consequently, we carried out a cost-effectiveness analysis of stroke prevention with apixaban or acenocoumarol in patients with NVAf.

METHODS

Study Design

A cost-effectiveness analysis¹⁷ was carried out by adapting the economic model proposed by Dorian et al¹⁸ to the Spanish health care setting. This model covers the life-long course (with a life expectancy of 80.4 years for both sexes) of a cohort of 1000 patients with NVAf^{18,19} whose characteristics were those of the patients in the ARISTOTLE trial.¹⁶ It is a Markov model (Figures 1 and 2), with 6-week cycles and 10 major health states. The entire patient cohort was in a state of NVAf and, after each cycle, they remained in NVAf or passed to other states, in accordance with certain transition probabilities.

Effectiveness Data

These probabilities of transition from one health state to another (stroke, systemic embolism, bleeding, death) for the drugs under comparison were obtained from the ARISTOTLE clinical trial¹⁶ and from other sources when necessary.^{20–27} According to the model, each patient can experience only 1 complication per cycle and only 1 recurrence of stroke (ischemic or hemorrhagic) is permitted. The simulation of avoided episodes was modeled throughout the patient's lifespan, based on the intention-to-treat analysis in the ARISTOTLE trial. Table 1 shows the rate of complications/100 person-years and the hazard ratio of these complications with acenocoumarol vs apixaban, adjusted according to the CHADS₂ (congestive heart failure, hypertension, age, diabetes, stroke [doubled]) score, and the international normalized ratio (INR) quality control index according to the time in therapeutic range (TTR).

Overall mortality in women and men older and younger than 75 years was obtained by adjusting published Spanish mortality data¹⁹ to a Gompertz function, for the purpose of predicting all-cause mortality and excluding that due to stroke and hemorrhage in order to avoid counting them twice. Treatment with acetylsalicylic acid was considered after interruption of previous

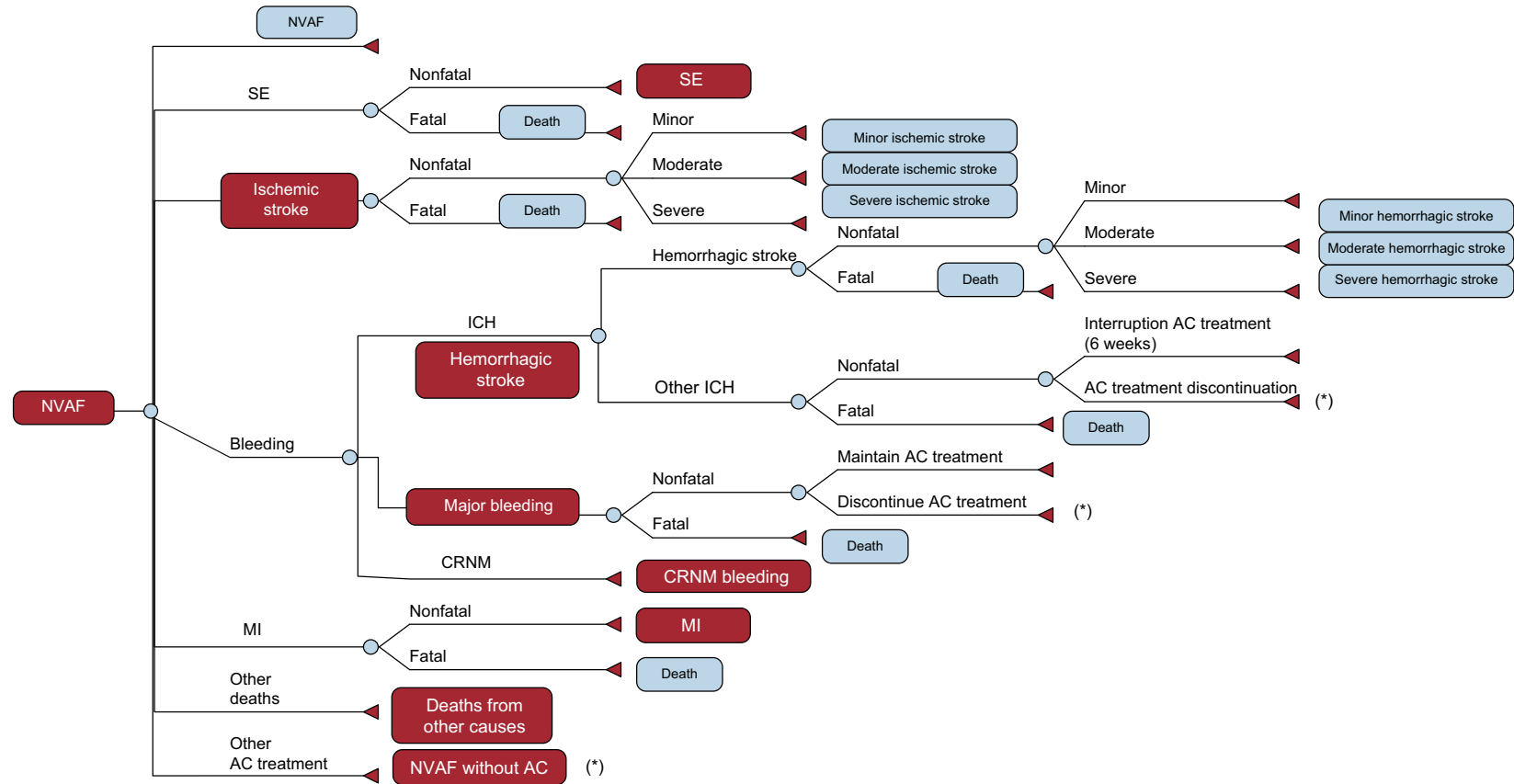


Figure 1. Markov economic model of stroke prevention in patients with nonvalvular atrial fibrillation. Course of a patient with nonvalvular atrial fibrillation. Patients who progress to the state of nonvalvular atrial fibrillation without anticoagulant, return to nonvalvular atrial fibrillation. Patients who progress to states of myocardial infarction or systemic embolism can die a posteriori as a consequence of these complications. AC, anticoagulant; CRNM, clinically relevant nonmajor; ICH, intracranial hemorrhage; MI, myocardial infarction; NVAf, nonvalvular atrial fibrillation; SE, systemic embolism. *Change of treatment to acetylsalicylic acid.

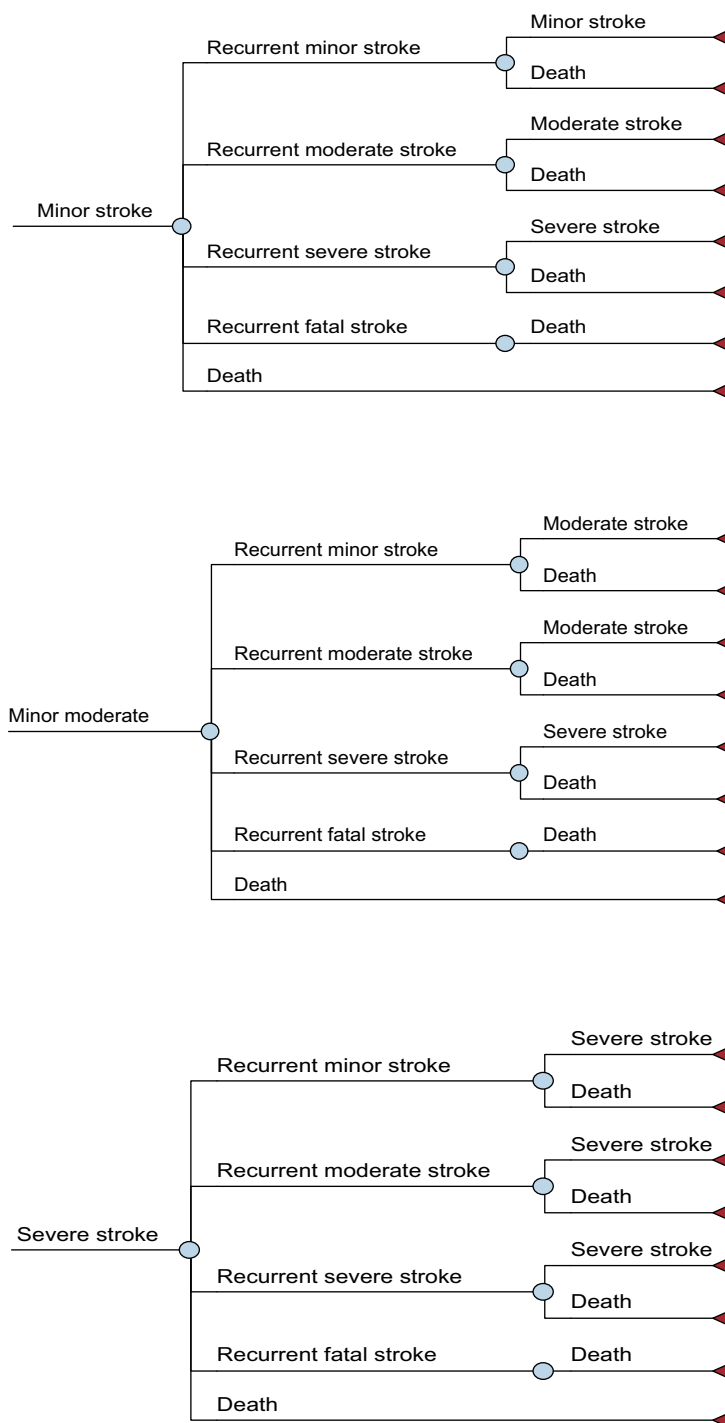


Figure 2. Markov economic model of stroke prevention in patients with nonvalvular atrial fibrillation. Course of a patient who has had a stroke (ischemic or hemorrhagic).

anticoagulation therapy (acenocoumarol or apixaban) due to major bleeding or other causes.²²

For example, with respect to the method of extrapolating the results for acute myocardial infarction from the ARISTOTLE clinical trial¹⁶ to the patient's entire lifespan, calculations were based on the risks of having an infarction with apixaban and with warfarin obtained in the clinical trial, with a rate of 100 person-years of 0.53 and 0.61, respectively. These annual risks were transformed into a risk model for a 6-week period (the duration of the cycles of the Markov model). Thus, every 6 weeks, a percentage of patients with NVAF from a hypothetical cohort of 1000 will have an infarction.

Some of these patients will die as a consequence of this complication and the remainder will survive. Those patients who have had an infarction complete the simulation at this time and are counted as failures in prevention, with the costs and utilities associated with the state of acute myocardial infarction.

Differences in the effectiveness of the treatments were measured in life years gained and in quality-adjusted life years (QALY) gained. The utilities of the different health states used to calculate the QALY were obtained from a study performed in the United Kingdom based on the EQ-5D (EuroQol 5D) questionnaire in patients with AF^{28,29} (Table 2). Determination of the loss of quality

Table 1
Population and Risks Considered in the Markov Model

Item	Mean	Range	References
Population characteristics			
Patients with an indication for VKA	Yes	—	Granger et al ¹⁶
Women	35.3%	—	Granger et al ¹⁶
Mean age, years	70	63-76	Granger et al ¹⁶
CHADS ₂ , mean	2.1	—	Granger et al ¹⁶
Complication rates/100 person-years^a			
<i>Stroke, excluding hemorrhagic stroke</i>			
Apixaban	0.981	—	Granger et al ¹⁶
Acenocoumarol	1.077	—	Granger et al ¹⁶
<i>Myocardial infarction</i>			
Apixaban	0.530	—	Granger et al ¹⁶
Acenocoumarol	0.610	—	Granger et al ¹⁶
<i>Systemic embolism</i>			
Apixaban	0.090	—	Granger et al ¹⁶
Acenocoumarol	0.100	—	Granger et al ¹⁶
<i>Other CV-related hospitalizations^b</i>			
Apixaban	10.460 ^c	—	Connolly ²²
Acenocoumarol	10.460 ^c	—	Connolly ²²
<i>Other reasons for discontinuing AC therapy^b</i>			
Apixaban	13.177	—	Granger et al ¹⁶
Acenocoumarol	14.405	—	Granger et al ¹⁶
<i>ICH</i>			
Apixaban	0.330	—	Granger et al ¹⁶
Acenocoumarol	0.800	—	Granger et al ¹⁶
<i>Other major bleeding</i>			
Apixaban	1.790	—	Granger et al ¹⁶
Acenocoumarol	2.270	—	Granger et al ¹⁶
<i>CRNM bleeding</i>			
Apixaban	2.083	—	Granger et al ¹⁶
Acenocoumarol	2.995	—	Granger et al ¹⁶
Recurrence of ischemic stroke	4.100	—	Mohan ²⁶
Recurrence of hemorrhagic stroke	2.996	—	Mohan ²⁶
Hazard ratios of apixaban vs acenocoumarol			
Stroke	0.79	0.65-0.95	Granger et al ¹⁶
Myocardial infarction	0.88	0.66-1.17	Granger et al ¹⁶
Systemic embolism	0.87	0.44-1.75	Granger et al ¹⁶
ICH	0.51	0.35-0.75	Granger et al ¹⁶
Other major bleeding	0.79	0.68-0.93	Granger et al ¹⁶
Major and CRNM bleeding	0.68	0.61-0.75	Granger et al ¹⁶
Additional risk of mortality with acenocoumarol vs apixaban			
NVAF	1.34	—	Granger et al ¹⁶
Stroke, minor/moderate/severe	3.18/5.84/15.75	—	Granger et al ¹⁶
Myocardial infarction (men/women)	4.16/2.56	—	Friberg et al ²³
Systemic embolism	1.34	—	Henriksson et al ²⁴
Other factors			
Adjustment factor for stroke risk for each decade of life	1.40	—	Huybrechts et al ²⁵
Adjustment factor for risk of hemorrhage for each decade of life	1.97	—	Bronnum et al ²¹
Hemorrhagic stroke in ICH (apixaban), %	77	—	No authors listed ²⁷
Hemorrhagic stroke in ICH (acenocoumarol), %	64	—	Ariesen et al ²⁰
GI hemorrhage in the other major bleeding (apixaban), %	38	—	Granger et al ¹⁶
GI hemorrhage in the other major bleeding (acenocoumarol), %	35	—	Granger et al ¹⁶
Treatment with ASA following discontinuation^d			
Rate of ischemic stroke/100 person-years	3.453	—	Connolly et al ²²
Rate of myocardial infarction/100 person-years	1.110	—	Connolly et al ²²
rate of ICH/100 person-years	0.322	—	Connolly et al ²²

Table 1 (Continued)

Population and Risks Considered in the Markov Model

Item	Mean	Range	References
Rate of other major bleeding/100 person-years	0.887	–	Connolly et al ²²
Rate of CRNM bleeding/100 person-years	2.936	–	Connolly et al ²²

AC, anticoagulants; ASA, acetylsalicylic acid; CHADS₂, congestive heart failure, hypertension, age, diabetes, stroke (double); CRNM, clinically relevant nonmajor; CV, cardiovascular; GI, gastrointestinal; ICH, intracranial hemorrhage; NVAf, nonvalvular atrial fibrillation; VKA, vitamin K antagonists.

^a Adjusted for CHADS₂ (congestive heart failure, hypertension, age, diabetes, stroke [doubled]).

^b Not due to stroke or myocardial infarction.

^c The same rate observed in patients with a contraindication for vitamin K antagonists is assumed.

^d Treatment with acetylsalicylic acid after discontinuation of the previous anticoagulation therapy was considered to be due to major bleeding or other causes; it was also considered that the distribution according to severity of the ischemic or hemorrhagic stroke would be the same as that observed with acetylsalicylic acid in the first-line treatment (AVERROES study).

of life associated with the need for monitoring required by the use of acenocoumarol was based on a study by Gage et al³⁰ (Table 2).

Health Care Costs and Resources

The per unit use and cost of resources were obtained from Spanish sources (in 2012 euros). The analysis was carried out from the perspective of the Spanish National Health System (considering only the direct health care costs) and of society (including direct nonhealth care costs, as well). The cost of the medications (RRP [recommended retail price] + VAT [value added tax], with a 7.5% reduction)³¹ was calculated by considering 10 mg/day (5-mg doses twice daily) of apixaban³² and 5 mg/day of acenocoumarol (the daily dose recommended by the World Health Organization). The cost of INR monitoring was estimated to be € 320 a year, according to a study by De Solà-Morales Serra and Elorza Ricart.³³ It was considered that all the patients, regardless of their treatment, visited their primary care physician every 3 months for routine follow-up of the AF. The cost of the complications of

NVAf during the acute phase was obtained by taking the mean of the retail prices corresponding to diagnosis-related groups in the Spanish autonomous communities; the cost of treatment after the acute phase of the complications was obtained from other Spanish sources^{7,34–38} (Table 3). The direct nonhealth care costs included in the analysis from the societal perspective consisted of those derived from informal care (aid to the dependent patient and home adaptations) of patients who have had an ischemic or hemorrhagic stroke⁷ (Table 3). An annual discount rate of 3.5% was applied for health care costs and results.

Base Case and Sensitivity Analysis

We analyzed a base case with the mean values of all the parameters. To confirm the stability of the results, simple univariate sensitivity analyses were performed (in each sensitivity analysis, the baseline value of a variable was modified, applying its extreme values) for the main variables of the model (Table 1). One of those analyzed was the percentage of TTR of the study population. According to the ARISTOTLE trial,¹⁶ in the base case of the analysis, 25% of the patients were equally distributed among the 4 established TTR intervals (< 52.38%; from ≥ 52.38% to < 66.02%; from ≥ 66.02% to < 76.51%, and ≥ 76.51%). In this respect, sensitivity analysis of the extreme values considering that 100% of the patients were in the worst (< 52.38% in TTR) or best (≥ 76.51% in TTR) of the intervals was carried out. Sensitivity analyses were also performed for acenocoumarol and apixaban, taking the extreme values of variables such as risk of stroke and intracranial hemorrhage, the probability of hospital admission, the cost of each visit for INR monitoring for acenocoumarol, and the loss of utilities associated with the use of acenocoumarol or apixaban (Figure 3). As the reduction in the risk of myocardial infarction vs warfarin was not statistically significant, a sensitivity analysis was carried out considering that apixaban did not reduce the number of myocardial infarctions vs warfarin, that is, taking the same rate of infarctions (0.530/100 person-years) for apixaban and warfarin. Finally, a probabilistic analysis was performed (Monte Carlo simulation with 2000 simulations in the 1000-patient cohort) which included, at the same time, all the variables of the analysis, adjusted for the appropriate statistical distributions in each case (beta for the transition probabilities and the utilities and gamma for costs). When the model simulated the course of a hypothetical cohort of 1000 patients with NVAf, the course of each patient in that cohort was different, since the modifications in all the variables of each patient (eg, the hazard ratio of stroke, myocardial infarction, systemic embolism, intracranial hemorrhage, costs, utilities, etc) occurred randomly in accordance with the previously defined statistical distributions. Thus, an attempt was made to imitate the real clinical course of the patients.

Table 2

Utilities Considered in the Markov Model

Item	Mean	References
<i>Utilities of the Markov states</i>		
Nonvalvular atrial fibrillation, baseline	0.7270	Sullivan et al ²⁸
Minor stroke ^a	0.6151	Sullivan et al ²⁸
Moderate stroke ^a	0.5646	Sullivan et al ²⁸
Severe stroke ^a	0.5142	Sullivan et al ²⁸
Systemic embolism	0.6265	Sullivan et al ²⁸
Myocardial infarction	0.6098	Sullivan et al ²⁸
<i>Loss of utilities, duration</i>		
Intracranial hemorrhage	0.1511 (6 weeks)	Sullivan et al ²⁸
Other major bleeding	0.1511 (2 weeks)	Sullivan et al ²⁸ , Freeman et al ²⁹
CRNM bleeding	0.0582 (2 days)	Sullivan et al ²⁸ , Freeman et al ²⁹
Hospitalization for other CV-related causes	0.1276 (6 days)	Sullivan et al ²⁸
Use of acenocoumarol, INR monitoring	0.0130 (treatment)	Sullivan et al ²⁸
Use of apixaban	0	Assumption ^b

CV, cardiovascular; INR, international normalized ratio; CRNM, clinically relevant nonmajor.

^a Ischemic or hemorrhagic.

^b A sensitivity analysis was performed, considering that, improbably, the loss of utilities with the use of apixaban was the same as that assumed for acenocoumarol.

Table 3
Costs Considered in the Markov Model

	Cost (€)	Unit	Duration	Source
Annual cost of monitoring	320.00	Annual	NA	De Solà-Morales et al ³³
Systematic control	35.32	Per visit	NA	Retail prices in the ACs
Stroke				
<i>Direct costs</i>				
Minor				
Acute phase	5970.09	Per episode	2 weeks	Retail prices in the ACs
Maintenance	120.01	Monthly	For life	Mar et al ³⁶
Moderate				
Acute phase	6281.38	Per episode	2 weeks	Retail prices in the ACs
Maintenance	742.59	Monthly	For life	Mar et al ³⁶
Severe				
Acute phase	6951.01	Per episode	2 weeks	Retail prices in the ACs
Maintenance	2081.85	Monthly	For life	Mar et al ³⁶
Fatal	5910.08	Per episode	NA	Retail prices in the ACs
<i>Direct nonhealth care costs</i>				
Minor				
Acute phase	252.39	Per episode	2 weeks	Beguiristain et al ⁷
Maintenance	1367.57	Monthly	For life	Beguiristain et al ⁷
Moderate				
Acute phase	666.11	Per episode	2 weeks	Beguiristain et al ⁷
Maintenance	1789.53	Monthly	For life	Beguiristain et al ⁷
Severe				
Acute phase	1031.69	Per episode	2 weeks	Beguiristain et al ⁷
Maintenance	1942.61	Monthly	For life	Beguiristain et al ⁷
Hemorrhagic stroke				
<i>Direct costs</i>				
Minor				
Acute phase	7575.44	Per episode	2 weeks	Retail prices in the ACs
Maintenance	120.01	Monthly	For life	Mar ³⁶
Moderate				
Acute phase	7886.73	Per episode	2 weeks	Retail prices in the ACs
Maintenance	742.59	Monthly	For life	Mar ³⁶
Severe				
Acute phase	8556.36	Per episode	2 weeks	Retail prices in the AC
Maintenance	2081.85	Monthly	For life	Mar ³⁶
Fatal	7515.44	Per episode	NA	Retail prices in the ACs
<i>Direct nonhealth care costs</i>				
Minor				
Acute phase	252.39	Per episode	2 weeks	Beguiristain et al ⁷
Maintenance	1367.57	Monthly	For life	Beguiristain et al ⁷
Moderate				
Acute phase	666.11	Per episode	2 weeks	Beguiristain et al ⁷
Maintenance	1789.53	Monthly	For life	Beguiristain et al ⁷
Severe				
Acute phase	1031.69	Per episode	2 weeks	Beguiristain et al ⁷
Maintenance	1942.61	Monthly	For life	Beguiristain et al ⁷
Other intracranial bleeding	7515.44	Per episode	NA	Retail prices in the ACs
Other major bleeding				
<i>GI hemorrhage</i>	3431.91	Per episode	NA	Monreal et al ³⁷
<i>Non intracranial/GI</i>	3431.91	Per episode	NA	Monreal et al ³⁷
CRNM hemorrhages	2304.66	Per episode	NA	Monreal et al ³⁷
Myocardial infarction				
<i>Acute phase</i>	10 513.37	Per episode	NA	Retail prices in the AC
<i>Maintenance</i>	164.81	Monthly	For life	Mar ³⁶

Table 3 (Continued)
Costs Considered in the Markov Model

	Cost (€)	Unit	Duration	Source
Systemic embolism				
Acute phase	2846.50	Per episode	2 weeks	Retail prices in the ACs
Maintenance	116.84	Monthly	For life	Mar et al ³⁶
Other CV-related hospitalizations	4729.67	Per episode	NA	Retail prices in the ACs
Dyspepsia-related costs	27.39	Monthly	NA	Ariza-Ariza et al ³⁴
Costs of renal monitoring	14.76	Annual	NA	Navarrete-Navarro et al ³⁸
Monthly costs related to dyspepsia and renal monitoring				
Apixaban	1.69	Monthly	NA	Calculated: according to renal monitoring and dyspepsia-related costs
Acenocoumarol	0.50	Monthly	NA	
Mean daily pharmacy costs (RRP - 7.5% of discount + VAT)				
Apixaban	2.80	Daily	NA	BOT PLus ³²
Acenocoumarol	0.15	Daily	NA	BOT PLus ³²

ACs, autonomous communities; CRNM, clinically relevant nonmajor; CV, cardiovascular; GI, gastrointestinal; NA, not applicable; RRP, recommended retail price; VAT, value added tax.

* Applicable only to acenocoumarol.

RESULTS

Episodes Avoided

According to the results produced by the model applied to a cohort of 1000 patients with NVAf, apixaban would prevent a considerable number of complications compared with acenocoumarol: 18 strokes (4 ischemic and 14 hemorrhagic), 71 hemorrhages (12 of which would be intracranial and 16 would be cases of major bleeding), 1 systemic embolism, and 2 myocardial infarctions. In contrast, apixaban would prevent 23 deaths related to thromboembolic or hemorrhagic episodes (Table 4).

Cost-effectiveness

Consequently, for each patient treated with apixaban rather than acenocoumarol we would obtain more life years (0.187 life years gained) and an increase in QALY (0.194 gained). The incremental costs per patient treated with apixaban would be € 2488 for the Spanish National Health System and € 1826 for society. This difference in costs is mainly due to the more marked decrease in mortality obtained with apixaban and its higher purchase price. The cost per life years gained for the Spanish National Health System and for society was € 13 305 and € 9765, respectively. The cost per QALY gained was € 12 825 and € 9412,

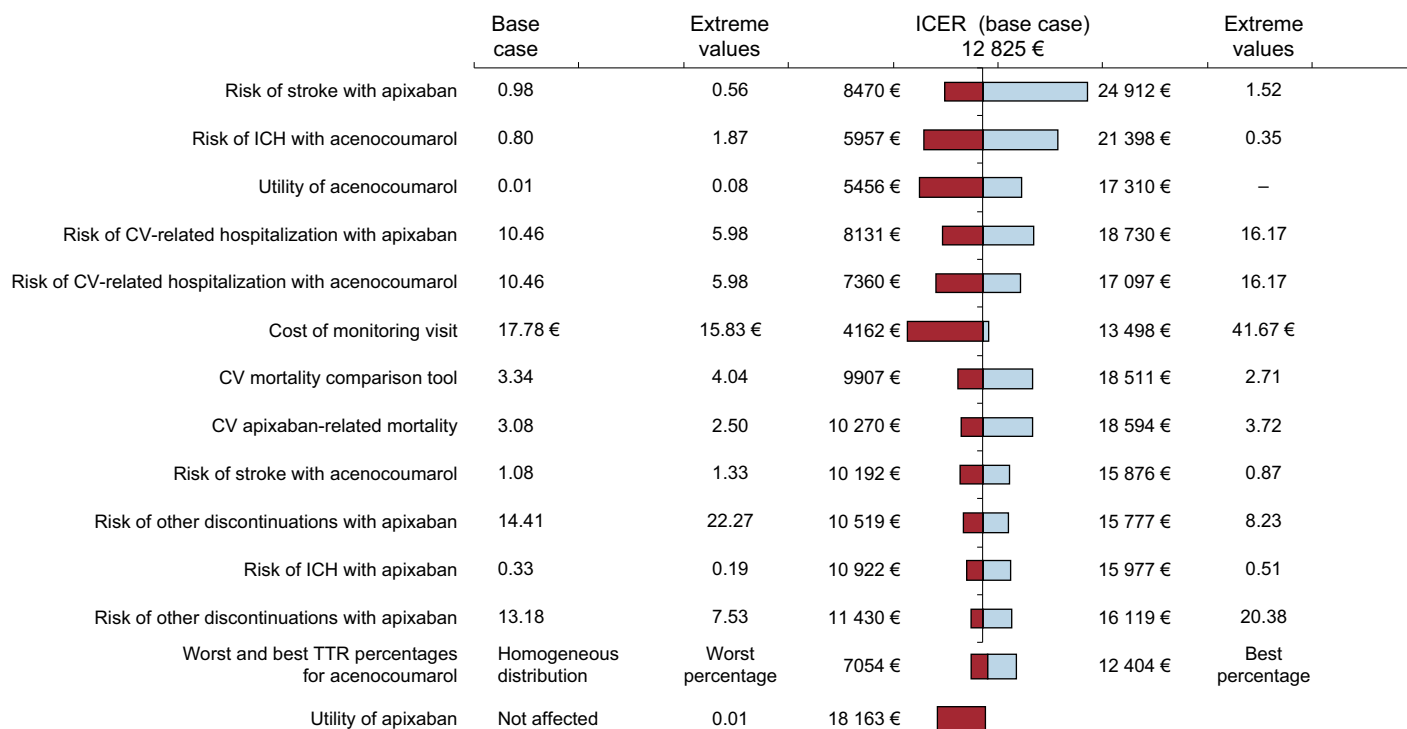


Figure 3. Deterministic sensitivity analysis from the perspective of the Spanish National Health System. Tornado diagram (the extreme values used are indicated to one side). Ratio of incremental cost-effectiveness (euros per quality-adjusted life years gained with apixaban vs acenocoumarol) (in 2012 euros). The figure shows the values of the base case and the extreme values used in the sensitivity analysis. The risks are expressed as rate/100 patient-years. Mortality is the rate of death during the clinical trial. CV, cardiovascular; ICER, incremental cost-effectiveness ratio; ICH, intracranial hemorrhage; TTR, time in therapeutic range.

Table 4
Number of Complications Predicted in the Life-long Follow-up of a Cohort of 1000 Patients With Nonvalvular Atrial Fibrillation

Complication	Apixaban	Acenocoumarol	Difference
Ischemic strokes*	263	267	-4
Hemorrhagic strokes*	29	43	-14
Intracranial hemorrhages	13	25	-12
Systemic embolisms	25	26	-1
Other major hemorrhages	169	185	-16
CRNM bleeding	295	338	-43
Myocardial infarctions	87	89	-2
Other CV-related hospitalizations	1219	1188	31
Other discontinuations of the treatment	644	640	4
Deaths per episodes (acute phase)	62	74	-12
Deaths per episodes (maintenance)	318	329	-11

CRNM, clinically relevant nonmajor; CV, cardiovascular.

* Indicates both a first stroke and recurrent strokes.

respectively (Table 5). These results indicate that, compared with acenocoumarol, apixaban is cost-effective in the prevention of stroke in patients with NVAF in Spain, as the costs per life years gained or for QALY gained are below € 30 000, which is the threshold that is generally accepted in Spain.³⁹

Sensitivity Analysis

The sensitivity analyses confirmed that apixaban is a cost-effective treatment compared with acenocoumarol. The changes in the most sensitive parameters of the study, such as the risks of complications with one treatment or the other, the loss of utilities associated with INR monitoring with acenocoumarol, and the costs of follow-up visits, do not affect the results of the analysis since, in every case, the costs of gaining 1 life year and the cost of gaining

Table 5
Results of the Cost-effectiveness Analysis of Apixaban vs Acenocoumarol

	Apixaban	Acenocoumarol	Difference
<i>Perspective of the Spanish National Health System</i>			
Life years	9.037	8.850	0.187
QALY	6.424	6.230	0.194
Total costs (€)	18 029	15 541	2488
Costs per LYG (€)	13 305		
Costs of gaining 1 QALY (€)	12 825		
<i>Societal perspective[†]</i>			
Life years	9.037	8.850	0.187
QALY	6.424	6.230	0.194
Total costs (€)	29 193	27 367	1826
Costs per LYG (€)	9765		
Costs of gaining 1 QALY (€)	9412		

LYG, life year gained; QALY, quality adjusted life year.

[†] Includes the direct non-health care costs for aid to the patient who is dependent due to stroke.

1 QALY with the most effective treatment (apixaban) were below the threshold of € 30 000 (Figure 3).

Considering that 100% of the patients were in the lowest percentage of TTR (< 52.38%), the cost of gaining 1 QALY would be € 7054. In the opposite case (≥ 76.51% in TTR), the cost per QALY gained would increase to € 12 404, in both cases, from the perspective of the Spanish National Health System (Figure 3). Should apixaban fail to reduce the number of myocardial infarctions compared with warfarin, the cost of gaining 1 QALY would be € 14 150.

According to the probabilistic sensitivity analysis, the probability of apixaban being cost-effective vs acenocoumarol was 87% (Figure 4).

DISCUSSION

Although acenocoumarol and warfarin are the usual treatments for AF, their use has limitations owing to their narrow therapeutic

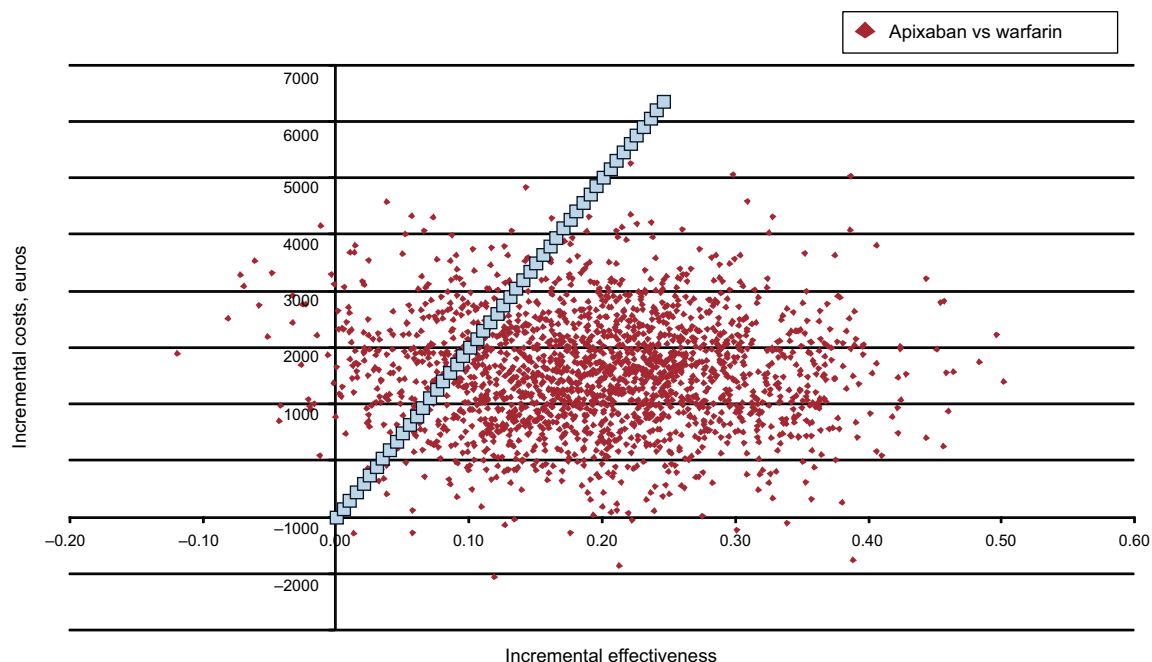


Figure 4. Probabilistic sensitivity analysis. The probability that apixaban is cost-effective (cost per quality-adjusted life year gained < € 30 000) compared with acenocoumarol is 87%.

margin, the risk of bleeding, and drug-drug and drug-food interactions.^{40,41} Patients treated with VKA require frequent INR monitoring and resulting dose adjustments. According to a meta-analysis by Baker et al,⁴² patients treated with warfarin remain in the therapeutic INR range only 55% of the time. Of anticoagulated patients who have a cardioembolic stroke, 67.6% have an INR below the therapeutic range at the time of the stroke.⁴³

Apixaban is a new anticoagulant that produces a statistically significant reduction in the risks of stroke, bleeding, and death due to these episodes compared with VKA.⁴⁰ In this respect, a study by Banerjee et al,⁴⁴ based on patients treated in real-world clinical practice, indicates that the net clinical benefit (balance between the risk of ischemic stroke and the risk of intracranial hemorrhage) of apixaban is greater than that of warfarin, for different CHADS₂ scores and risk of bleeding.

According to the present model and the adopted premises, apixaban can be a cost-effective treatment compared with acenocoumarol in the prevention of stroke in NVAF patients in Spain.

Limitations of the Model

In the assessment of these results, we must take into account the fact that this is a theoretical model that is, by definition, a simplified simulation of reality. Pharmacoeconomic models enable the creation of economic simulations of complex drug-related health care processes. They are especially useful when the intention is to simulate the course of a disease beyond the period of clinical tests.¹⁷ Markov models with Monte Carlo simulation are preferred over deterministic models when dealing with chronic diseases like NVAF, as they are better at simulating the course of the disease over the long term. The Markov deterministic model is based on the course of a hypothetical patient cohort. However, the Monte Carlo probabilistic analysis simulates the course of individual patients, based on the values of randomly chosen variables, which more closely resembles clinical reality. The data on efficacy and on adverse effects utilized in the model were obtained from a randomized clinical trial involving 18 201 patients with NVAF,¹⁶ providing a high level of evidence.

One of the main suppositions of the model is the therapeutic equivalence between warfarin and acenocoumarol. Thus, we adopted the effectiveness values obtained for acenocoumarol in the ARISTOTLE clinical trial, which compared it with warfarin.¹⁶ This assumption can be considered a limitation of the study, given that, although the 2 drugs could have similar effectiveness in clinical practice,¹² an observational study found no significant differences in the quality of INR control, but did report a longer duration of the TTR in the patients treated with acenocoumarol than in those treated with warfarin (37.6% vs 35.7%; $P = .0002$).¹³ Nevertheless, in other previously published Spanish economic studies, acenocoumarol and warfarin were considered to be perfect substitutes for each other, both in efficacy and safety and the in the resource use associated with each.^{45,46}

The costs assumed for the acute phase of the strokes and hemorrhages in the model were obtained from the diagnosis-related groups published by the Spanish autonomous communities, prices that could differ from the real direct costs of the processes.

The cost of the drugs was calculated considering a dose of 5 mg/d of acenocoumarol, the daily dose recommended by the World Health Organization. Nevertheless, it should be considered that this premise serves only for the calculation of the cost of treatment with acenocoumarol, a variable that does not significantly affect the result because of the low price of the drug.

The utilities of the model were obtained from a study performed in the United Kingdom based on the EQ-5D

questionnaire in patients with AF.^{28,29} Concerning the validity of these utility data corresponding to the Spanish population, a study based on 83 000 evaluations of 44 health states, with the EQ-5D applied in 6 European countries (including Spain) observed wider variability between individuals than between countries.⁴⁷

Despite the aforementioned limitations of the model, the results obtained concur, as the result favoring apixaban is maintained both in deterministic sensitivity analyses and in the Monte Carlo analysis, with a high probability (87%) that apixaban is more cost-effective than acenocoumarol.

The present report is the first analysis of the cost-effectiveness of apixaban in NVAF performed in Spain. Two analyses comparing the cost-effectiveness of apixaban and warfarin in NVAF have recently been published in the United States.^{48,49} These studies found that apixaban would be cost-effective in 98% and 62% of the simulations for primary and secondary stroke prevention, respectively.

Two economic analyses of oral anticoagulants vs acenocoumarol in the prevention of stroke in patients with NVAF in Spain have recently been published.^{45,46} From the perspective of the Spanish National Health System, the cost per QALY gained would be € 17 581 with dabigatran⁵ and € 11 274 with rivaroxaban.⁴⁶ The results of the economic models of apixaban, dabigatran, and rivaroxaban are not directly comparable, since they differ in the structure of the Markov models used; however, they reflect the fact that the oral anticoagulants available in Spain are cost-effective options in the current Spanish health care context.

CONCLUSIONS

According to the premises assumed in this model, it can be concluded that it is highly probable (probability of 87% according to the probabilistic analysis) that apixaban could be a cost-effective treatment compared with acenocoumarol in the prevention of stroke in patients with NVAF, in accordance with the cost-effectiveness threshold generally accepted in Spain.³⁹ The stability of the results obtained in the base case of the analysis were confirmed in the deterministic and probabilistic sensitivity analyses.

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CONFLICTS OF INTEREST

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