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ORIGINAL RESEARCH

Cost-effectiveness of apixaban in non-valvular atrial fibrillation (NVAF) based on effectiveness data from a Spanish study in clinical practice (real-world evidence)

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ABSTRACT

Objective: To analyze the cost-effectiveness of apixaban in the prevention of stroke in adult patients with non-valvular atrial fibrillation (NVAF), compared to other direct-acting oral anticoagulants (dabigatran, rivaroxaban, edoxaban) and the vitamin K antagonist acenocoumarol, based on data on effectiveness in clinical practice in Spain obtained in the FANTASIIA study.

Research design and methods: A probabilistic Markov economic model (second-order Monte Carlo simulation) was performed to analyze the costs and utilities (quality-adjusted life years, QALYs) associated with the compared treatments, according to the different probabilities of stroke, major bleeding and death observed in FANTASIIA.

Results: The cost per QALY gained in the patient treated with apixaban versus comparators ranged from €2,919 to €7,462. The probability of apixaban being cost-effective ranges from 91.1% (vs dabigatran 150 mg), 97.8% (vs dabigatran 110 mg), and 100% (vs. rivaroxaban, edoxaban, and acenocoumarol).

Conclusions: Based on the results of the FANTASIIA study, apixaban is a cost-effective treatment (below a willingness to pay of €25,000 per QALY gained) compared to dabigatran, rivaroxaban, edoxaban, and acenocoumarol in treating patients with NVAF.

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1. Introduction

Apixaban is a direct-acting oral anticoagulant (DOAC) indicated for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF) with one or more risk factors, such as previous stroke or transient ischemic attack, age ≥75 years, hypertension, diabetes mellitus or symptomatic heart failure (≥NYHA Class 2) [1].

Economic analyses of apixaban in this indication in Spain have been carried out based on efficacy data from randomized clinical trials [2–6]. The efficacy of a medicine is usually demonstrated under the ideal conditions of randomized clinical trials. These conditions are unlikely to be accurately reproduced in clinical practice, so it is imperative to test the effectiveness of the medicines in *ad hoc* studies [7]. In this regard, several observational studies in patients *(real-world evidence*) have reported the effectiveness of apixaban in indicating NVAF [8–13]. Specifically, the FANTASIIA clinical practice study [8,9]is a cohort study that enrolled between June 2013 and March 2014 adult patients with a confirmed diagnosis of NVAF, treated with vitamin K antagonists (VKA) or DOAC, and followed for 3 years [8]. Based on the results of 1,645 patients treated with VKAs, a real-world analysis of the effectiveness of DOACs was performed [9], calculating the estimated rates (if patients had been treated with DOACs instead of VKAs) of stroke, major bleeding and all-cause mortality. This was done from the pooled *hazard ratios* (HR) obtained for each adverse event in the four clinical trials that provided the effect (RE-LY, ARISTOTLE, ROCKET-AF and ENGAGE-AF studies) [14–17] and *odds ratios* (ORs) from meta-analyses of clinical practice studies of dabigatran, rivaroxaban, apixaban and edoxaban [18–21], compared with rates observed in VKA-anticoagulated patients in the FANTASIIA registry [9]. Unlike the other observational studies, the FANTASIIA-based study includes edoxaban. According to the FANTASIIA results, apixaban would have a lower risk of stroke and major bleeding than dabigatran (150 mg) and rivaroxaban [9]. Specifically, in the FANTASIIA study, the annual stroke rate was 0.89% (95%CI 0.63–1.23%) with apixaban, 0.97% (95%CI 0.70–1.33%) with dabigatran 150 mg and 0.92% (95%CI 0.65–1.26%) with rivaroxaban; for major bleeds it was 2.09% (95%CI 1.69–2.61%) with apixaban, 2.65% (95%CI 2.18–3.20%) with dabigatran 150 mg and 3.25% (95%CI 2.71–2.82%) with rivaroxaban [9]. FANTASIIA also found lower all-cause mortality with apixaban (3.16%) than with dabigatran 150 mg (3.88%) and rivaroxaban (5.76%) [9].

This study aimed to analyze the cost-effectiveness of apixaban in the prevention of stroke and systemic embolism in adult patients with NVAF, compared with the other DOACs (dabigatran, rivaroxaban, edoxaban) and the VKA acenocoumarol, based on data on effectiveness in clinical practice in Spain obtained in the FANTASIIA study.

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2. Methods

2.1. Model design and structure

A probabilistic Markov economic model (second-order Monte Carlo simulation) was done, the structure of which is shown in Figure 1. It consists of six Markov states. Patients with NVAF, treated with one of the anticoagulants compared, may remain stable or develop an acute stroke or major bleeding. After the acute stroke or major bleeding, patients would move to a post-stroke or post-bleeding state. In either state, patients may die. These Markov states, the most representative of the disease, were analyzed in FANTASIIA [9]. Apixaban was compared with the other ACODS (dabigatran, rivaroxaban, edoxaban) and the VKA acenocoumarol. The model was run using TreeAge Pro Healthcare Software 2023 R2.0.

2.2. Population

The model population was that of the FANTASIIA study: patients over 18 years of age, diagnosed with NVAF, and on stable oral anticoagulant therapy for at least 6 months [9]. Baseline clinical characteristics of patients included in the FANTASIIA registry are presented in SUPPLEMENT 1.

2.3. Perspectives and time horizon

The perspective of the study is that of the National Health System (NHS). Therefore, only direct health costs were considered. Additional analysis has been carried out from a societal perspective, and also considering both direct non-health costs (costs of social services, such as nursing homes or other socio-health services and home care, as well as informal care and other non-health costs, such as adapted medical transport and renovations for physical adaptation of spaces) and indirect costs (due to lost productivity according to the human capital method). These costs were obtained from a Spanish study published in 2021 [22].

The simulation of the economic model had a lifetime time horizon. Given that the median age of the FANTASIIA patients treated with DOACs was 73 years [9], a time horizon of 30 years was considered to ensure that the entire cohort of patients would have died by the end of the simulation, as in other previously published studies [2,23]. The cycles (when patients move from one state to another in the model) were 3 months [24]. Since the mean age of FANTASIIA patients was 73 years, we performed a sensitivity analysis considering a time horizon of 11 years (according to life expectancy in Spain: 84 years of age).

2.4. Transition probabilities

The quarterly transition probabilities (Table 1) were calculated from the annual probabilities of the FANTASIIA study [9]. Other annual probabilities were obtained from various literature sources [2,9,25,26].

The probability of a patient with stable NVAF having a stroke or major bleeding was obtained from the FANTASIIA study [9]. 91.3% of strokes were considered ischemic, and the remaining 8.7% were hemorrhagic, according to the study by Loucera et al. [27], and 53.5% of strokes are severe, according to the study by Hylek et al. [28]. Mortality from stroke (0.1525 per year) and major bleeding (0.2620 per year) was obtained from published studies [2,25,26].

For the probabilistic analysis, alpha and beta statistics were calculated for each probability, considering a beta distribution for the probabilities.

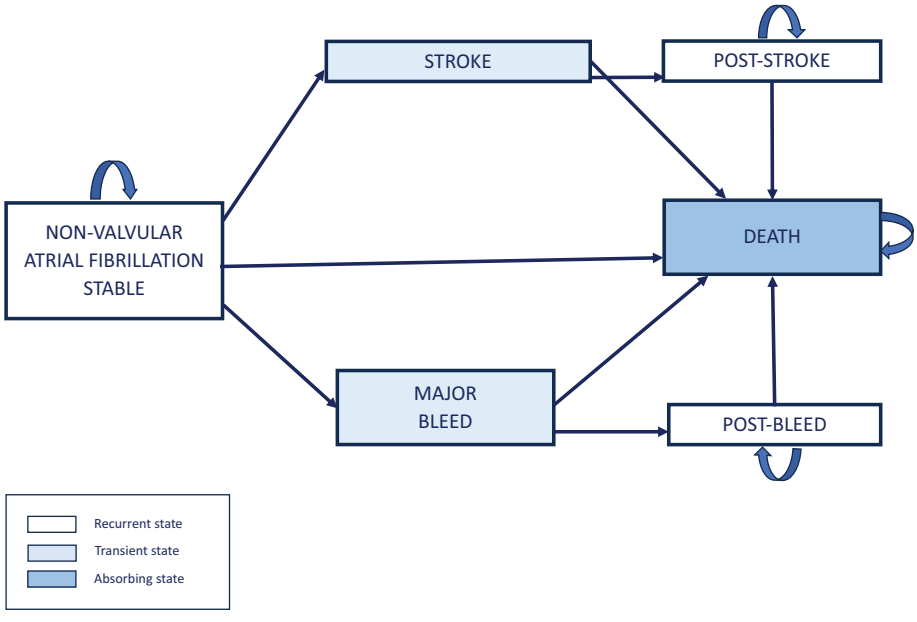

Figure 1. Structure of the Markov model.

Table 1. Quarterly transition probabilities [9,26].

	Medium	Minimum	Maximum	SD
Apixaban				
Acute stroke	0.0022	0.0016	0.0031	0.0004
Major bleeding	0.0052	0.0042	0.0065	0.0006
Death	0.0079	0.0067	0.0094	0.0007
Dabigatran 110 mg				
Acute stroke	0.0018	0.0012	0.0025	0.0003
Major bleeding	0.0062	0.0050	0.0075	0.0006
Death	0.0110	0.0095	0.0126	0.0008
Dabigatran 150 mg				
Acute stroke	0.0024	0.0018	0.0033	0.0004
Major bleeding	0.0066	0.0055	0.0080	0.0007
Death	0.0097	0.0083	0.0113	0.0008
Rivaroxaban				
Acute stroke	0.0023	0.0016	0.0032	0.0004
Major bleeding	0.0081	0.0068	0.0071	0.0001
Death	0.0144	0.0127	0.0163	0.0009
Edoxaban				
Acute stroke	0.0023	0.0016	0.0031	0.0004
Major bleeding	0.0066	0.0054	0.0080	0.0007
Death	0.0125	0.0109	0.0142	0.0009
Acenocoumarol				
Acute stroke	0.0027	0.0020	0.0037	0.0004
Major bleeding	0.0082	0.0069	0.0098	0.0008
Death	0.0139	0.0121	0.0159	0.0010

SD: standard deviation.

2.5. Costs

The quarterly costs were calculated from unit health costs obtained from various Spanish literature sources (Table 2) [2,5,6,22,24,27–32]. The following costs were considered: purchase of anticoagulants (apixaban, dabigatran, rivaroxaban, edoxaban and acenocoumarol), acute stroke, post-stroke, major bleeding and the patient's Markov state after experiencing the major bleed (see Post-bleed state in Figure 1). The cost of medicines was calculated from retail prices plus 4% VAT (PVP-IVA) in the Botplus database [33]. In the base case of the analysis, the PVP-IVA for generic dabigatran and the branded prices for the other medicines were considered. Price sensitivity analyses were conducted for generic apixaban and rivaroxaban.

For the probabilistic analysis, alpha and beta statistics were calculated for each cost, considering a gamma distribution.

2.6. Utilities

Quarterly utilities were taken from previously published studies (Table 3) [2,34,35]. It was felt that major bleeds and using acenocoumarol would lead to a loss of utilities. There would also be a loss of utilities in patients treated with acenocoumarol due to the need for INR monitoring. Utilities were expressed as quality-adjusted life years (QALYs).

For the probabilistic analysis, alpha and beta statistics were calculated for each utility, considering a gamma distribution.

2.7. Analyses performed

The following analyses were performed: (i) a deterministic analysis, with mean values of all variables; (ii) a univariate deterministic sensitivity analysis (tornado diagram) of all

Table 2. Quarterly costs included in the economic model (€ 2023).

Item	Medium	Minimum	Maximum	SD	References
Markov states					
Acute stroke	€ 10333	€ 8,670	€ 10492	€ 465	[22,27]
Post-stroke (NHS perspective)	€ 5,518	€ 1,577	€ 7,578	€ 1,531	[2,6,27,30]
Post-stroke (society perspective)	€ 11383	€ 6,268	€ 14616	€ 2,129	[2,27]
Major bleeding	€ 3,579	€ 3,141	€ 5,235	€ 534	[5,24,32]
Post-major bleeding	€ 15	€ 12	€ 18	€ 2	[24]
Anticoagulant treatment* (dose/day)					
Apixaban (10 mg/day)	€ 307	€ 245	€ 368	€ 31	[2,33]
Apixaban (generic) (10 mg/day)	€ 194	€ 156	€ 233	€ 20	[2,31,33]
Dabigatran 110 mg (generic) (300 mg/day)	€ 263	€ 210	€ 316	€ 27	[2,33]
Dabigatran 150 mg (generic) (300 mg/day)	€ 194	€ 156	€ 233	€ 20	[2,33]
Rivaroxaban (20 mg/day)	€ 307	€ 245	€ 368	€ 31	[2,33]
Rivaroxaban (generic) (20 mg/day)	€ 223	€ 179	€ 268	€ 23	[2,33]
Edoxaban (60 mg/day)	€ 307	€ 245	€ 368	€ 31	[2,33]
Acenocoumarol (5 mg/day)	€ 170	€ 136	€ 204	€ 27	[2,29,33]

*To the fixed price (approved PVP-IVA) of the medications, the variable cost of primary care consultations is added (1 quarterly), with an average unit cost of €57.34 in the autonomous communities for all DOACs and also the cost of INR control for acenocoumarol (€374 annually) (2,29). Medications (laboratory) considered in the model: Apixaban: Eliquis 2,5 mg, 60 tablets (Bristol Myers Squibb); Dabigatran: Dabigatran Etexilato Accord EFG 110 mg & 150 mg, 60 capsules (Accord); Rivaroxaban: Xarelto 20 mg, 28 tablets (Bayer Hispania); Rivaroxaban (generic): Rivaroxaban Tad EFG 20 mg, 28 tablets (KRKA Farmacéutica); Edoxaban: Lixiana 30 mg, 28 tablets (Daiichi Sankyo España); Acenocoumarol: Acenocumarol Aurovitas EFG 4 mg, 20 tablets (Aurovitas Spain).

DOAC: direct-acting oral anticoagulant; INR: international normalized ratio; NHS: National Health System; PVP-IVA: Retail price with Value added tax; SD: standard deviation.

Table 3. Quarterly utilities included in the economic model.

Markov states	Medium	Minimum	Maximum	SD	References
Stable NVAF	0.2423	0.1939	0.2908	0.0247	[2,35]
Acute stroke	0.1882	0.1506	0.2259	0.0192	[2,34,35]
Post-stroke	0.1831	0.1465	0.2198	0.0187	[2,35]
Major bleeding	0.1920	0.1536	0.2304	0.0196	[2,35]
NVAF and Acenocoumarol use	0.2380	0.1904	0.2856	0.0243	[2,35]

NVAF: non-valvular atrial fibrillation; SD: standard deviation.

model variables (probabilities, costs and utilities); (iii) deterministic sensitivity analyses considering the PVP-IVA of generic apixaban and rivaroxaban; and (iv) a probabilistic analysis (second-order Monte Carlo simulations), performing 1,000 iterations for all variables (probabilities, costs and utilities). Analyses (i) to (iv) were conducted from an NHS perspective. Therefore, finally, a (v) analysis from a societal perspective was carried out. An additional sensitivity analysis was performed considering a time horizon of 11 years (given that the average age of FANTASIIA patients was 73 years and that life expectancy in Spain is 84 years).

A treatment is considered cost-effective against the comparator if it is more effective and the cost of gaining a QALY is less than the willingness to pay, estimated at €25,000 [36].

3. Results

3.1. NHS perspective

The overall results of the deterministic analysis are presented in Table 4. As can be seen, the cost per QALY gained in the apixaban-treated patient versus comparators ranged from €2,919 to €7,462, well below a willingness to pay of €25,000 per QALY gained.

In all deterministic sensitivity analyses (tornado diagram), apixaban was cost-effective compared to the other comparators (SUPPLEMENT 2).

As seen in the cost-effectiveness plane of the comparisons performed (SUPPLEMENT 3) and in Table 4, the probability of apixaban being cost-effective against the other treatments (calculated in the probabilistic analyses) ranged from 97.8% to 100% of the analyses. Reducing the time horizon to 11 years had a small impact on the outcomes, with cost-effectiveness probabilities ranging from 83.7% (vs dabigatran 150 mg), 97.4% (vs dabigatran 110 mg) to 100% (vs rivaroxaban, edoxaban and acenocoumarol). Considering the PVP-IVA of generic apixaban (Table 2), it was also cost-effective against all comparators, with costs per QALY gained ranging from €352 (compared to edoxaban) to €3,815 (compared to dabigatran 110 mg) (Table 5). The higher cost per patient treated with generic apixaban is partly explained by its lower mortality than dabigatran, rivaroxaban, edoxaban and acenocoumarol and the cost of more prolonged survival.

Table 5. Sensitivity analysis considering the generics of apixaban and rivaroxaban.

Apixaban	Comparator	Cost of gain a QALY with apixaban
Generic drug	Dabigatran 110 mg	€ 3,815
Generic drug	Dabigatran 150 mg	€ 1,450
Generic drug	Rivaroxaban	€ 1,341
Generic drug	Rivaroxaban generic	€ 2,396
Generic drug	Edoxaban	€ 352
Generic drug	Acenocoumarol	€ 1,775

QALY: quality-adjusted life-years.

3.2. Societal perspective

The results from the societal perspective, including both direct non-healthcare costs and indirect costs in the post-stroke period, are presented in Table 6. Apixaban was also cost-effective against all comparators, with a probability of 87.1% to 100% compared to dabigatran 150 mg and acenocoumarol, respectively.

4. Discussion

According to the analyses performed, based on the results of the FANTASIIA study, apixaban is a cost-effective treatment compared to dabigatran, rivaroxaban, edoxaban and acenocoumarol in the treatment of patients with NVAF.

The strengths of the present study are, firstly, the fact that all the analyses performed confirm the result with probabilities above 90%, according to the probabilistic analyses performed using second-order Monte Carlo simulations with 1,000 iterations (or, *lato sensu*, 1,000 patients), a methodology that allows the analysis of the uncertainty of the model variables [37]; secondly, the use of effectiveness data obtained in clinical practice in Spain, in the FANTASIIA study; thirdly, the clinical validation performed by two Spanish cardiologists (MA, FM), being at the same time investigators of the study.

Regarding the weaknesses of the study, it should be noted that it is a theoretical model, which, by definition, is a simplified

Table 4. Deterministic and probabilistic results from the economic analysis. NHS perspective.

	Costs			QALY			Cost/QALY	Probability
Comparison	Apixaban	Comparator	Difference	Apixaban	Comparator	Difference	Apixaban	CE Apixaban
Apixaban vs Dabigatran 110 mg	€ 37091	€ 27644	€ 9,447	12.431	11.165	1.266	€ 7,462	97.8%
Apixaban vs Dabigatran 150 mg	€ 37091	€ 31242	€ 5,849	12.431	11.583	0.848	€ 6,897	91.1%
Apixaban vs Rivaroxaban	€ 37091	€ 29257	€ 7,834	12.431	10.035	2.396	€ 3,270	100.0%
Apixaban vs Edoxaban	€ 37091	€ 31836	€ 5,255	12.431	10.631	1.800	€ 2,919	100.0%
Apixaban vs Acenocoumarol	€ 37091	€ 28456	€ 8,635	12.431	10.168	2.263	€ 3,816	100.0%

NHS: National Health System; QALY: quality-adjusted life-years.

Table 6. Deterministic and probabilistic results from the economic analysis. Societal perspective.

	Costs			QALY			Cost/QALY	Probability
Comparison	Apixaban	Comparator	Difference	Apixaban	Comparator	Difference	Apixaban	CE Apixaban
Apixaban vs Dabigatran 110 mg	€ 60643	€ 45057	€ 15586	12.431	11.165	1.266	€ 12311	88.4%
Apixaban vs Dabigatran 150 mg	€ 60643	€ 54645	€ 5,998	12.431	11.583	0.848	€ 7,073	87.1%
Apixaban vs Rivaroxaban	€ 60643	€ 48500	€ 12143	12.431	10.035	2.396	€ 5,068	100.0%
Apixaban vs Edoxaban	€ 60643	€ 52749	€ 7,894	12.431	10.631	1.800	€ 4,386	99.6%
Apixaban vs Acenocoumarol	€ 60643	€ 51045	€ 9,598	12.431	10.168	2.263	€ 4,241	100.0%

QALY: quality-adjusted life-years.

simulation of reality. Moreover, it should be noted that the results obtained are opposite to a Spanish study published in 2020 [24], also based on clinical practice data. The probability of cost-effectiveness versus VKAs for rivaroxaban, dabigatran and apixaban would be 94%, 86% and 35%, respectively, for a willingness to pay of €22,000 per QALY gained. In this respect, a number of considerations should be made about the possible reasons for the discrepancy between the results of the two studies. The effectiveness data for the present model were obtained from the FANTASIIA study, which included 2,178 patients with NVAF, and concluded that apixaban would have a lower risk of stroke and major bleeding than dabigatran (150 mg) and rivaroxaban [9]. The economic model of Escobar et al. [24] used part of the results of a meta-analysis published in 2019 [38]. The Coleman et al. meta-analysis results differ from those obtained in two meta-analyses of 'real-life' studies [39,40]. According to this meta-analysis [38] used in the above economic analysis [24] the hazard ratio (HR) of ischemic stroke versus VKA was 1.01 (95%CI 0.87–1.17) and 0.83 (95%CI 0.75–0.93) for apixaban and rivaroxaban, respectively. However, this result differs widely from the meta-analysis obtained by Zhang et al. [40], with HRs of 0.39 (95%CI 0.27–0.65) and 0.63 (95%CI 0.47–0.85) for apixaban and rivaroxaban versus VKA, respectively. On the other hand, in the economic analysis of Escobar et al. [24], major bleeding status was not considered, being a highly relevant clinical outcome. For this reason, the HR for major bleeding from the meta-analysis by Coleman et al. [38] (HR: 0.69 [95%CI 0.63–0.75] and 0.80 [95%CI 0.71–0.91] for apixaban and rivaroxaban, respectively) was not included in that model. This result for major bleeding would be in line with that obtained in another meta-analysis published in 2022 [39], according to which the HR for major bleeding would be 0.63 (95%CI 0.57–0.68) and 0.95 (95%CI 0.87–1.03) with apixaban and rivaroxaban, respectively, compared to VKAs. Furthermore, it is striking that the above-mentioned economic analysis included a Markov state for myocardial infarction and, in the absence of data for apixaban, estimated an HR of 1.0, an assumption of dubious justification [24].

This analysis is based on clinical data obtained in the FANTASIIA study, which focused on estimating the occurrence of serious events associated with the treatment of NVAF (acute stroke, major bleeding, death). This study did not record the change of DOAC during follow-up, nor the rate of discontinuation of the different DOAC, so these aspects were not considered in the model. This aspect could be considered as a weakness of the economic model.

In addition to the possible methodological problems indicated above, it should be noted that the FANTASIIA, a cohort study that performed an indirect comparison of DOACs, results favoring apixaban over rivaroxaban and dabigatran have been corroborated in several studies published in recent years. In a large cohort study (59,172 patients treated with apixaban and 40,706 treated with rivaroxaban for 288 and 291 days, respectively), 6.6 and 8.0 stroke events per 1,000 person-years with apixaban and rivaroxaban (HR = 0.82; 95%CI 0.68–0.98), respectively, as well as 12.9 and 21.9 bleeding episodes per 1,000 person-years (HR = 0.58; 95%CI 0.52–0.66) were observed, respectively [41]. In another population-based study of apixaban compared with rivaroxaban, in a propensity score-matched cohort of 19,894 patients with NVAF (9,947 in each group), apixaban was associated with a lower rate of ischemic stroke or systemic embolism (HR, 0.57 [95%CI, 0.40 to 0.80]) and bleeding (HR, 0.51 [CI, 0.41 to 0.62]) [42]. In a third retrospective cohort study [13] involving 421,523 patients with NVAF, rivaroxaban showed a slightly increased risk (HR 1.11, 95% 95%CI: 1.06–1.16) than VKAs. In contrast, apixaban and dabigatran reduced the risk, with an HR of 0.76 (95%CI: 0.69–0.84) and 0.85 (95%CI 0.75–0.96), respectively.

5. Conclusions

Based on the analyses performed, according to the results of the FANTASIIA study (under clinical practice conditions), it can be concluded that apixaban is a cost-effective treatment compared to dabigatran, rivaroxaban, edoxaban and acenocoumarol in the treatment of patients with NVAF. The probability of apixaban being cost-effective ranges from 91.1% (vs dabigatran 150 mg), 97.8% (vs dabigatran 110 mg) to 100% (vs rivaroxaban, edoxaban and acenocoumarol).

Considering the PVP-IVA of generic apixaban, it was also cost-effective versus all comparators, with costs per QALY gained ranging from €352 (compared to edoxaban) to €3,815 (compared to dabigatran 110 mg).

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Declaration of interest

D Rubio-Rodríguez and C Rubio-Terrés are senior consultant and director, respectively, of Health Value and were paid consultants to Pfizer and Bristol Myers Squibb in connection with the development of this manuscript. J Soto and S Fernández are employees of Pfizer SLU, Madrid, Spain. M Anguita and F Marín were paid consultants to Pfizer and Bristol Myers Squibb in connection with 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.

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Authors contributions

M Anguita, F Marín, J Soto, S Fernández, D Rubio-Rodríguez and C Rubio-Terrés made the conceptualization of the economic model. D Rubio-Rodríguez and C Rubio-Terrés designed and conducted the economic model and wrote the first draft. All authors interpreted the data, reviewed, edited and agreed on the final version.

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