

Original article

# Cost-effectiveness of Dabigatran for Stroke Prevention in Non-valvular Atrial Fibrillation in Spain

José R. González-Juanatey,<sup>a</sup> José Álvarez-Sabin,<sup>b</sup> José M. Lobos,<sup>c</sup> Antoni Martínez-Rubio,<sup>d</sup> Joan C. Reverter,<sup>e</sup> Itziar Oyagüez,<sup>f</sup> Nuria González-Rojas,<sup>g</sup> and Virginia Becerra<sup>g,\*</sup>

<sup>a</sup>Servicio de Cardiología, Hospital Clínico Universitario de Santiago, Santiago de Compostela, A Coruña, Spain

<sup>b</sup>Unidad Neurovascular, Servicio de Neurología, Hospital Universitario Vall d'Hebron, Universidad Autónoma de Barcelona, Barcelona, Spain

<sup>c</sup>Centro de Salud Jazmín, Área Este, Atención Primaria, Madrid, Spain

<sup>d</sup>Servicio de Cardiología, Hospital Universitari Parc Taulí, Sabadell, Barcelona, Spain

<sup>e</sup>Servicio de Hemoterapia y Hemostasia, Hospital Clínic, Barcelona, Spain

<sup>f</sup>Pharmacoeconomics and Outcomes Research Iberia, Madrid, Spain

<sup>g</sup>Departamento de Economía y Resultados en Salud, Boehringer Ingelheim, Barcelona, Spain

Article history:

Received 16 February 2012

Accepted 6 June 2012

Available online 6 September 2012

Keywords:

Cost-effectiveness

Stroke prevention

Atrial fibrillation

ABSTRACT

**Introduction and objectives:** Assessment of the cost-effectiveness of dabigatran for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation in Spain, from the perspective of the National Health System.

**Methods:** Adaptation of a Markov chain model that simulates the natural history of the disease over the lifetime of a cohort of 10 000 patients with non-valvular atrial fibrillation. Model comparators were warfarin in a first scenario, and a real world prescribing pattern in a second scenario, in which 60% of the patients were treated with vitamin K antagonists, 30% with acetylsalicylic acid, and 10% received no treatment. Deterministic and probabilistic sensitivity analyses were performed.

**Results:** Dabigatran reduced the occurrence of clinical events in both scenarios, providing gains in quantity and quality of life. The incremental cost-effectiveness ratio for dabigatran compared to warfarin was 17 581 euros/quality-adjusted life year gained and 14 118 euros/quality-adjusted life year gained when compared to the real world prescribing pattern. Efficiency in subgroups was demonstrated. When the social costs were incorporated into the analysis, dabigatran was found to be a dominant strategy (ie, more effective and less costly). The model proved to be robust.

**Conclusions:** From the perspective of the Spanish National Health System, dabigatran is an efficient strategy for the prevention of stroke in patients with non-valvular atrial fibrillation compared to warfarin and to the real-world prescribing pattern; incremental cost-effectiveness ratios were below the 30 000 euros/quality-adjusted life year threshold in both scenarios. Dabigatran would also be a dominant strategy from the societal perspective, providing society with a more effective therapy at a lower cost compared to the other 2 alternatives.

© 2012 Sociedad Española de Cardiología. Published by Elsevier España, S.L. All rights reserved.

## Análisis coste-efectividad de dabigatrán para la prevención de ictus y embolia sistémica en fibrilación auricular no valvular en España

RESUMEN

**Introducción y objetivos:** Análisis coste-efectividad de dabigatrán para la prevención de ictus y embolia sistémica por fibrilación auricular no valvular en España, según la perspectiva del Sistema Nacional de Salud.

**Métodos:** Adaptación de un modelo de Markov secuencial que simula la historia natural de la enfermedad para una cohorte de 10.000 pacientes con fibrilación auricular no valvular a lo largo de su vida. Los comparadores son warfarina en un primer escenario y el patrón de prescripción habitual (el 60% con antagonistas de la vitamina K, el 30% con ácido acetilsalicílico y el 10% no tratados) en el segundo. Se realizaron análisis de sensibilidad determinístico y probabilístico.

**Resultados:** En ambos escenarios dabigatrán disminuyó los eventos sufridos y consiguió ganancias en cantidad y calidad de vida. La razón coste-efectividad incremental de dabigatrán comparado con warfarina fue de 17.581 euros/año de vida ajustado por calidad ganado y de 14.118 euros/año de vida ajustado por calidad ganado respecto al patrón de prescripción habitual. Se demostró eficiencia en subgrupos. Incorporando los costes sociales al análisis, dabigatrán es una estrategia dominante (más efectiva y de menor coste). El modelo demostró ser robusto.

Palabras clave:

Coste-efectividad

Prevención de ictus

Fibrilación auricular

\* Corresponding author: Prat de la Riba s/n, Sector Turó Can Matas, 08173 Sant Cugat del Vallès, Barcelona, Spain.

E-mail address: [virginia.becerra@boehringer-ingenelheim.com](mailto:virginia.becerra@boehringer-ingenelheim.com) (V. Becerra).

**Conclusiones:** Desde la perspectiva del Sistema Nacional de Salud, dabigatrán resulta una estrategia eficiente para la prevención de ictus en pacientes con fibrilación auricular no valvular en comparación con warfarina y con el patrón de prescripción habitual; en ambas comparaciones realizadas, los valores de la razón coste-efectividad incremental estuvieron por debajo del umbral de 30.000 euros/año de vida ajustado por calidad. Desde la perspectiva de la sociedad, dabigatrán sería además una estrategia dominante que aporta más efectividad y menores costes que las dos alternativas.

© 2012 Sociedad Española de Cardiología. Publicado por Elsevier España, S.L. Todos los derechos reservados.

### Abbreviations

AF: atrial fibrillation  
 INR: international normalized ratio  
 QALY: quality-adjusted life year  
 RE-LY: Randomized Evaluation of Long-term anticoagulation therapy  
 RRR: relative risk reduction  
 VKA: vitamin K antagonist

### INTRODUCTION

Atrial fibrillation (AF), the most common cardiac arrhythmia, is the cause of a high percentage of ischemic strokes, and its importance as an etiological factor in these events increases with age.<sup>1</sup>

In Spain, the overall prevalence of AF is 4.8% in the general population,<sup>2</sup> rising to 8.5% among patients over 60 years of age, and reaching 16.5% among those over 85 years.<sup>3</sup>

The hospital costs associated with stroke in Spain in 2004 was 1526 million euros.<sup>4</sup> If, in addition to this cost, we considered the indirect costs and other direct non-health care costs, we would obtain estimates of the total cost of stroke similar to 5% of Spanish public health expenditures.<sup>5</sup>

The profiles of strokes in patients with AF differ from those affecting patients in sinus rhythm.<sup>6</sup> From the clinical point of view, the former are usually more extensive and produce a greater initial neurological deficit. Moreover, the sequelae are more important. Thus, the probability of a stroke associated with AF resulting in disability is 2.23-fold higher than that of a stroke in an individual with sinus rhythm.<sup>7</sup>

This greater severity implies a longer hospital stay and a lower probability of the patient being discharged to his or her home.<sup>8</sup>

The presence of AF is also an independent risk factor for in-hospital death in patients with ischemic stroke, especially women and the elderly population,<sup>9</sup> and this risk is greater for both in-hospital and out-of-hospital mortality.<sup>10</sup>

All these circumstances account for the greater economic and social impact of stroke with AF compared to stroke without AF.

Considering the poor outcome of this type of stroke, the management of patients with AF should include both treatment of the arrhythmia and the prevention of emboli. Evidence-based clinical guidelines<sup>11</sup> recommend anticoagulation therapy for patients with AF who have associated embolic risk.

For the last 50 years, the only available oral anticoagulants have been vitamin K antagonists (VKA), which include warfarin and acenocoumarol. These drugs have been shown to be effective in the prevention of strokes and emboli.<sup>12,13</sup> However, because of their unpredictable pharmacokinetics and pharmacodynamics, and their individual and interindividual variability, added to their narrow therapeutic window, monitoring the degree of anticoagulation and periodic dose adjustment<sup>14</sup> are required to reduce the risk of stroke or hemorrhage when the patients are not within the therapeutic range (international normalized ratio [INR]=2–3).

Moreover, VKA are frequently subject to interactions with foods and drugs.

With each patient having the INR checked an average of 13 times a year, monitoring this parameter is a burden on the patients and on the health care system. Moreover, the aim is not always achieved, since it has been estimated that patients treated with VKA remain outside the therapeutic INR range nearly half the time.<sup>15</sup>

Because of the aforementioned inconveniences of VKA, many patients are unable to receive thromboprophylaxis or the treatment they receive is inadequate,<sup>16–18</sup> meaning that their need for the prevention of stroke due to AF is not being covered.

Dabigatran etexilate is a direct thrombin inhibitor recently authorized by the European Medicines Agency<sup>19</sup> for the prevention of stroke and systemic embolism in adult patients with non-valvular AF and with 1 or more of the following risk factors: previous stroke, transient ischemic attack or systemic embolism; left ventricular ejection fraction less than 40%; symptomatic heart failure in New York Heart Association functional class II or higher; age 75 years or older; and age 65 years or older associated with diabetes mellitus, coronary heart disease, or hypertension. Dabigatran has predictable pharmacokinetics and pharmacodynamics and a broad therapeutic window and, thus, in contrast to VKA, does not require coagulation monitoring. The prospective, randomized study, the RE-LY (Randomized Evaluation of Long-term anticoagulation therapy) trial, included 18 113 patients and compared 2 blinded doses of dabigatran etexilate (150 mg or 110 mg, both taken twice daily) with warfarin in terms of efficacy and safety for stroke prevention in patients with non-valvular AF.<sup>20,21</sup>

After a median follow-up period of 2 years, the efficacy of dabigatran 150 mg administered twice daily was found to be superior to that of warfarin in terms of the primary efficacy variable studied: prevention of stroke and systemic embolism (relative risk reduction [RRR], 35%). It also significantly reduced the risk of ischemic stroke (RRR, 24%), hemorrhagic stroke (RRR, 74%), vascular death (RRR, 15%), intracranial hemorrhage (RRR, 59%), life-threatening hemorrhage (RRR, 20%), and major and minor bleeding combined (RRR, 9%). The rate of gastrointestinal bleeding was higher (relative risk increase, 48%). The 110-mg dose twice daily was noninferior to warfarin with respect to the primary efficacy variable, was superior in terms of the primary safety variable, major bleeding (RRR, 20%), and significantly reduced hemorrhagic stroke (RRR, 69%), intracranial hemorrhage (RRR, 70%), life-threatening hemorrhage (RRR, 33%), major bleeding (RRR, 20%), and major and minor bleeding combined (RRR, 22%). Likewise, in terms of the net clinical benefit, the 150-mg dose was superior (RRR, 10%) to warfarin and the 110-mg dose was noninferior.

Once the efficacy and safety of an alternative strategy have been demonstrated, its efficiency in terms of costs and benefits should be evaluated to optimize the use of health care resources and patient access to the most efficient therapies.

The objective of the present study was to evaluate the cost-effectiveness of the utilization of dabigatran for the prevention of stroke and systemic embolism in adult patients with non-valvular AF with 1 or more thromboembolic risk factors, from the perspective of the Spanish health authorities.

## METHODS

### Design

We used a Markov model to simulate the natural history of patients with non-valvular AF over their entire lifetime. The conceptual model had been developed and reported previously,<sup>22</sup> and has been used in other economic evaluations of dabigatran<sup>23</sup> that have been analyzed by the agencies for health technology assessment of several countries, such as the National Institute for Health and Clinical Excellence in the United Kingdom.<sup>24</sup>

The model utilized in this study includes 23 health states (15 permanent and 8 temporary) based on the patient's level of disability, history of stroke, and treatment regimen. Figure 1 shows a diagram of the model, which takes into account 3 levels of disability: no disability (score on the Rankin scale  $\leq 2$ <sup>25</sup>), moderate disability (Rankin 3–4), and total disability (Rankin=5). Likewise, 3 treatment regimens are considered: the initial regimen, in which the patients are treated with the therapies being analyzed; the second, involving acetylsalicylic acid; and the third, in which the patients receive no treatment.

Once the simulation commences, each patient is susceptible to developing 1 of the clinical events considered (primary and recurrent ischemic stroke, hemorrhagic stroke, transient ischemic attack, systemic embolism, acute myocardial infarction, intracranial hemorrhage, extracranial hemorrhage) and/or can die.

In the diagram, the arrows indicate the transitions permitted between the different health states. These transitions are produced as a consequence of variations in the level of dependence of the patient or due to discontinuation of or changes in the treatment regimen, and take place in accordance with the assumptions of the model presented in Table 1. The duration of the Markov cycles was 3 months. The half-cycle correction was applied.

The adaptation of the model to the Spanish population was carried out by a multidisciplinary expert panel, the members of which are the authors of this manuscript. Using structured questionnaires, data were collected on the use of resources and

routine clinical practice in Spain, agreed on by consensus in a face-to-face meeting and compared with those reported in the available scientific literature.

### Scenarios

The first scenario considered compared the alternatives evaluated in the RE-LY trial<sup>21</sup>: dabigatran and warfarin. The second compared dabigatran with the prescribing pattern in clinical practice in Spain; in agreement with the available evidence,<sup>26</sup> it was assumed that 60% of the population receives VKA therapy, 30% takes acetylsalicylic acid, and 10% receives no treatment at all.

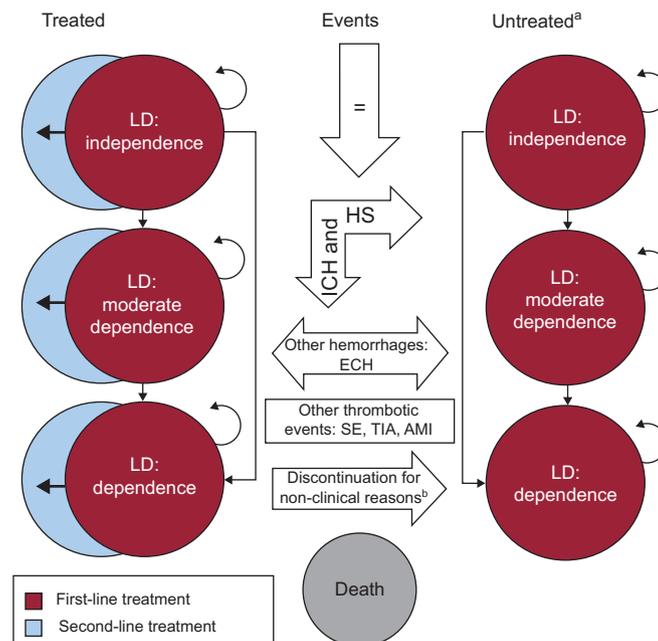
In the case of dabigatran, a chain model was developed; simulating the conditions of the technical specifications, the patients began the intervention with a 150-mg dose of dabigatran 2 times a day and, upon reaching the age of 80 years, changed to a 110-mg dose twice daily, being subject in each stage to the respective probabilities of experiencing an event observed for each dose in the RE-LY trial.<sup>19</sup>

### Population

The population was a hypothetical cohort of 10 000 patients with non-valvular AF that simulated the profile of the patients in the RE-LY trial. At the initiation of the simulation, the mean age of the patients was 69.1 years; all the patients started out with no disability and remained in the model until they made the transition to the state of "death". The distribution of the cohort according to stroke risk and time within therapeutic INR range for the patients receiving warfarin was that of the RE-LY trial.

### Mortality, Clinical Efficacy, Disability, and Utilities

The overall risk of mortality was that of the Spanish population according to age and sex.<sup>27</sup>



**Figure 1.** Markov diagram. AMI, acute myocardial infarction; ECH, extracranial hemorrhage; HS, hemorrhagic stroke; ICH, intracranial hemorrhage; LD, level of disability; SE, systemic embolism; TIA, transient ischemic attack. <sup>a</sup>History of stroke was included in the model but is not shown in the diagram. <sup>b</sup>Discontinuation due to non-major hemorrhagic events.

**Table 1**

## Model Assumptions.

<i>Clinical efficacy (probabilities of experiencing events)</i>
Dabigatran and warfarin: RE-LY trial post hoc analysis stratified by age
Acetylsalicylic acid and no treatment: meta-analysis of indirect comparisons
<i>Discontinuation rates: from the original model<sup>22</sup></i>
Dabigatran and warfarin: according to the RE-LY trial
Acetylsalicylic acid: according to the BAFTA trial
<i>Rates of mortality and disability, and utilities</i>
Overall mortality: Spanish population by age and sex
Additional mortality and disability due to events: from the original model <sup>22</sup>
<i>Utilities: from the original model<sup>22</sup></i>
Obtained from EQ-5D scores and incorporated according to the patient's level of dependence
Disutilities were associated with the development of some clinical events
<i>Other premises of the model. In the base case, it is assumed that:</i>
The patients receive no anticoagulation medication concomitantly with the medication included in the model
Dabigatran does not interact with any other medication
The transition of a patient to a higher level of disability is only associated with the occurrence of cerebral events (stroke or intracranial hemorrhage)
Patients cannot transition to lower levels of disability
The probability of a patient transitioning to a worse level of disability after an event is not related to a history of previous strokes
Patients continue to be treated with the initial medication for the rest of their lives, except in cases of authorized treatment discontinuation
Patients who experience an intracranial hemorrhage or hemorrhagic stroke discontinue the treatment permanently for the remainder of the simulation
After experiencing an intracranial hemorrhage, the patient can discontinue the treatment temporally (50% of the cases during a 3-month cycle) or permanently (the remaining 50%)
Temporary treatment interruptions following development of an extracranial hemorrhage are not associated with changes in the risk of the occurrence of any of the events
In cases of permanent treatment discontinuation for reasons other than the development of ischemic stroke or intracranial hemorrhage, 70% of the patients change to a second-line treatment regimen
A maximum of 2 treatment regimens is allowed per patient throughout the entire simulation
In the prescribing pattern scenario, the patients initially treated with acetylsalicylic acid who discontinue this treatment do not receive any other therapy as second-line treatment
Patients are allowed to experience only 1 of the clinical events described (with the exception of minor bleeding) or death for each 3-month cycle. Minor bleeding can occur at any time in the cycle, either alone or in association with any of the other events, although minor bleeding does not increase the risk of developing any of the other events of greater importance in that cycle
No association is established between death due to stroke, intracranial hemorrhage, or extracranial hemorrhage and the existence of a history of stroke
The efficacy of the treatments is assumed as a constant over time
Temporary treatment interruptions for short periods of time (1–2 weeks), which can take place following stroke or during perioperative periods, are not associated with significant impacts on the efficacy or the cost of the treatments
INR monitoring of the patients being treated with vitamin K antagonists (warfarin or acenocoumarol) is not associated with disutilities in addition to those derived from the level of disability of the patient or from the development of the clinical events considered

BAFTA, Birmingham Atrial Fibrillation Treatment of the Aged; INR, international normalized ratio; RE-LY, Randomized Evaluation of Long-term anticoagulation therapy. Source: our own data, based on Sorensen et al.<sup>22,23</sup>

The clinical efficacy (probability of experiencing an event in the simulation), the rates of additional mortality, disability due to events and discontinuation, and utilities were taken from the original model.<sup>22</sup>

### Perspective, Time Horizon, and Discount Rates

The perspective of the analysis was that of the Spanish National Health System, and the time horizon covered the lifetime of the patient (assumed maximum life expectancy, 100 years). The costs and benefits were discounted at an annual rate of 3%.

### Use of Resources and Costs

In the model base case, only direct health care costs associated with the therapies evaluated were considered. All the costs are expressed in 2010 euros. The necessary cost updates were

performed according to the corresponding annual Consumer Price Index.<sup>28</sup>

Medication costs were calculated on the basis of the retail price<sup>29</sup> considering the 7.5% discount in medications covered by Spanish Royal Decree 8/2010.<sup>30</sup>

The costs of the clinical events were obtained from diagnosis-related groups<sup>31</sup> or from the literature.<sup>32</sup> In events with associated follow-up costs (stroke and hemorrhagic stroke), the cost associated with the level of dependence of the patient was added to the cost of the event.

The monitoring of the INR constitutes an additional cost in VKA therapy, and has been included in the cost of the medication. To estimate this, we considered the different care modalities utilized in Spain, taking into account the technique for obtaining the blood sample and the setting in which monitoring is performed, and the costs reported by de Solà-Morales et al.<sup>33</sup> were applied. Likewise, for this calculation, we assumed that, on a general basis, anticoagulation is poorly controlled in 30% of the patients.<sup>34</sup>

**Table 2**

Estimation of the Annual Cost of International Normalized Ratio Monitoring (2010 Euros).

Monitoring setting and type of blood sample collection (venous or capillary)	Patients per setting, %	Annual cost according to usual patient control level	
		Good control (70% of the patients, monitored 13 times a year)	Poor control (30% of the patients, monitored 19.5 times a year)
Hospital (10% venous)	3	173.63	260.44
Hospital (90% capillary)	27	378.00	462.31
Primary care (100% capillary)	67	378.00	462.31
Home (100% capillary)	2	673.31	905.28
Self-monitoring (100% capillary)	1	883.90	1221.16
<b>Total</b>	<b>100</b>	<b>382.83</b>	<b>472.70</b>

It was assumed that 30% of the patients are usually outside the therapeutic range (poor control) and undergo 50% more international normalized ratio measurements than the average. Thus, the current cost allocations related to monitoring doubled.

Source: Spanish expert panel and de Solà-Morales Serra et al.<sup>33</sup>

**Table 3**

Costs Corresponding to the Model Base Case (2010 Euros).

Therapeutic alternative	Daily cost, retail price + VAT <sup>a</sup>	Source
<i>Dabigatran 150 mg (twice daily)</i>	3.03	MSPSI <sup>29</sup>
<i>Dabigatran 110 mg (twice daily)</i>	3.03	MSPSI <sup>29</sup>
<i>Warfarin 2.1 mg</i>	0.05	MSPSI <sup>29</sup>
<i>Acetylsalicylic acid, weighted means of 100 mg (70%) and 300 mg (30%)</i>	0.10	MSPSI <sup>29</sup>
Clinical event	Cost	Source
Fatal ischemic stroke	4237.76	MSPSI <sup>31</sup>
Ischemic stroke, independent	4407.58	MSPSI, <sup>31</sup> López-Bastida et al. <sup>b</sup>
Ischemic stroke, moderately dependent	4827.18	MSPSI, <sup>31</sup> López-Bastida et al. <sup>b</sup>
Ischemic stroke, totally dependent	5483.06	MSPSI, <sup>31</sup> López-Bastida et al. <sup>b</sup>
Fatal systemic embolism	1834.94	MSPSI <sup>31</sup>
Non-fatal systemic embolism	1834.94	MSPSI <sup>31</sup>
Transient ischemic attack	2453.36	MSPSI <sup>31</sup>
Fatal intracranial hemorrhage	5830.96	MSPSI <sup>31</sup>
Intracranial hemorrhage, independent	6000.78	MSPSI, <sup>31</sup> López-Bastida et al. <sup>b</sup>
Intracranial hemorrhage, moderately dependent	6250.56	MSPSI, <sup>31</sup> López-Bastida et al. <sup>b</sup>
Intracranial hemorrhage, totally dependent	6486.84	MSPSI, <sup>31</sup> López-Bastida et al. <sup>b</sup>
Fatal hemorrhagic stroke	5830.96	MSPSI <sup>31</sup>
Hemorrhagic stroke, independent	6000.78	MSPSI, <sup>31</sup> López-Bastida et al. <sup>b</sup>
Hemorrhagic stroke, moderately dependent	6250.56	MSPSI, <sup>31</sup> López-Bastida et al. <sup>b</sup>
Hemorrhagic stroke, totally dependent	6486.84	MSPSI, <sup>31</sup> López-Bastida et al. <sup>b</sup>
Fatal extracranial hemorrhage	3724.68	MSPSI <sup>31</sup>
Nonfatal, non-gastrointestinal extracranial hemorrhage	2581.82	MSPSI <sup>31</sup>
Nonfatal, gastrointestinal extracranial hemorrhage	2581.82	MSPSI <sup>31</sup>
Minor bleeding	188.96	Oblikue Consulting <sup>32</sup>
Fatal acute myocardial infarction	4072.94 <sup>c</sup>	MSPSI <sup>31</sup>
Nonfatal acute myocardial infarction	4072.94 <sup>c</sup>	MSPSI <sup>31</sup>
Associated degree of disability	Cost per every 3 months of follow-up	Source
Following stroke, independent	169.82	López-Bastida et al. <sup>b</sup>
Following stroke, moderately dependent	419.60	López-Bastida et al. <sup>b</sup>
Following stroke, totally dependent	655.88	López-Bastida et al. <sup>b</sup>
International normalized ratio monitoring	Annual cost	
Patients usually exhibiting good control	382.83	Table 2
Patients usually exhibiting poor control	472.70	Table 2

MSPSI, Ministerio de Sanidad, Política Social e Igualdad (Spanish Ministry of Health, Social Policy and Equality); VAT, value added tax.

<sup>a</sup> With a 7.5% reduction in accordance with Spanish Royal Decree 8/2010<sup>30</sup>.

<sup>b</sup> Source: López-Bastida J, Oliva Moreno J, Worbes Cerezo M, Perestelo Pérez L, Serrano-Aguilar P, et al. The Social Economic Costs and Health-Related Quality of Life of Stroke Survivors in the Canary Islands, Spain. Working paper. (J. López-Bastida, personal communication, 15 November, 2011).

<sup>c</sup> It is considered that 11% are silent.

Table 2 shows the calculation of the total annual cost of INR monitoring (total amount weighted according to setting). The costs included in the model are detailed in Table 3.

### Sensitivity Analysis

Deterministic and probabilistic sensitivity analyses were performed to confirm the robustness of the model and identify the parameters with the greatest influence on the results.

In the deterministic analysis, the parameters with the greatest uncertainty were modified; they included the time horizon, discount rate, subpopulation of patients of 80 years or older (only treated with dabigatran 100 mg), and the percentage of time within the therapeutic range in INR monitoring (57.1% and 72.6%), with the same cutoff points as those utilized in a post hoc analysis of the RE-LY trial data.<sup>35</sup>

A deterministic sensitivity analysis was also carried out to observe the efficacy in 4 subgroups: patients with poor or good INR control (defined as time within the therapeutic range <57.1% or 72.6%), patients taking acetylsalicylic acid, and untreated patients, in order to examine the societal perspective. This included non-health care costs<sup>36</sup> and assessment of the informal care received by stroke survivors with some level of dependence,<sup>37,38</sup> and the value added tax was deduced from the price of the medications (Table 4).

The probabilistic analysis performed (10 000 Monte Carlo simulations) modified the values of the parameters simultaneously, according to the functions of beta distribution to describe baseline risks and utilities, log normal distribution to describe relative risks, and gamma distribution to describe costs.

## RESULTS

In the model employed, dabigatran reduced the number of ischemic strokes, cases of systemic embolism, transient ischemic attacks, intracranial hemorrhages, and hemorrhagic strokes compared both to warfarin (scenario 1) and to the prescribing pattern (scenario 2), but it increased the number of extracranial hemorrhages (attributable to nonfatal gastrointestinal hemorrhage) and acute myocardial infarctions (Table 5).

**Table 4**

Deemed Incremental Costs for the Deterministic Sensitivity Analysis From the Societal Perspective, According to Disability (2010 Euros).

	Independent and history of stroke	Moderately dependent	Totally dependent	Source
<i>Applied to the price of drugs</i>	Deduction of VAT and discounts (applied to the retail price)			MSPSI <sup>29</sup>
<i>Applied to the disabling event, ischemic or hemorrhagic stroke and intracranial hemorrhage</i>				
Investment (eg, home remodeling)	0	31.1	31.1	Hervás-Angulo et al. <sup>36,a</sup>
Public institutional assistance	0	125.8	125.8	Hervás-Angulo et al. <sup>36,a</sup>
<i>Applied to follow-up of stroke patients performed every 3 months</i>				
Private institutional assistance	0	76.9	76.9	Hervás-Angulo et al. <sup>36,a</sup>
Nursing homes and/or day care centers	0	426.6	426.6	Hervás-Angulo et al. <sup>36,a</sup>
Informal care (hourly rate, 10.6 euros) <sup>a</sup>	5970.1	9596.6	11 958.9	Hidalgo et al., <sup>37</sup> Jiménez-Martín et al., <sup>38</sup> and Oliva-Moreno et al. <sup>b</sup>

MSPSI: *Ministerio de Sanidad, Política Social e Igualdad*; (Spanish Ministry of Health, Social Policy and Equality); VAT, value added tax.

Estimation of the hours of informal and non-professional care, provided to stroke survivors with some degree of dependence by relatives or friends and exclusively as a consequence of a personal bond. Based on primary data from the Survey on Disabilities, Personal Autonomy, and Situations of Dependency 2008 (*Encuesta sobre Discapacidades, Autonomía personal y situaciones de Dependencia 2008*) (Spanish National Statistics Institute), using replacement cost methodology, censoring at 16 h a day as the maximum duration of informal care and considering only the main caregiver (no additional or occasional caregivers). Based on the cited report, we calculated the average hourly rate for care in the scenarios assessed (7.67 euros and 12.71 euros), and their categories of dependence were adapted to ours as follows: non-dependence to independence with a history of stroke, moderate dependence, and the average of severe dependence and high dependence to total dependence.

<sup>a</sup> Based on the average of years 2 and 3 of the cited work.

<sup>b</sup> Oliva-Moreno J, Aranda-Reneo I, Vilaplana C, González-Domínguez A, Hidalgo-Vega A. Informal care of cerebrovascular accident survivors with activities of daily living limitations (mimeo). (J. Oliva-Moreno, personal communication, 15 November 2011).

In the 2 scenarios, dabigatran reduced the number of fatal events by 295 and 434, respectively, and the number of events that result in some type of disability by 250 and 463, respectively; of these disabling events avoided, 98% and 73% led to complete dependence (Rankin=5) in scenarios 1 and 2, respectively.

With regard to life years gained and quality-adjusted life years (QALY) gained, dabigatran produced a lifetime gain of 2514 life years and 2759 QALY in the first scenario and of 3625 life years and 4085 QALY in the second.

In the cost-effectiveness analysis carried out, we obtained a value of 17 581 euros/QALY gained for the comparison of dabigatran versus warfarin, and a value of 14 118 euros/QALY gained versus the prescribing pattern (Table 6).

### Sensitivity Analysis

From the perspective of the Spanish National Health System, the changes in the incremental cost-effectiveness ratio observed in the univariate deterministic analysis in the first scenario ranged between 14 651 and 57 719 euros/QALY. In scenario 2, the cost-effectiveness ranged between 11 519 euros/QALY and 52 160 euros/QALY.

In the analysis from the societal perspective, dabigatran proved to be a dominant strategy as it showed a higher effectiveness and lower cost when compared with warfarin and with the prescribing pattern, with a reduction of 6 957 025 euros and 41 237 148 euros, respectively (Table 7).

The key parameters having the greatest effect on the incremental cost-effectiveness ratio were the time horizon, the perspective from which the analysis was carried out, the degree of INR control achieved in patients treated with warfarin, the reduction of stroke risk, and the decrease in long-term disability that dabigatran achieved with respect to both comparators, as well as the cost associated with INR monitoring in the patients being treated with warfarin (Table 3).

In the probabilistic sensitivity analysis, considering a willingness-to-pay threshold of 30 000 euros/QALY gained,<sup>39</sup> dabigatran would be a cost-effective strategy vs warfarin in 96.4% of the simulations, and in 99.9% of the simulations vs the prescribing pattern (Fig. 2). In the comparisons by subgroups, dabigatran

**Table 5**  
Clinical Events Observed in the Overall Cohort of 10 000 Patients According to Alternative

Clinical events	Dabigatran	Warfarin	PP	Δ dabigatran vs warfarin	Δ dabigatran vs PP
<i>Ischemic stroke</i>	4244	4407	5170	-162	-926
Fatal	1606	1596	1870	9	-264
Independent	1435	1598	1841	-164	-406
Moderately dependent	734	688	807	46	-72
Totally dependent	470	524	653	-54	-183
<i>Systemic embolism</i>	508	563	680	-56	-173
Fatal	2	2	2	0	-1
Non-fatal	506	561	678	-55	-172
<i>Transient ischemic attack</i>	1301	1535	1674	-234	-372
<i>Intracranial hemorrhage and hemorrhagic stroke</i>	480	1078	909	-598	-429
Fatal	200	512	377	-312	-177
Independent	48	93	93	-44	-44
Moderately dependent	55	106	105	-51	-50
Totally dependent	176	367	334	-191	-158
<i>Extracranial hemorrhage</i>	4336	3884	3790	452	546
Fatal	52	47	46	5	7
Non fatal, non-gastrointestinal	3360	3147	3073	213	287
Non-fatal, gastrointestinal	924	690	672	234	251
<i>Acute myocardial infarction</i>	1419	1161	1267	257	152
Fatal	16	13	14	3	2
Non-fatal	1403	1148	1253	255	150
<i>Total dependence (Rankin=5)</i>	646	891	987	-245	-341
<i>Total fatal events</i>	1875	2170	2309	-295	-434
<i>Total events</i>	12 288	12 628	13 490	-340	-1203

PP, prescribing pattern.

**Table 6**  
Results of the Cost-effectiveness Analysis in Euros per Quality-adjusted Life Year Gained per Patient

Per patient, for the entire time horizon	Cost of medication and monitoring*	Cost of events*	Cost of follow-up*	Total cost*	LYG	QALY	Incremental cost	Incremental QALY	ICER, (€/QALY)
<i>Scenario 1 (dabigatran vs warfarin, RE-LY)</i>									
Warfarin	3475	3678	3190	10 343	11.13	8.45	4851	0.28	17 581
Dabigatran	8857	3409	2927	15 193	11.39	8.73			
<i>Scenario 2 (dabigatran vs prescribing pattern)</i>									
Prescribing pattern	2178	3889	3358	9426	11.02	8.32	5769	0.341	14 118
Dabigatran	8857	3409	2927	15 193	11.39	8.73			

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life years; RE-LY, Randomized Evaluation of Long-term anticoagulation therapy.  
\* In 2010 euros.

proved to be a cost-effective strategy in 99.4% and 99.3% of the simulations in the case of patients with poor and good INR control, respectively, and in 99.5% and 99.9% in the case of patients taking acetylsalicylic acid and those receiving no treatment, respectively.

## DISCUSSION

In this chain model, dabigatran reduced the number of events compared with both warfarin and the prescribing pattern in routine clinical practice, resulting in gains in patients' quantity and quality of life.

The substantial reduction of the number of cases of hemorrhagic stroke and of fatal intracranial hemorrhage was the major factor contributing to the gain in life years observed in the dabigatran arm. Likewise, in this simulation, dabigatran achieved an overall reduction in the ischemic strokes, intracranial hemorrhages, and

hemorrhagic strokes that cause disability (Rankin $\geq$ 3) of 15% compared to warfarin and 24% compared to the prescribing pattern in Spain, circumstances that are associated with a decrease in the costs of long-term treatment and care.

In all the comparisons in the deterministic analysis, the values of the incremental cost-effectiveness ratio were lower than the reference threshold of 30 000 euros/QALY gained,<sup>39</sup> except for the 5-year and 10-year time horizons in scenario 1 and the 5-year time horizon in scenario 2. The latter finding is explained by the chronicity of AF and the benefits received over the patients' lifetime. Because of the consequences of strokes with respect to medium- and long-term disability, the benefits of the treatments considered in the context of the patient's lifetime horizon need to be evaluated, and this is the ideal analysis.

With a cost-effectiveness threshold of 30 000 euros/QALY gained, the probability of dabigatran being an efficient strategy is 96.4% compared to warfarin, and 99.9% compared to the

**Table 7**  
Results of the Deterministic Sensitivity Analysis.

Parameter	BC value	SA value	Dabigatran vs warfarin, RE-LY		Dabigatran vs PP	
			ICER (€/QALY)	Change with respect to BC	ICER (€/QALY)	Change with respect to BC
<i>BC results</i>			17 581		14 118	
Discount rate	3%	0	15 127	-14%	11 971	-15%
		5%	19 348	10%	15 684	+11%
Time horizon	Patient lifetime	5 years	57 719	228%	52 160	+269%
		10 years	32 001	82%	27 829	+97%
Relative risk of ischemic stroke with dabigatran vs warfarin	<80 years: 0.77; >80 years: 0.82	<80 years: 0.58; >80 years: 0.51	13 217	-25%	11 519	-18%
		<80 years: 1.03; >80 years: 1.33	32 175	+83%	20 520	+45%
Patients with total disability due to ischemic stroke	RE-LY (150 mg: 4.1%; 110 mg: 0.1%)	150 mg: 13.3%; 110 mg: 14.6%	21 475	+22%	16 137	+14%
%TTR for INR*	64.5%	72.6%	21 095	20%	15 072	+7%
		57.1%	13 952	-21%	12 776	-10%
Patient age at initiation, mean	69.1	+80 (82.9)	24 034	37%	17 501	+24%
Cost of INR monitoring (Table 3)	€382.8 €472.7	+30%	14 014	-20%	12 672	-10%
		-30%	21 149	+20%	15 564	+10%
Total health care costs	Drugs, events, and follow-up of the BC (Table 3)	+20%	21 097	20%	16 666	+18%
		-20%	14 651	-17%	11 765	-17%
Dabigatran vs patients with ASA	30%	100%	Not applicable		13 317	-5%
Dabigatran vs untreated patients	10%	100%	Not applicable		7104	-50%
Societal perspective, incorporates social costs	Perspective of the Spanish National Health System	Costs as detailed in Table 6	Dominant		Dominant	

%TTR, percentage time in therapeutic range; ASA, acetylsalicylic acid; BC, base case; ICER; incremental cost-effectiveness ratio; INR, international normalized ratio; PP, prescribing pattern; QALY, quality-adjusted life year; RE-LY, Randomized Evaluation of Long-term anticoagulation therapy; SA, sensitivity analysis.

\* The percentages of time above and below therapeutic range of INR maintained the original ratio of the base case (INR<2=15.2% when TTR=72.6 and INR<2=23.9% when TTR=57.1).

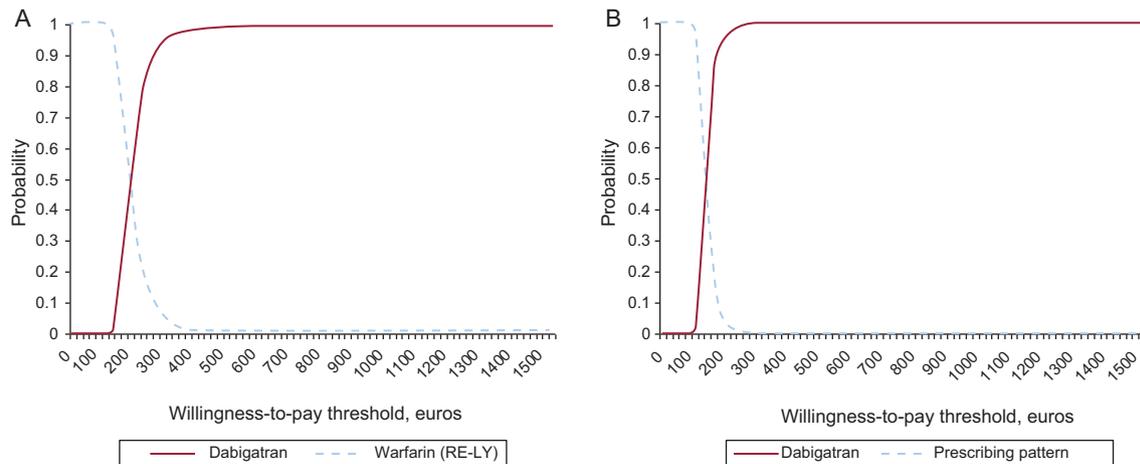
prescribing pattern, a finding that supports the robustness of the results obtained.

**Limitations and Strengths**

Importantly, there are a number of limitations and possible biases in this economic evaluation. For example, the data from

clinical trials have limitations that can determine the external validity of the model. However, the scenario in which dabigatran is compared to routine prescription in Spain may constitute a closer approximation to real-world clinical practice.

We have identified limitations inherent in the adaptation of the model to the Spanish context. First, the disparate sources of the information on health care costs obliged us to carry out a careful selection of the values, grouping the information according to



**Figure 2.** Acceptability curves according to the scenario of the comparison. A: dabigatran vs warfarin in the Randomized Evaluation of Long-term anticoagulation therapy trial. B: dabigatran vs the prescribing pattern. RE-LY, Randomized Evaluation of Long-term anticoagulation therapy.

levels of disability and opting for more conservative alternatives. Second, the data on utilities employed in the model refer to the United Kingdom due to the limited references on utilities in the Spanish population and the impossibility of adapting them to the levels of disability following stroke that the design demanded. Despite this circumstance, the probabilistic sensitivity analysis was carried out using different values for the costs and utilities, and there was no evidence that these variations affected the robustness of the results.

Finally, although the anticoagulation therapy employed in Spain is acenocoumarol, rather than warfarin, we consider the 2 drugs to be perfectly interchangeable in terms of both efficacy and safety, and of the resource use they involve.

One strength of this economic evaluation is the follow-up of the disability caused by ischemic stroke or intracranial hemorrhage, an issue of vital importance given the elevated cost of long-term care, which is not usually evaluated in other economic studies.<sup>40</sup>

A second strength of the present report concerns the conservative assumptions adopted with respect to INR control. For both scenarios, a time within therapeutic range of 64.4% was assumed, a value observed in the RE-LY trial, when, in real-world clinical practice, it may be lower. Equally, the model produced no decreases in the utility of INR monitoring.

Notably, the model was designed before results from the RE-LY trial had been obtained, and the specifications of the economic analysis were established in parallel to the clinical development. Likewise, its development enabled us to include the results of the RE-LY trial in the simulation, patient by patient, rather than the group as a whole,<sup>40</sup> and to derive results on stroke according to the levels of disability.

Seven economic evaluations of dabigatran have been published to date.<sup>23,40–46</sup> In the adaptations of this same model to the Canadian,<sup>23</sup> United Kingdom<sup>42</sup>, and Danish<sup>46</sup> contexts, dabigatran proved to be a cost-effective strategy vs both warfarin and the local prescribing pattern. In the United States, Kamel et al.,<sup>45</sup> taking a societal perspective and a cost of dabigatran therapy per day of 6.75 dollars concluded that it is a cost-effective alternative for patients with previous stroke or transient ischemic attack.

The other 3 publications<sup>40,41,43,44</sup> concluded that dabigatran 150 mg administered twice daily was cost-effective only in certain subgroups analyzed. However, these 3 reports incorporated a few hypotheses that favor warfarin over dabigatran and increase the observed incremental cost-effectiveness ratio: they factored in a cost of dabigatran higher than the list price (treatment cost of 8 dollars/day or higher),<sup>40,43,44</sup> considered the risk of ischemic stroke and of intracranial hemorrhage as being independent of age,<sup>43</sup> or employed lower rates of disability and costs of intracranial hemorrhage, when dabigatran markedly reduces the risk of intracranial hemorrhage.<sup>41</sup> Pink et al.<sup>41</sup> assigned to intracranial hemorrhage, an event that can produce a greater disability than stroke, a rate of permanent disability of only 0.0524, vs 0.233 for stroke, and assigned a low cost to intracranial hemorrhage, similar to that of extracranial hemorrhage. In contrast, Freeman et al.<sup>40,44</sup> and Shah et al.<sup>43</sup> evaluated the 150-mg and 110-mg doses of dabigatran separately. The evaluation of the 110-mg dose twice daily is not applicable in the context of the United States, as it has not been authorized by the U.S. Food and Drug Administration. We consider that, since the results of the evaluation presented here were obtained with the chain model, they better meet the technical specifications of the drug and real-world prescribing patterns.

For their part, different agencies for health technology assessment (United Kingdom, Scotland, Denmark, Sweden, Australia, and Canada) have evaluated dabigatran in terms of this indication and have considered it to be cost-effective for the entire population.

VKA constitute a therapeutic option that has been on the market for 50 years; these drugs are inexpensive, but are less effective and/or safe and have serious limitations compared to dabigatran. First, the reduction of the risk of ischemic and hemorrhagic stroke achieved with dabigatran offers greater quantity and quality of life and, moreover, this drug does not require INR monitoring. Together, these aspects result in a reduction of the associated costs. Thus, this evaluation cannot be reduced to the standpoint of hermetic budgets based merely on a comparison of the pharmaceutical cost.

The analysis from a societal perspective included direct non-health care costs (nursing homes, adaptations to home care, caregivers, etc.) that, not being financed by the Spanish National Health System, could be partly supported by Spanish Social Security funds. Due to methodological difficulties and a lack of sufficient evidence, certain costs, such as those incurred by the patient as a result of INR monitoring, the opportunity cost in terms of the productive time of survivors with some degree of dependence, and the value of the life lost, were not included.

According to a recent report, the economic impact on hours of informal care given to stroke survivors in Spain would range between 6183.57 and 10 246.83 million euros (corresponding to 2008).<sup>37,38</sup> Incorporating these data and other direct non-health care costs<sup>35</sup> into our analysis, we observed that dabigatran is associated with greater effectiveness and lower costs compared to the other 2 alternatives, and therefore, a saving for society. Thus, dabigatran is a dominant strategy in both scenarios.<sup>47</sup>

Despite the limitations mentioned above, the premises adopted in the present model appear to be reasonable and conservative, and the results of the sensitivity analyses confirm the robustness of the model and the results obtained.

The conclusive results with regard to efficacy and safety demonstrated in the RE-LY trial and its subsequent subanalyses support the view that dabigatran is indicated as a first-line treatment in oral anticoagulation therapy for the prevention of stroke in patients with non-valvular AF.<sup>11,48</sup>

The results of the present economic evaluation show that, considering a willingness-to-pay threshold of 30 000 euros/additional QALY,<sup>39</sup> dabigatran etexilate is a cost-effective therapy for patients with non-valvular AF in Spain.

## CONCLUSIONS

From the perspective of the Spanish National Health System, dabigatran is an effective strategy for stroke prevention in patients with non-valvular AF when compared to warfarin and to the prescribing pattern in routine clinical practice. From the societal perspective, dabigatran would also be a dominant strategy, as it would offer society greater effectiveness at lower costs than the other 2 alternatives.

## ACKNOWLEDGMENTS

The authors thank Anuraag Kansal and Sonja Sorensen of United BioSource Corporation, Maryland, United States.

## CONFLICTS OF INTEREST

All the authors have made a substantial contribution to the design and development of the study, according to the international recommendations in this regard. Two of the authors (NGR and VB) are employees of Boehringer Ingelheim. Another author (IO) is a member of PORIB (Pharmacoeconomics & Outcomes Research Iberia), a consultancy organization specialized in

economic evaluation that has provided consultancy services to Boehringer Ingelheim in connection with this study. However, this circumstance has in no case influenced the results reported here.

## REFERENCES

- García-Castelo A, García-Seara J, Otero-Raviña F, Lado M, Vizcaya A, Vidal JM, et al.; Barbanza Group Investigators. Prognostic impact of atrial fibrillation progression in a community study: AFBAR Study (Atrial Fibrillation in the Barbanza Area Study). *Int J Cardiol*. 2011;153:68-73.
- García-Acuña JM, González-Juanatey JR, Alegría E, González I, Listerri JL. La fibrilación auricular permanente en las enfermedades cardiovasculares en España. Estudio CARDIOTENS 1999. *Rev Esp Cardiol*. 2002;55:943-52.
- Cea-Calvo L, Redón J, Lozano JV, Fernández C, Martí JC, Listerri JL, et al. Prevalencia de fibrilación auricular en la población española de 60 o más años de edad. Estudio PREV-ICTUS. *Rev Esp Cardiol*. 2007;60:616-24.
- Sánchez C. Impacto sociosanitario de las enfermedades neurológicas en España. Informe FEEN. Madrid: Fundación Española de Enfermedades Neurológicas; 2006.
- Jorgensen N, Cabañas M, Oliva J, Rejas J, León T. Los costes de los cuidados informales asociados a enfermedades neurológicas discapacitantes de alta prevalencia en España. *Neurología*. 2008;23:29-39.
- Miller PSJ, Andersson FL, Kalra L. Are cost benefits of anticoagulation for stroke prevention in atrial fibrillation underestimated? *Stroke*. 2005;36:360-6.
- Dulli DA, Stanko H, Levine RL. Atrial fibrillation is associated with severe acute ischemic stroke. *Neuroepidemiology*. 2003;22:118-23.
- Roquer J, Rodríguez-Campello A, Gomis M, Ois A, Martínez-Rodríguez JE, Munteis E, et al. Comparison of the impact of atrial fibrillation on the risk of early death after stroke in women versus men. *J Neurol*. 2006;20:1-7.
- Vidal-Pérez R, Otero-Raviña F, Domínguez-López J, Fabeiro-Romero D, Gómez-Vázquez JL, De Blas-Abad P, et al. Clinical features and prognosis of patients with chronic cerebrovascular disease (ICBAR study). *Rev Neurol*. 2011;53:449-56.
- Lin HJ, Wolf PA, Kelly-Hayes M, Beiser AS, Kase CS, Benjamin EJ, et al. Stroke severity in atrial fibrillation. The Framingham Study. *Stroke*. 1996;27:1760-4.
- Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, et al. Guidelines for the management of atrial fibrillation: The Task Force for the management of atrial fibrillation of the European Society of Cardiology. *Eur Heart J*. 2010;31:2369-429.
- Singer DE, Chang Y, Fang MC, Borowsky LH, Pomernacki NK, Udaltsova N, et al. The net clinical benefit of warfarin anticoagulation in atrial fibrillation. *Ann Intern Med*. 2009;151:297-305.
- Hobbs FD, Leach I. Challenges of stroke prevention in patients with atrial fibrillation in clinical practice. *QJM*. 2011;104:739-46.
- Hylek EM, Go AS, Chang Y, Jensvold NG, Henault LE, Selby JV, et al. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. *N Engl J Med*. 2003;349:1019-26.
- Baker WL, Cios DA, Sander SD, Coleman CI. Meta-analysis to assess the quality of warfarin control in atrial fibrillation patients in the United States. *J Manag Care Pharm*. 2009;15:244-52.
- De Caterina R, Hylek EM. Stroke prevention in atrial fibrillation: current status and near-future directions. *Am J Med*. 2011;124:793-9.
- Barrios V, Calderón A, Escobar C, De la Figuera M. Pacientes con fibrilación auricular asistidos en consultas de atención primaria. Estudio Val-FAAP. *Rev Esp Cardiol*. 2012;65:47-53.
- Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med*. 2007;146:857-67.
- European Medicines Agency. European Public Assessment Report (EPAR) for Pradaxa [updated 23 Aug 2011]. Available at: [http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000829/human\\_med\\_000981.jsp&mid=WC0b01ac058001d124](http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000829/human_med_000981.jsp&mid=WC0b01ac058001d124)
- Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139-51.
- Connolly SJ, Ezekowitz MD, Yusuf S, Reilly PA, Wallentin L. Randomized Evaluation of Long-Term Anticoagulation Therapy Investigators. Newly identified events in the RE-LY trial. *N Engl J Med*. 2010;363:1875-6.
- Sorensen SV, Dewilde S, Singer DE, Goldhaber SZ, Monz BU, Plumb JM. Cost-effectiveness of warfarin: trial versus "real-world" stroke prevention in atrial fibrillation. *Am Heart J*. 2009;157:1064-73.
- Sorensen SV, Kansal A, Connolly S, Peng S, Linnehan J, Bradley-Kennedy C, et al. Cost-effectiveness of dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation: a Canadian payer perspective. *Thromb Haemost*. 2011;105:908-19.
- National Institute for Health and Clinical Excellence (NICE). Final Appraisal Determination. Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation. Available at: <http://guidance.nice.org.uk/TA/Wave21/10/FAD/FinalAppraisalDetermination/pdf/English>
- Van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJA, Van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*. 1988;19:604-8.
- Bertomeu-González V, Cordero A, Mazón P, Moreno-Arribas J, Fácila L, Nuñez J, et al. Anticoagulation prescription in atrial fibrillation. *Expert Opin Pharmacother*. 2011;12:1473-9.
- Instituto Nacional de Estadística. Tasa de mortalidad de la población de España año 2009. Available at: <http://www.ine.es/>
- Instituto Nacional de Estadística. Índice de Precios de Consumo. Available at: <http://www.ine.es/>
- Ministerio de Sanidad, Política Social e Igualdad. Nomenclador DIGITALIS-INTEGRA. Marzo 2011. Available at: <http://www.msc.es/profesionales/farmacologia/nomencladorDI.htm>
- Real Decreto-ley 8/2010. BOE de 24 de mayo de 2010:126. Available at: <http://www.boe.es/boe/dias/2010/05/24/pdfs/BOE-A-2010-8228.pdf>
- Ministerio de Sanidad, Política Social e Igualdad. Análisis y desarrollo de los GDR en el Sistema Nacional de Salud. Available at: <http://www.msc.es/estadEstudios/estadisticas/inforRecopilaciones/anaDesarrolloGDR.htm>
- Oblikue Consulting. Base de datos sanitarios eSalud. Available at: <http://www.oblikue.com/bddcostes/>
- de Solà-Morales Serra O, Elorza Ricart JM. Coagulómetros portátiles. Revisión de la evidencia científica y evaluación económica de su uso en el autocontrol del tratamiento anticoagulante oral. Barcelona: AATRM, CatSalut, Generalitat de Catalunya; 2003.
- Navarro JL, Cesar JM, Fernández MA, Fontcuberta J, Reverter JC, Gol-Freixa J. Morbilidad y mortalidad en pacientes con tratamiento anticoagulante oral. *Rev Esp Cardiol*. 2007;60:1226-32.
- Wallentin L, Yusuf S, Ezekowitz MD, Alings M, Flather M, Franzosi MG, et al. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalized ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. *Lancet*. 2010;376:975-83.
- Hervas-Angulo A, Cabases-Hita JM, Forcen-Alonso T. Costs deriving from strokes from a social perspective. A retrospective incidence approach with a follow-up at three years. *Rev Neurol*. 2006;43:518-25.
- Hidalgo A, Oliva J, González A, Aranda I. Cuidados informales asociados a la limitación de la autonomía en supervivientes a accidentes cerebrovasculares. *Gac Sanit*. 2011;25(Espec Congr 1):1-2.
- Jiménez-Martín S, Oliva J, Vilaplana Prieto C. Sanidad y dependencia, matrimonio o divorcio: atención sanitaria y servicios sociales ¿una cuestión de integración o sólo de coordinación?. Madrid: Círculo de la Sanidad; 2011. Available at: <http://www.circulodelasanidad.com/documentos/sanidadydependencia.pdf>
- Sacristán JA, Oliva J, Del Llano J, Prieto L, Pinto JL. ¿Qué es una tecnología sanitaria eficiente en España? *Gac Sanit*. 2002;16:334-43.
- Freeman JV, Zhu RP, Owens DK, Garber AM, Hutton DW, Go AS, et al. Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in atrial fibrillation. *Ann Intern Med*. 2011;154:1-11.
- Pink J, Lane S, Pirmohamed M, Hughes DA. Dabigatran etexilate versus warfarin in management of non-valvular atrial fibrillation in UK context: quantitative benefit harm and economic analyses. *BMJ*. 2011;343:d6333.
- Kansal AR, Sorensen AV, Gani R, Robinson P, Pan F, Plumb J, et al. Cost-effectiveness of dabigatran etexilate for the prevention of stroke and systemic embolism in UK patients with atrial fibrillation. *Heart*. 2012;98:573-8.
- Shah SV, Gage BF. Cost-effectiveness of dabigatran for stroke prophylaxis in atrial fibrillation. *Circulation*. 2011;123:2562-70.
- Freeman JV, Turakhia MP. Revised dabigatran base-case cost-effectiveness estimates and comment responses. *Ann Intern Med*. 2011;154:570.
- Kamel H, Johnston SC, Easton JD, Kim AS. Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in patients with atrial fibrillation and prior stroke or transient ischemic attack. *Stroke*. 2012;43:881-3.
- Langkilde LK, Bergholdt Asmussen M, Overgaard M. Cost-effectiveness of dabigatran etexilate for stroke prevention in non-valvular atrial fibrillation. Applying RE-LY to clinical practice in Denmark. *J Med Econ*. 2012;15:695-703.
- Drummond MF, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. Oxford: Oxford University Press; 1987.
- Schwartz NE, Albers GW. Dabigatran challenges warfarin's superiority for stroke prevention in atrial fibrillation. *Stroke*. 2010;41:1307-9.