Volume 16

Number 5

September - October 2014

EUROPEAN JOURNAL *of* Clinical Pharmacy

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JOURNAL EDITED BY
RASGO EDITORIAL, S. L.
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ORIGINAL

COST-EFFECTIVENESS ANALYSIS OF APIXABAN VERSUS DABIGATRAN FOR PREVENTION OF STROKE IN PATIENTS WITH NON-VALVULAR ATRIAL FIBRILLATION IN SPAIN

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ABSTRACT

Objective: To assess the cost-effectiveness of apixaban vs. dabigatran in stroke prevention in patients with non-valvular atrial fibrillation (NVAF) in Spain.

Method: A Markov model was developed, with cycles of six weeks, throughout the patient's life and 10 health states. The analysis was done from the Spanish National Health System (SNS) and societal perspective. The safety and efficacy of the drugs were obtained from a meta-analysis of pairwise indirect comparisons. Drug costs (apixaban 10 mg/day [5 mg bid]; dabigatran: 220 [110 mg bid] or 300 [150 mg bid] mg/day), NVAF complications and disease management costs were obtained from Spanish sources. An annual discount rate of 3.5% for costs and health outcomes was applied.

Results: In a cohort of 1,000 patients with NVAF during their lifetime, apixaban were projected to avoid numerous complications versus dabigatran (24 ischemic strokes and 28 related deaths vs. dabigatran 110 mg bid; 11 ischemic strokes, 29 bleedings and 19 deaths vs. dabigatran 150 mg bid). Consequently, each patient treated with apixaban could obtain more years of life (0.126 and 0.084 LYG, respectively) and more quality-adjusted life-years (0.107 and 0.071 QALY, respectively).

Apixaban generated higher overall costs per patient vs. dabigatran 110 mg bid from the SNS perspective (€139) but savings would arise from the societal perspective (–€524), with a cost per LYG and QALY gained of €1,103 and €1,299 for the SNS, and apixaban being dominant (more effective with less cost than dabigatran 110 mg bid) for the Society. The cost per QALY gained, from the SNS and societal perspective, compared with dabigatran 150 mg bid would be €6,591 and €10,676, respectively. Deterministic and probabilistic sensitivity analyses confirmed the stability of these results.

Conclusion: According to the model outcomes, apixaban would be cost-effective versus dabigatran for the prevention of stroke in patients with NVAF in Spain.

Apixaban – Dabigatran – Cost-effectiveness – Non-valvular Atrial Fibrillation

RESUMEN

Objetivo: Llevar a cabo un análisis de coste-efectividad de apixaban frente a dabigatrán en la prevención del ictus en pacientes con fibrilación auricular no valvular (FANV) en España.

Método: Modelo de Markov, con ciclos de seis semanas, durante toda la vida del paciente y 10 estados de salud como ictus, sangrados y otras complicaciones cardiovasculares. La seguridad y eficacia de los fármacos se obtuvieron de

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This study has been jointly financed by Bristol-Myers Squibb, S.A. and Pfizer S.L.U. Lourdes Betegón, Cristina Canal and Víctor Fernández Gallego are employees of Bristol-Myers Squibb, S.A. Marina de Salas is an employee of Pfizer S.L.U. The rest of the authors have received payment from Bristol-Myers Squibb, S.A. and Pfizer S.L.U. for their participation in the study.

Eur J Clin Pharm 2014; 16(5): 325-38.

Received: 13/03/2014.
Accepted: 14/05/2014.

un metaanálisis de comparaciones indirectas por parejas. Las perspectivas del análisis consideradas fueron la del Sistema Nacional de Salud (SNS) y de la sociedad. El cálculo del coste de los medicamentos se realizó según las dosis recomendadas (apixaban: 10 mg/día [5 mg bid]; dabigatrán: 220 [110 mg bid] y 300 [150 mg bid] mg/día). El coste de las complicaciones de la FANV y del manejo de la enfermedad se obtuvo de fuentes españolas. Para costes y resultados sanitarios se aplicó una tasa de descuento del 3,5% anual.

Resultados: En una cohorte de 1.000 pacientes con FANV, con apixaban se evitarían un gran número de complicaciones (24 ictus isquémicos y 28 muertes relacionadas en comparación con dabigatrán 110 mg bid; 11 ictus isquémicos, 29 sangrados y 19 muertes frente a dabigatrán 150 mg bid). Así mismo, en cada paciente tratado con apixaban se obtendrían más años de vida (0,126 y 0,084 AVG, respectivamente) y más años de vida ajustados por calidad (0,107 y 0,071 AVAC ganados, respectivamente). Con apixaban se generarían más costes por paciente que con dabigatrán 110 mg bid para el SNS (139 €), pero se producirían ahorros desde la perspectiva social (–524 €), con un coste por AVG y AVAC ganado de 1.103 € y 1.299 € para el SNS, siendo apixaban dominante (más eficaz con menos costes que dabigatrán 110 mg bid) desde la perspectiva de la sociedad. El coste por AVAC ganado, desde la perspectiva del SNS, en comparación con dabigatrán 150 mg bid es de 6.591 €. Los análisis de sensibilidad determinísticos y probabilísticos confirmaron la estabilidad del caso base para ambas perspectivas.

Conclusión: Según el presente estudio, se puede llegar a la conclusión de que apixaban es un tratamiento coste-efectivo en comparación con dabigatrán en la prevención del ictus en pacientes con FANV.

Apixaban – Dabigatrán – Coste-efectividad – Fibrilación auricular no valvular

INTRODUCTION

Atrial fibrillation (AF) is a cardiac arrhythmia associated to aging, arterial hypertension, valve disease and other heart disorders.[1] Atrial fibrillation is associated to an increased mortality risk (2-fold compared with the absence of AF), cerebrovascular disease (5-fold) and systemic embolism.[1]

Atrial fibrillation has an important impact in Spain, with an estimated prevalence of 2% in the general population[1] and a mean annual cost per patient of €2,365.[2] The economic impact of the disease is moreover increased by the high cost of its associated complications in both the acute phase and at long term. As an example, the estimated cost of cardioembolic stroke in the first 38 days after the event is €13,647 (of which 49.2% is generated by hospital stay and 24.8% by rehabilitation).[3]

The vitamin K antagonists (acenocoumarol and warfarin, vitamin K antagonists [VKA]) are currently the standard treatment for the prevention of stroke in patients with AF.[4] However, despite the recommendations of the treatment guides, approximately 30-50% of all patients with AF and at moderate to high risk of suffering stroke receive ineffective treatment or even no treatment.[5, 6] On the other hand, the use of VKA is limited by bleeding risk, a narrow therapeutic margin and inconveniences for the patient derived from the need for monitoring and interactions with drugs and foods. Although dose-adjusted VKA reduce the risk of stroke by 64% versus placebo, they also double the risk of additional and intracranial bleeding.[7]

Since 2011 a new family of oral anticoagulants has become available, with indications for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF) in Europe. At present there are three new oral anticoagulants (NOA): dabigatran (a direct thrombin inhibitor), apixaban and rivaroxaban (direct inhibitors of coagulation factor Xa).

According to the recommendations of the European Society of Cardiology,[8] the NOA (apixaban, rivaroxaban and dabigatran) are preferable to the VKA in treating most cases of NVAF, since they are comparatively not inferior in terms of efficacy and moreover reduce the number of intracranial bleeding episodes.

Two clinical trials have compared apixaban and dabigatran, respectively, versus warfarin. The ARISTOTLE study, a randomized, double-blind clinical trial, compared the efficacy and safety of apixaban versus warfarin in 18,201 patients with NVAF.[9] The results of this study showed apixaban 5 mg administered twice a day to be superior to warfarin in preventing stroke and systemic embolism (HR 0.79; 95% CI, 0.66-0.95; $p < 0.001$), with fewer major bleeding episodes (HR 0.69; 95% CI, 0.6-0.8; $p < 0.001$), and lesser mortality due to any cause (HR 0.89; 95% CI, 0.8-0.99; $p = 0.047$).[9] The RE-LY study, another randomized, double-blind clinical trial, compared the efficacy and safety of two dabigatran doses (150 or 110 mg), both administered twice a day, versus warfarin in 18,113 patients with NVAF.[10] Dabigatran 150 mg administered twice a day showed greater efficacy than warfarin in preventing stroke and systemic embolism (relative risk reduction [RRR] 35%), with a significant decrease in the risk of intracranial bleeding (RRR 59%). Dabigatran 110 mg administered twice a

TABLE 1. Population and risks considered in the Markov model.

Item		*Mean*	*Interval*	*References*
Population characteristics				
— Patients in which VKA are indicated		Yes	–	9
— Females		35.3%	–	9
— Mean age (years)		70	–	9
— Mean $CHADS_2$ score		2.1	–	9
Hazard ratios of dabigatran versus apixaban				
— Stroke (excluding hemorrhagic stroke)	Dabigatran (110 mg bid)	1.198	0.878-1.635	20
	Dabigatran (150 mg bid)	0.823	0.593-1.141	20
— Myocardial infarction	Dabigatran (110 mg bid)	1.474	0.958-2.269	20
	Dabigatran (150 mg bid)	1.456	0.948-2.238	20
— Systemic embolism	Dabigatran (110 mg bid)	1	–	Assumption*
	Dabigatran (150 mg bid)	1	–	Assumption*
— Other CV hospitalizations [1]	Dabigatran (110 mg bid)	1	–	Assumption*
	Dabigatran (150 mg bid)	1	–	Assumption*
— Other AC treatment suspensions [1]	Dabigatran (110 mg bid)	1.452	1.309-1.611	20
	Dabigatran (150 mg bid)	1.505	1.357-1.668	20
— IC bleeding	Dabigatran (110 mg bid)	0.733	0.428-1.257	20
	Dabigatran (150 mg bid)	1.02	0.619-1.681	20
— Other major bleeding	Dabigatran (110 mg bid)	1.205	0.965-1.504	20
	Dabigatran (150 mg bid)	1.371	1.102-1.705	20
— Clinically relevant non-major bleeding	Dabigatran (110 mg bid)	1.155	0.986-1.354	20
	Dabigatran (150 mg bid)	1.303	1.113-1.526	20
— Anticoagulant treatment suspension	Dabigatran (110 mg bid)	1.452	1.309-1.611	20
	Dabigatran (150 mg bid)	1.505	1.357-1.668	20
— Additional mortality risk	NVAF	1.34	–	24
	Stroke (mild/moderate/severe)	3.18/5.84/15.75	–	25
	MI (males/females)	4.16/2.56	–	22
	Systemic embolism	1.34	–	22
— Stroke risk adjustment factor per decade of life		1.4	–	27
— Bleeding risk adjustment factor per decade of life		1.97	–	21
— % hemorrhagic stroke in IC bleeding	Dabigatran (110 mg bid)	64%	–	10
	Dabigatran (150 mg bid)	41%	–	10
— % GI bleeding in other major bleeding	Dabigatran (110 mg bid)	41%	–	10
	Dabigatran (150 mg bid)	49%	–	10
ASA treatment after suspension [2]				
— Ischemic stroke rate (per 100 persons-year)		3.453	–	23
— MI rate (per 100 persons-year)		1.11	–	23
— Intracranial bleeding rate (per 100 persons-year)		0.322	–	23
— Other major bleeding rate (per 100 persons-year)		0.887	–	23
— CRNM bleeding rate (per 100 persons-year)		2.936	–	23

1: Not due to stroke or MI.
2: Treatment with ASA was considered after suspension of the previous AC treatment due to major bleeding or other reasons. It was also considered that the severity distribution of ischemic or hemorrhagic stroke would be equal to that observed with ASA in first-line treatment (AVERROES study).
*: Due to the lack of data, the same risk as observed with apixaban is assumed.
Abbreviations: AC: anticoagulant; ASA: acetylsalicylic acid; CRNM: Clinically Relevant Non-Major bleeding; CV: Cardiovascular; GI: Gastrointestinal; HR: Hazard Ratio; IC: Intracranial; MI: Myocardial Infarction; VKA: antagonists of vitamin K (acenocoumarol);.

day was not found to be superior to warfarin in preventing stroke and systemic embolism, though it was associated with a significantly lesser risk of major bleeding (RRR 20%). The results referred to apixaban were therefore the only data showing statistically significant differences in the following three efficacy variables: prevention of stroke or systemic embolism, reduction of major bleeding risk, and reduction of mortality due to any cause.[9, 10]

To date, no clinical trials have directly compared the NOA. However, there are several indirect comparison meta-analyses which in general do not suggest relevant differences in efficacy among the NOA [11-14] —though the frequency of major bleeding appears to be lower with apixaban 5 mg twice a day (bid) and with dabigatran 110 mg bid.[8, 11, 14] A recent network meta-analysis [15] suggests that apixaban 5 mg bid and dabigatran 110 mg bid may offer the best benefit-risk ratio in the prevention of stroke in NVAF.

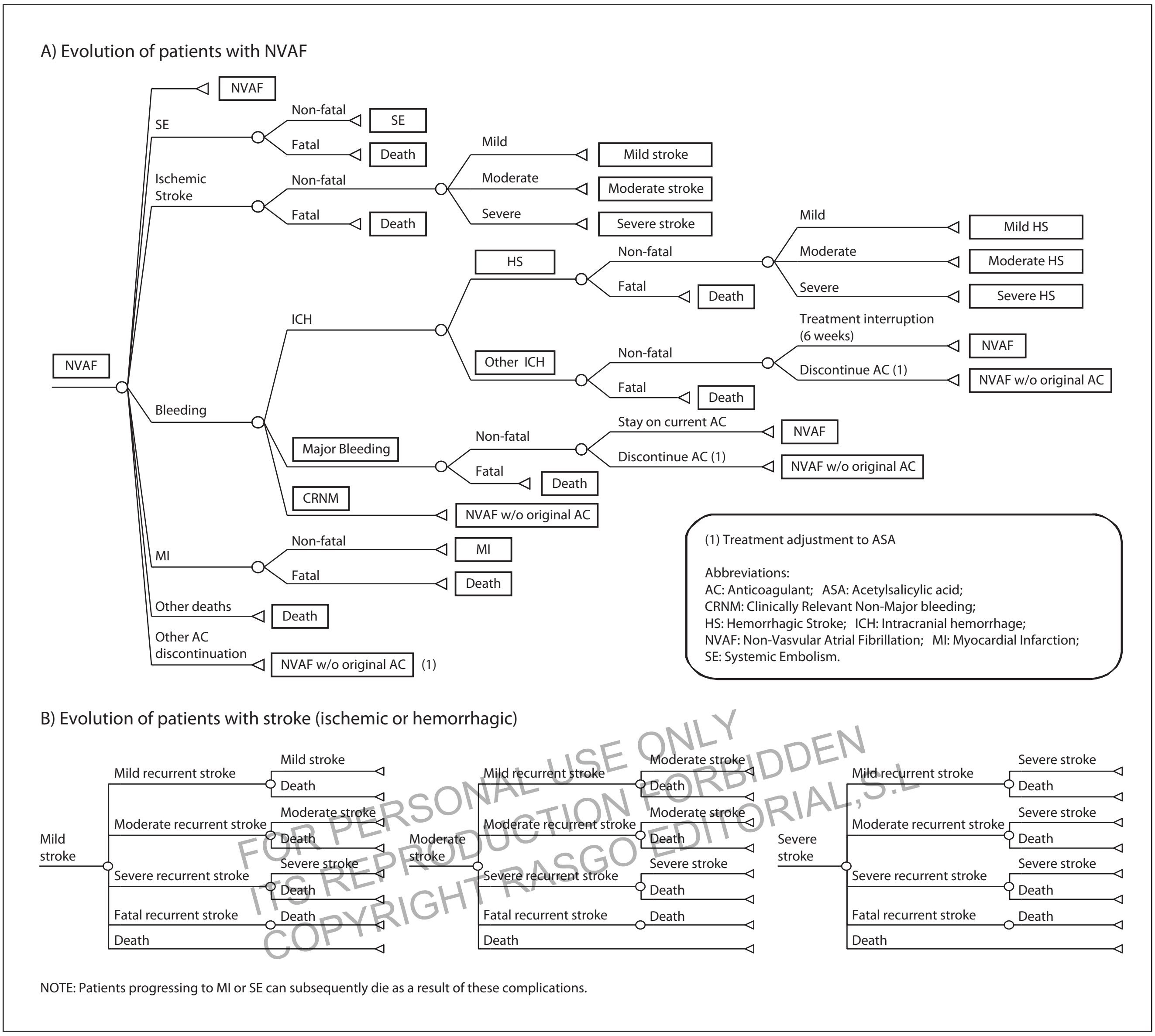

FIG. 1. **Markov economic model for stroke prevention in patients with NVAF.**

The present study aims to conduct a cost-effectiveness analysis of the prevention of stroke and systemic embolism with apixaban or dabigatran in patients with NVAF.

METHOD

Cost-effectiveness analysis is a particularly useful instrument that facilitates decision making by the policy makers of the Spanish National Health System (*Sistema Nacional de Salud*, SNS), since it allows integration and comparison of the effectiveness and cost of two drugs in a single efficiency variable: the cost per life year gained (LYG) or the cost per quality-adjusted life year gained (QALY) with the most effective of the comparator treatments. These analyses are generally made based on economic models, which allow us to simulate the long-term evolution of hypothetical patient cohorts using the efficacy and safety data obtained from clinical trials in real patients. These models moreover allow introduction of the Spanish healthcare costs and resources associated to the mentioned patient evolution.[16]

The characteristics of the present model have been published elsewhere.[17, 18] It was designed to compare the efficiency of apixaban and dabigatran in patients with NVAF, analyzing the lifetime course (with a life expectancy of 80.4 years for both sexes) of a hypothetical cohort of 1,000 patients with NVAF and exhibiting the characteristics of those subjects included in the ARISTOTLE trial, which compared the efficacy and safety of apixaban and warfarin in application to AF.[9] These characteristics were: patients in which VKA are indicated; 35.3% females; mean age 70 years; and a mean $CHADS_2$ score of 2.1 (Table 1). It should be underscored that these characteristics are very similar to those of the patients included in the RE-LY trial (patients in which VKA are indicated; 36.8% females; mean age 71.5 years; and a mean $CHADS_2$ score of 2.1).[10]

TABLE 2. Utilities considered in the Markov model.

Item	*Mean*	*References*
Utilities of the Markov states		
— Non-valvular atrial fibrillation (basal)	0.727	29
— Mild stroke [1]	0.6151	29
— Moderate stroke [1]	0.5646	29
— Severe stroke [1]	0.5142	29
— Systemic embolism	0.6265	29
— Myocardial infarction	0.6098	29
Loss of utilites (duration)		
— Intracranial bleeding	0.1511 (6 weeks)	29
— Other major bleeding	0.1511 (2 weeks)	29, 30
— CRNM bleeding	0.0582 (2 days)	29, 30
— CV hospitalization due to other causes	0.1276 (6 days)	29
— Use of apixaban and dabigatran	0	Estimate

1: Ischemic or hemorrhagic; CV: cardiovascular; CRNM: Clinically Relevant Non-Major bleeding.

The model used is the Markov design (the best type of model for simulating chronic diseases)[19] (Fig. 1), with cycles of 6 weeks and 10 main health states: (i) NVAF; (ii) ischemic stroke; (iii) hemorrhagic stroke; (iv) other intracranial bleeding; (v) other major bleeding; (vi) clinically relevant non-major bleeding; (vii) myocardial infarction; (viii) systemic embolism; (ix) NVAF with suspension of anticoagulant therapy; and (x) death due to other causes different from the above complications. Stroke (ischemic or hemorrhagic) was classified as mild, moderate or severe. The entire patient cohort starts in NVAF, and in each cycle the subjects either remain in NVAF or progress towards the other states, according to certain transition probabilities. These probabilities of transition among the different health states, referred to the efficacy (prevention of stroke and of other vascular complications or recurrences) and safety (bleeding, deaths) of the comparator drugs, were mainly collected from an *ad hoc* indirect comparisons meta-analysis[20] and from other sources where necessary.[10, 21-27] According to the model, in each patient only one complication can occur per cycle, and only one recurrence of stroke (ischemic or hemorrhagic) is allowed. The rate of complications per 100 persons-year and the hazard ratios (HR) of these complications with dabigatran versus apixaban, which were adjusted according to the $CHADS_2$, and the quality of INR (international normalized ratio) control according to the TTR (time in therapeutic range), are shown in Table 1.

The general mortality among females and males under or over 75 years of age was obtained by adjusting the published Spanish mortality data (www.mortality.org)[28] to a Gompertz function in order to predict mortality due to all causes and exclude mortality due to stroke and bleeding —thereby avoiding double counts. It was assumed that after suspending anticoagulant therapy (dabigatran or apixaban) due to major bleeding or for other reasons, the patients would switch to acetylsalicylic acid (ASA, aspirin). In the event of such a change in treatment, we applied the severity distribution of the cases of stroke produced during treatment with ASA as observed with ASA in first-line treatment (AVERROES study).[23]

The differences in treatment efficacy were measured in terms of life years gained (LYG) and quality-adjusted life years gained (QALY). The utilities of the different health states (according to patient perception) used to calculate the corresponding QALY were obtained from a study conducted in the United Kingdom, based on an EQ-5D type questionnaire among patients with AF.[29] The utilities of the health conditions and the loss of utilities associated to the complications considered in the model, indicated in Table 2, were likewise obtained from the literature.[30] These utilities are identical for both treatments, and no utility loss associated to the use of dabigatran and apixaban was assumed.

The data referred to resource utilization and the unit costs were obtained from Spanish sources (€ of 2012) (Table 3). The cost-effectiveness analysis was performed from two perspectives: that of the Spanish National Health system (SNS) (considering only the direct healthcare costs) and that of society (including also the direct non-healthcare costs). The following direct healthcare costs were included: purchasing cost of the anticoagulants (dabigatran and apixaban having the same cost per day of treatment); cost of the acute episodes and posterior treatment of the vascular complications; cost associated to the dyspepsia which may be generated by anticoagulant therapy (1.7%, 3.7% and 4.5% with apixaban and dabigatran 110 mg and 150 mg bid, respectively)[9, 10] and to the renal monitoring required by the treatment (one control a year for both treatments); and the cost of the routine control visits of the patients with NVAF. The cost of the medications —retail price with VAT applying the 7.5% deduction contemplated by Spanish Royal Decree 8/2010— was calculated on the basis of the doses recommended in the respective Summaries of Product Characteristics (apixaban: 10 mg/day, administered as

TABLE 3. Costs considered in the Markov model.

			Cost (€)	*Unit*	*Duration*	*Source*
Routine control			35.32	Per visit	NA	AC public prices
Ictus						
— Direct costs	Mild	Acute phase	5,970.09	Per episode	2 weeks	AC public prices
		Maintenance	120.01	Monthly	For life	35
	Moderate	Acute phase	6,281.38	Per episode	2 weeks	AC public prices
		Maintenance	742.59	Monthly	For life	35
	Severe	Acute phase	6,951.01	Per episode	2 weeks	AC public prices
		Maintenance	2,081.85	Monthly	For life	35
	Fatal		5,910.08	Per episode	NA	AC public prices
— Indirect costs	Mild	Acute phase	252.39	Per episode	2 weeks	33
		Maintenance	1,367.57	Monthly	For life	33
	Moderate	Acute phase	666.11	Per episode	2 weeks	33
		Maintenance	1,789.53	Monthly	For life	33
	Severe	Acute phase	1,031.69	Per episode	2 weeks	33
		Maintenance	1,942.61	Monthly	For life	33
Hemorrhagic stroke						
— Direct costs	Mild	Acute phase	7,575.44	Per episode	2 weeks	AC public prices
		Maintenance	120.01	Monthly	For life	35
	Moderate	Acute phase	7,886.73	Per episode	2 weeks	AC public prices
		Maintenance	742.59	Monthly	For life	35
	Severe	Acute phase	8,556.36	Per episode	2 weeks	AC public prices
		Maintenance	2,081.85	Monthly	For life	35
	Fatal		7,515.44	Per episode	NA	AC public prices
— Indirect costs	Mild	Acute phase	252.39	Per episode	2 weeks	33
		Maintenance	1,367.57	Monthly	For life	33
	Moderate	Acute phase	666.11	Per episode	2 weeks	33
		Maintenance	1,789.53	Monthly	For life	33
	Severe	Acute phase	1,031.69	Per episode	2 weeks	33
		Maintenance	1,942.61	Monthly	For life	33
Other intracranial bleeding			7,515.44	Per episode	NA	AC public prices
Other major bleeding						
— GI bleeding			3,431.91	Per episode	NA	36
— Non-intracranial/GI bleeding			3,431.91	Per episode	NA	36
CRNM			2,304.66	Per episode	NA	36
— MI	Acute phase		10,513.37	Per episode	NA	AC public prices
	Maintenance		164.81	Monthly	For life	35
— SE	Acute phase		2,846.5	Per episode	2 weeks	AC public prices
	Maintenance		116.84	Monthly	For life	34
Other CV hospitalizations			4,729.67	Per episode	NA	AC public prices
Cost of dyspepsia			27.39	Monthly	NA	32
Cost of renal monitoring			14.76	Annually	NA	37
Monthly cost of anticoagulant management						
— Apixaban			1.69	Monthly	NA	Calculated using the cost of dyspepsia and the % of patients with dyspepsia and the cost of renal monitoring and the % of patients with renal monitoring
— Dabigatran 110 mg bid			2.24	Monthly	NA	
— Dabigatran 150 mg bid			2.24	Monthly	NA	
Mean daily drug cost (retail price with VAT –7.5% discount)						
— Apixaban			2.8	Daily	NA	31
— Dabigatran 110 mg bid			2.8	Daily	NA	31
— Dabigatran 150 mg bid			2.8	Daily	NA	31

AC: Autonomous Community; ASA: acetylsalicylic acid; CRNM: Clinically Relevant Non-Major bleeding; CV: cardiovascular; GI: gastrointestinal; MI: Myocardial Infarction; NA: Not Applicable; SE: Systemic Embolism.

TABLE 4. Expected number of episodes during follow-up for life in a cohort of 1,000 patients with NVAF. Comparisons with dabigatran (110 and 150 mg bid).

Complication	*Apixaban*	*Dabigatran 110 mg bid*	*Difference*
Ischemic stroke*	263	287	–24
Hemorrhagic stroke*	29	19	10
Intracranial bleeding	13	13	0
Systemic embolism	25	27	–2
Other major bleeding	169	160	9
CRNM	295	295	0
Myocardial infarction	87	99	–12
Other CV hospitalizations	1,219	1,210	9
Other treatment suspensions	644	721	–77
Deaths per episodes (acute phase)	62	67	–5
Deaths per episodes (maintenance)	318	341	–23

Complication	*Apixaban*	*Dabigatran 150 mg bid*	*Difference*
Ischemic stroke*	263	274	–11
Hemorrhagic stroke*	29	19	10
Intracranial bleeding	13	19	–6
Systemic embolism	25	28	–3
Other major bleeding	169	174	–5
CRNM	295	313	–18
Myocardial infarction	87	100	–13
Other CV hospitalizations	1,219	1,227	–8
Other treatment suspensions	644	736	–92
Deaths per episodes (acute phase)	62	67	–5
Deaths per episodes (maintenance)	318	332	–14

Abbreviations: CRNM: Clinically Relevant Non-Major bleeding.
* Indicates both initial and recurrent stroke.

two 5-mg doses; dabigatran: 300 and 220 mg/day, administered as two doses of 150 mg and 110 mg, respectively).[31] Dose selection is based on the data obtained from the individualized assessment of thromboembolic risk and bleeding risk in each patient. The patient characteristics are: age between 75-80 years, individuals with moderate renal failure, gastritis, esophagitis or gastroesophageal reflux, or other subjects with increased bleeding risk. On the basis of expert opinion, it was considered that all the patients, independently of the treatment received, would report for a routine AF follow-up visit every three months in the clinical practice setting. The cost of the complications of NVAF in the acute phase (based on diagnosis-related groups [DRG], including all the costs of the period in which the patient is hospitalized) was obtained from the mean of the public prices in the different Spanish Autonomous Communities. The cost of the treatment of the complications after the acute phase, estimated in terms of the monthly cost for life, was obtained from other Spanish sources[32-37] (Table 3). Regarding the direct non-healthcare costs included in the analysis from the perspective of society, we included those derived from informal care (help for dependent patients and adaptation of the home) of individuals who suffer ischemic or hemorrhagic stroke[33] (Table 3). With the purpose of converting the healthcare costs and outcomes expected in future (over the entire life of the patients) to values corresponding to the current year, we applied an annual 3.5% discount rate to the healthcare costs and outcomes.

A base case with the mean values of all the parameters was analyzed from the perspective of the SNS and society. In order to corroborate the stability of the results obtained in the base case, we conducted simple univariate sensitivity analyses (modifying the baseline value of a variable in each sensitivity analysis, applying its extreme values) for all the variables considered in the model —presenting only those results of the variables with the greatest impact. Lastly, we performed a probabilistic analysis (Monte Carlo simulation with 2,000 simulations in the cohort of 1,000 patients) simultaneously including all the variables of the analysis, adjusted to the statistical distributions pertinent in each case (beta for the transition and utility probabilities, and gamma for the costs).[38]

RESULTS

Episodes avoided. Considering a cohort of 1,000 patients with NVAF, apixaban would avoid many complications in the course of the patient lifetime (24 cases of ischemic stroke and 28 related deaths compared with dabigatran 110 mg bid; 11 cases of ischemic stroke, 29 cases of bleeding [including intracranial bleeding, major bleeding,

TABLE 5. Results of the cost-effectiveness analysis of apixaban versus dabigatran.

Comparison with dabigatran 110 mg bid	*Apixaban*	*Dabigatran*	*Difference*
Perspective of the SNS			
— Life years	9.037	8.911	0.126
— Quality-adjusted life years	6.424	6.317	0.107
— Total costs (€)	18,029	17,890	139
— Cost per LYG (€)		1,103	
— Cost per QALY (€)		1,299	
Perspective of society *			
— Life years	9.037	8.911	0.126
— Quality-adjusted life years	6.424	6.317	0.107
— Total cost (€)	29,193	29,717	–524
— Cost per LYG		Apixaban dominantes **	
— Cost per QALY		Apixaban dominantes **	
Comparison with dabigatran 150 mg bid	*Apixaban*	*Dabigatran*	*Difference*
Perspective of the SNS			
— Life years	9.037	8.953	0.084
— Quality-adjusted life years	6.424	6.353	0.071
— Total costs (€)	18,029	17,561	468
— Cost per LYG (€)		5,571	
— Cost per QALY (€)		6,591	
Perspective of society *			
— Life years	9.037	8.953	0.084
— Quality-adjusted life years	6.424	6.353	0.071
— Total costs (€)	29,193	28,435	758
— Cost per LYG (€)		9,024	
— Cost per QALY (€)		10,676	

* Including the direct non-healthcare costs corresponding to the help of patients with dependency due to stroke.
** Apixaban is more effective and with fewer costs than dabigatran.
Abbreviations: LYG: Life-Year Gained; QALY: Quality-Adjusted Life Years; SNS: Spanish National Health System.

and clinically relevant non-major bleeding] and 19 deaths compared with dabigatran 150 mg bid) (Table 4).

Cost-effectiveness. Consequently, for each patient treated with apixaban we would obtain more life years (0.126 and 0.084 LYG compared with dabigatran 110 mg bid and 150 mg bid, respectively) and more quality-adjusted life years (0.107 and 0.071 QALY, respectively) (Table 5).

From the perspective of the SNS, apixaban would generate more costs (€139 and €468, respectively). This is mainly due to the fact that on average, patients treated with apixaban live longer than patients treated with dabigatran; consequently the duration of treatment with apixaban is comparatively longer. The additional cost of apixaban versus dabigatran 150 mg bid is greater than with the 110 mg bid dose, fundamentally because of the lesser frequency of ischemic stroke and the greater incidence of treatment suspension related to bleeding with the larger dabigatran dose (Tables 4 and 5). The cost per LYG and QALY associated with apixaban respectively would be €1,103 and €1,299 (low dabigatran dose) and €5,571 and €6,591 (high dabigatran dose) (Table 5). In all cases this is less than the €30,000 threshold or cutoff point generally accepted in Spain, below which a new treatment is considered to be cost-effective.

From the perspective of society, apixaban would be the dominant treatment (more effective and with fewer costs) versus dabigatran 110 mg bid, and the cost per LYG and QALY versus dabigatran 150 mg bid would be €9,024 and €10,676, respectively (Table 5).

Sensitivity analysis. The sensitivity analyses confirmed that apixaban is cost-effective compared with dabigatran. According to the deterministic sensitivity analysis, the variation of the most sensitive study variables (risk of ischemic stroke, risk of cardiovascular hospital admission during treatment with apixaban or ASA in second-line therapy, cost of hemorrhagic stroke, etc.) exerted no relevant effect upon the analytical results, since in all cases the cost of one LYG or the cost of one QALY with the most effective treatment (apixaban) was below the mentioned cutoff point of €30,000 (Fig. 2).

According to the probabilistic sensitivity analysis, the probability that apixaban is cost-effective would be 99.3% versus the low dabigatran dose and 91.6% versus the high dabigatran dose (Fig. 3).

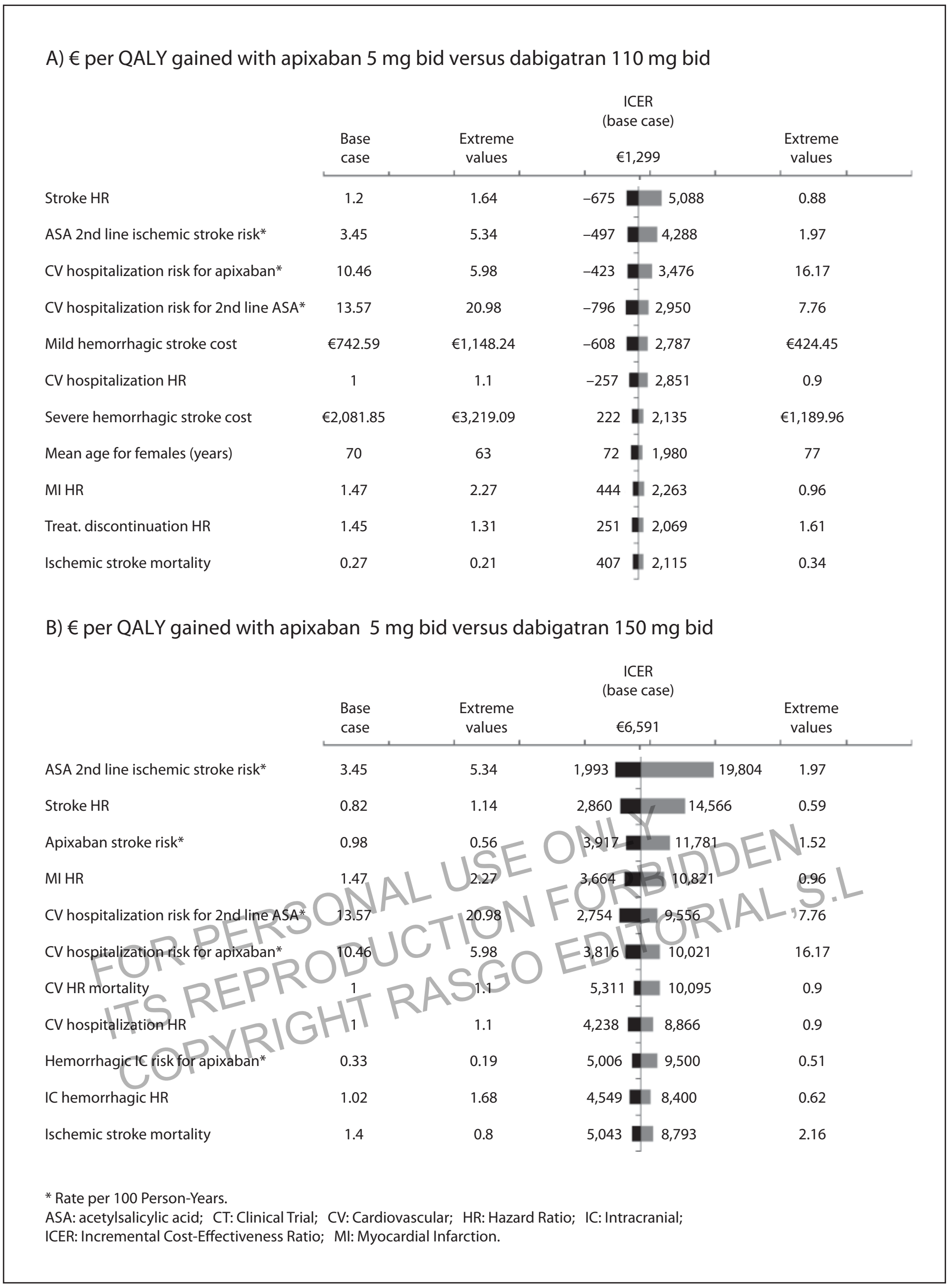

FIG. 2. Deterministic sensitivity analysis conducted from the perspective of the National Health System. Tornado chart. (€ in 2012).

DISCUSSION

Pharmacoeconomic models allow us to conduct economic simulations of complex healthcare processes related to drugs. Such models are useful when no pragmatic clinical trials are available, thanks to their great external validity, and in simulating the evolution of a disease beyond the duration of clinical trials.[16] Markov models are preferable to deterministic constructs, particularly in the case of chronic disorders such as NVAF, since they are better able to simulate the long-term clinical course of the disease.[19]

According to our economic model, apixaban would avoid a considerable number of complications (stroke, bleeding), treatment suspensions and deaths, and constitutes a cost-effective treatment compared with dabigatran for the prevention of stroke in Spanish patients with NVAF. From the perspective of society, apixaban would be the dominant treatment (more effective, with fewer costs) versus dabigatran 110 mg bid, due to inclusion of the costs corresponding to informal care.

In evaluating these results, a number of study limitations and consistency factors must be taken into account. Firstly, this is a theoretical model, i.e., by definition it constitutes a simplified simulation of reality. On the other hand, the data referred to efficacy and adverse effects have been obtained from an *ad hoc* indirect comparisons meta-analysis,[20] due to the lack of clinical trials estab-

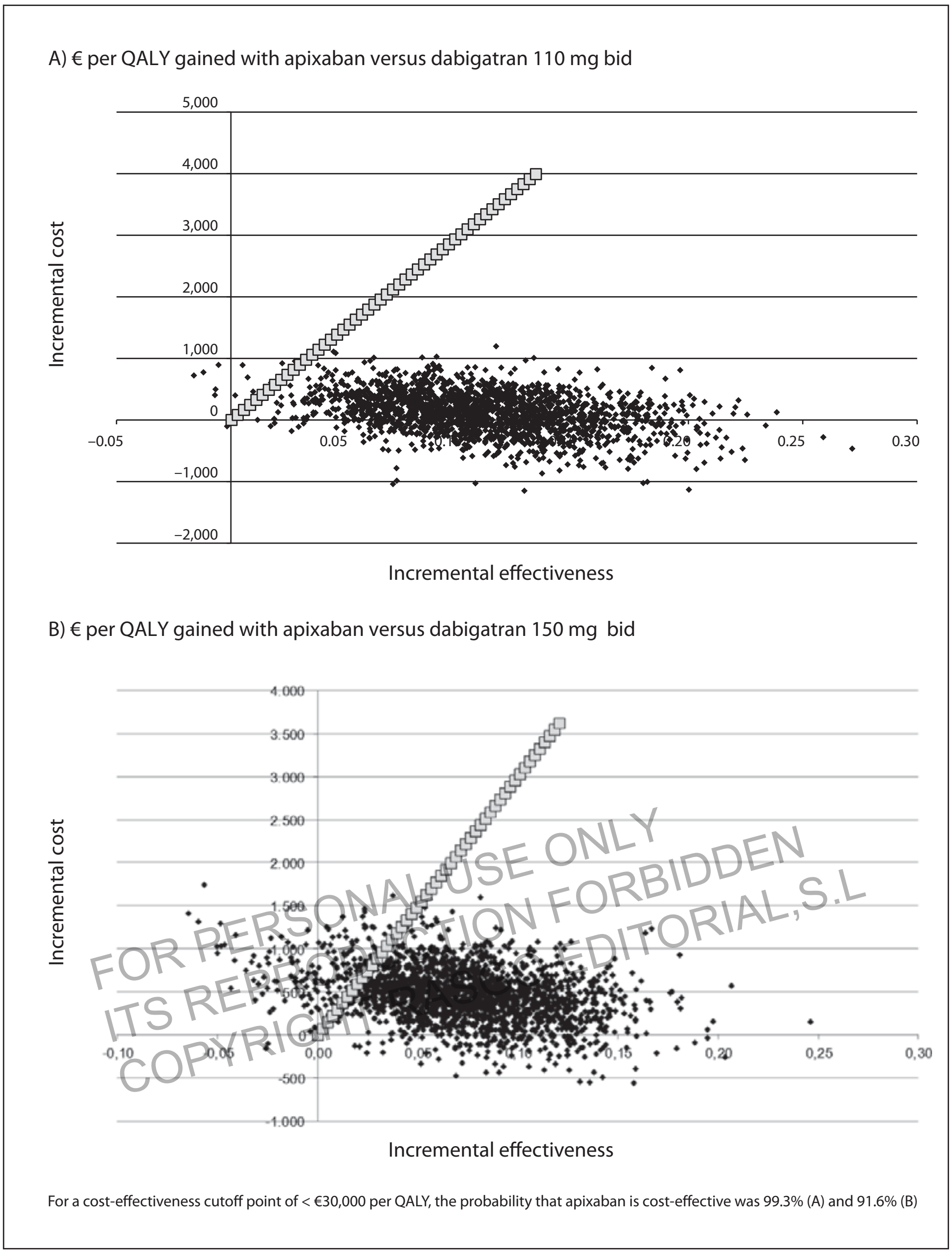

FIG. 3. Probabilistic sensitivity analysis conducted from the perspective of the National Health System. Incremental cost-effectiveness ratio (€ in 2012).

lishing direct comparisons of the different treatments. Nevertheless, provided they are conducted with rigor and using adequate methodology, indirect comparisons meta-analyses are useful tools, as recognized by drug evaluation agencies such as the National Institute for Health and Clinical Excellence [39] or the GENESIS group,[40] in those cases in which studies directly comparing the alternatives are not available. On the other hand, the stability of the results obtained in the base case of the analysis has been confirmed by deterministic and probabilistic sensitivity analyses, indicating a high probability that apixaban is cost-effective versus dabigatran (99.3% and 91.6% compared with the 110 mg bid and 150 mg bid doses, respectively).

The present study represents the first cost-effectiveness analysis of apixaban versus dabigatran in NVAF conducted in Spain. We have identified an economic analysis (Markov model) carried out in the United States, in which the cost-effectiveness of apixaban, dabigatran and rivaroxaban versus warfarin was compared in NVAF.[41] According to the Monte Carlo simulation made in this study, the probability of being cost-effective versus warfarin (< 50,000 USD) would be 45.1% for apixaban, 40% for dabigatran, and 14.9% for rivaroxaban. This model is very different in terms of its structure and premises from our own model, and the results are therefore not comparable. Other economic analyses have compared the cost-effectiveness of apixaban versus warfarin[42] and ASA,[43] and of dabigatran versus warfarin,[30, 44-53] ASA[54] and rivaroxaban,[54] in the primary prevention of stroke in NVAF. However, these analyses are of scant interest for the comparison of apixaban and dabigatran. The literature also offers an effectiveness model based on microsimulations and indirect comparisons between apixaban (ARISTOTLE study), dabigatran (RE-LY study) and rivaroxaban (ROCKET-AF study), with warfarin as common comparator drug, in the management of patients with NVAF. The results indicate that for a life-long time horizon, 0.130, 0.106 and 0.095 QALY would be gained per patient, respectively. Thus, according to these analyses, apixaban would be the most effective treatment.[55]

According to our findings, it can be concluded that apixaban constitutes a cost-effective treatment compared with dabigatran for the prevention of stroke in patients with NVAF, on the basis of the cost-effectiveness cutoff point generally accepted in Spain.[56] CP

ACKNOWLEDGMENTS

The authors thank Teresa Lanitis and Thitima Kongnakorn for their work in the development of the cost-effectiveness model that has served as the basis for the present study, adapted to Spain.

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