Cost and burden of poor anticoagulation control with vitamin K antagonists in patients with nonvalvular atrial fibrillation in Spain

Vivencio Barrios, Sergio Cinza-Sanjurjo, Olga Gavín, Isabel Egocheaga, Ramón Burgos-Pol, Javier Soto, Carlos Polanco, Jorge Suárez, and Miguel Angel Casado

ABSTRACT

Introduction and objectives: The aim of this analysis was to evaluate the burden and cost of complications due to poor anticoagulation control in patients with nonvalvular atrial fibrillation (NVAF) treated with vitamin K antagonists (VKA) in Spain.

Methods: An analytical model was used to estimate annual differences in ischemic stroke, major bleeding, deaths, costs, and potential years of life lost between patients with poor anticoagulation control (time in therapeutic range < 65%) and adequate control (time in therapeutic range ≥ 65%) with a 1-year time horizon. Information on the target population (patients ≥ 65 years), event rates, and costs were obtained from national sources. Direct costs in euros (2018) were included from the perspective of the national health system (NHS) and direct and indirect costs from the societal perspective. A sensitivity analysis was performed with post-hoc data from the SPORTIF III/V trials.

Results: We analyzed a hypothetical cohort of 594,855 patients, 48.3% with poor anticoagulation control, with an increase of 2321 ischemic strokes, 2236 major bleeding events and 14,463 deaths, and an annual incremental cost between €29,578,306 from the NHS perspective and €75,737,451 from the societal perspective. The annual impact of mortality was 170,502 potential years of life lost. The results of the sensitivity analysis showed that the annual cost would reach €97,787,873 from the societal perspective.

Conclusions: Poor anticoagulation control with AVK has a strong impact on loss of health and on increased spending for the NHS.
INTRODUCCIÓN

Los anticoagulantes orales son el tratamiento de elección para la prevención de los accidentes cerebrovasculares y la mortalidad en los pacientes con fibrilación auricular no valvular (NVAF) que están a mayor riesgo de tromboembolia según el score CHA2DS2-VASc. Aunque los antagonistas de la vitamina K (VKA) disminuyen el riesgo de accidente cerebrovascular hasta en un 54% comparado con placebo,2 requieren un monitoreo cuidadoso con ajustes de dosis frecuentes debido a su oscilación terapéutica. Hay evidencia sólida de que los pacientes con anticoagulación ineficaz (con un threshold de TTR < 65%) tienen un mayor riesgo de accidente cerebrovascular, complicaciones hemorrágicas y mortalidad.3-6

En España, la prevalencia de NVAF es de alrededor de 4.4% en personas mayores de 40 años y que llegan a una edad de 17.7% entre los 60-69 años.7 Según el registro europeo PREFER de tromboembolismo, el 80% de los pacientes con NVAF que reciben VKA en España no tienen un control adecuado (TTR < 65%).8 Aunque en los últimos años esta proporción ha disminuido debido a la introducción de los anticoagulantes directos, varios estudios han explorado el control de la anticoagulación en pacientes con NVAF y han identificado un número más alto de pacientes con control inadecuado según el score CHA2DS2-VASc.9,10

Algunos estudios españoles han reportado datos sobre la situación real de los pacientes con NVAF tratados con VKA y el costo de sus complicaciones, sin embargo, no hay información disponible sobre el impacto socioeconomico de la anticoagulación ineficaz en pacientes con NVAF tratados con VKA en el Servicio Nacional de Salud (SNS).

El objetivo de este estudio fue evaluar el costo y el impacto de las complicaciones clínicas para el sistema de salud (SNS) en los pacientes con NVAF debido a un control inadecuado de la anticoagulación (determinado por TTR según el método de Rosendaal) en pacientes con NVAF tratados con VKA.

RESULTADOS: Se analizó una cohorte hipotética de 594.855 pacientes, el 48.3% de ellos con mal control de la anticoagulación, con un aumento de 2.321 ictus isquémicos, 2.236 hemorragias graves y 14.463 muertes, y un costo incremental anual de 29.578.306 euros desde la perspectiva del SNS y 75.737.451 euros desde la perspectiva social. El impacto anual de la mortalidad fue de 170.502 años potenciales de vida perdidos. Los resultados del análisis de sensibilidad muestran que el costo anual alcanzaría los 97.787.873 euros desde la perspectiva social.

CONCLUSIONES: El mal control de la anticoagulación con AVK conlleva un gran impacto en pérdida de salud y aumento del gasto del SNS.

© 2020 Sociedad Española de Cardiología. Publicado por Elsevier España, S.L.U. Todos los derechos reservados.

**Abreviaturas**

INR: internacional normalized ratio  
NHS: National Health Service  
NVAF: nonvalvular atrial fibrillation  
PYLL: potential years of life lost  
TTR: time in therapeutic range  
VKA: vitamin K antagonists

**METHODS**

**Type of analysis**

Un análisis costo-efectivo se realizó utilizando un modelo analítico en Microsoft Excel 2013 para calcular los resultados y los costos asociados a NVAF tratados con VKA, según el control de anticoagulación. Los resultados se expresan como la diferencia en eventos y costos entre pacientes con control de anticoagulación ineficaz (TTR < 65%) y aquellos con control adecuado (TTR ≥ 65%). El análisis fue realizado desde la perspectiva del NHS y las perspectivas sociales y de la vida con un horizonte de 1 año.

**Target population**

La población objetivo para el estudio consistió en pacientes mayores de 65 años con NVAF y tratados con VKA en España. Información del Instituto Nacional de Estadística (INE)9-14 fue consultada para determinar la población de pacientes con NVAF mayores de 65 años, y el estudio aplicó el análisis de prevalencia por edad en el estudio OPRECE15 y el porcentaje de pacientes con NVAF con CHADS2 ≥ 2 tratados con VKA según el estudio VAL-FAAP15.

Por lo tanto, el tratamiento de anticoagulación es un factor determinante para prescribir tratamiento directo en pacientes con NVAF, la revisión de literatura estructurada se realizó para identificar estudios epidemiológicos en el tratamiento de anticoagulación y eventos asociados al control de anticoagulación en España. Los pacientes fueron seleccionados según el TTR según el método de Rosendaal, y aquellos con control adecuado fueron definidos como TTR < 65% y aquellos con control adecuado como TTR ≥ 65%.16

**Characteristics of patients** (age, sex, cardiovascular and bleeding risk according to CHADS2, CHA2DS2-VASc, and HAS-BLED scales) and the percentage of patients with poor or adequate control were obtained by simple averaging of the values from the references.9,10,17-24 The extreme (lowest and highest) prevalences of anticoagulation control were used to define the range for clinical event outcomes and costs9,16 (table 1) to evaluate outcome variability. The study data considered and the characteristics of patients with cardiovascular and bleeding risk are listed in table 1 of the supplementary data.

**Health outcomes**

Para el análisis, los eventos clínicos fueron ictus, hemorragia y mortalidad total. Los eventos clínicos derivados de los  

**Abbreviations**

INR: international normalized ratio  
NHS: National Health Service  
NVAF: nonvalvular atrial fibrillation  
PYLL: potential years of life lost  
TTR: time in therapeutic range  
VKA: vitamin K antagonists
**Figure 1.** Schematic representation of the model. NVAF, nonvalvular atrial fibrillation; VKA, vitamin K antagonists.

**Table 1**
Determination of the target population and event rate

<table>
<thead>
<tr>
<th>Determination of target population</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AF prevalence, segregated by age bracket</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>65-69</td>
<td>4.60%</td>
<td>OFRECE study&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
<tr>
<td>70-74</td>
<td>9.30%</td>
<td>OFRECE study&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
<tr>
<td>75-79</td>
<td>9.30%</td>
<td>OFRECE study&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
<tr>
<td>80-84</td>
<td>17.70%</td>
<td>OFRECE study&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
<tr>
<td>&gt; 85</td>
<td>17.70%</td>
<td>OFRECE study&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Proportion of patients with NVAF and CHADS&lt;sub&gt;2&lt;/sub&gt; ≥ 2 receiving VKA therapy</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>68%</td>
<td>ValFAAP study&lt;sup&gt;15&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**TTR-based anticoagulation control in Spain**<sup>c</sup>

<table>
<thead>
<tr>
<th>Poor control</th>
<th>Adequate control</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor control</td>
<td>48.26%</td>
<td>Mean value&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lowest prevalence, poor control</td>
<td>39.40%</td>
<td>PAULA study&lt;sup&gt;9&lt;/sup&gt;</td>
</tr>
<tr>
<td>Higher prevalence, poor control</td>
<td>57.20%</td>
<td>ESPARTA study&lt;sup&gt;10&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Event rates**

<table>
<thead>
<tr>
<th>Poor control</th>
<th>Adequate control</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic stroke</td>
<td>2.02%</td>
<td>1.84%</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>ND</td>
<td>0.20%</td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>ND</td>
<td>0.07%</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>3.03%</td>
<td>3.85%</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>11.62%</td>
<td>4.20%</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; BC, base case; INR, international normalized ratio; ND, no data; NVAF, nonvalvular atrial fibrillation; SA, sensitivity analysis; TTR, time in therapeutic range; VKA, vitamin K antagonists.

<sup>a</sup> The same prevalence was assumed for the 10-year age brackets of the OFRECE study.

<sup>b</sup> The population was considered to be patients treated with oral anticoagulants and with combined oral anticoagulant and antiplatelet therapy.

<sup>c</sup> Poor control expressed as TTR < 65% and adequate control expressed as TTR ≥ 65%.

<sup>d</sup> Refer to table 1 of the supplementary data.

<sup>e</sup> Poor control with INR < 60% and adequate control with INR > 75%.
Calculation of total deaths per year due to poor anticoagulant control

\[ \text{Target population by age bracket} \times \text{Mortality rate} = \text{Mortality, poor control} \]

Mortality, adequate control

Annual incremental mortality due to poor control according to age bracket

Calculation of potential years of life lost (PYLL) in 1 year

\[ \text{Fixed mortality rate, poor control} \times \text{Life expectancy by age bracket} = \text{Annual PYLL by age bracket} \]

Mortality, adequate control

Calculation of annual PYLL per patient-year

\[ \frac{\text{Annual PYLL by age bracket}}{\text{Target population by age bracket}} = \text{Annual PYLL per patient-year by age bracket} \]

Major bleeding

Figure 2. Calculation of potential years of life lost. PYLL, potential years of life lost. "Weighting based on the weight of each age bracket. Once the age adjustment was applied, the PYLL/patient-year were summed for the various age brackets."

Impact of mortality: potential years of life lost

All-cause deaths in the comparison groups were measured in potential years of life lost (PYLL), by applying the mortality rate to the population aged ≥ 65 years with NVAF treated with VKA with poor anticoagulant control and adequate control by age bracket. Because there was no information according to age bracket, 2 fixed mortality rates were obtained: 1 for poor anticoagulant control and 1 for adequate control in each age bracket, based on the target population and according to the degree of anticoagulant control. Additionally, PYLL are expressed as the difference in mortality between patients with poor control and adequate control, multiplied by the mean life expectancy for each age bracket, taken from National Statistics Institute sources. Last, PYLL and PYLL/patient-year data were obtained by converting the PYLL results for each age bracket divided by the age-adjusted population, i.e., each age bracket was proportionally represented according to the weight of the various age brackets compared with the entire target population (figure 2).

Costs

All clinical events, except all-cause mortality, led to costs and were updated to year 2018 euros based on the consumer price index (CPI) increase since the cost year reported in the original source.26 Direct health, direct nonhealth, and indirect costs of ischemic and hemorrhagic stroke were evaluated from data published by CONOCES,22 an epidemiologic study of first-year costs in patients admitted to stroke units in Spain.

The cost of major bleeding was determined from diagnosis-related groups 174 (gastrointestinal bleeding with complications), 175 (gastrointestinal bleeding without complications), and 810 (intracranial bleeding).25 The proportions of major bleeding (73.7% gastrointestinal bleeding and 26.3% intracranial bleeding) were taken from a study that analyzed bleeds in patients with NVAF and CHADS2 ≥ 2 treated with VKA listed in the National Primary Care Database (SIDIAP)27 (table 2).

Validation

The model structure and the parameters included were validated by an expert panel composed of 4 medical specialists related to management of the disease (1 cardiologist, 1 hematologist, and 2 primary care physicians).

RESULTS

The hypothetical cohort for this study included 594,855 patients with a mean age of 75.4 ± 4.3 years (48.9% women) at high cardioembolic and bleeding risk: 74.4% with CHADS2 ≥ 2 (91.8% if CHA2DS2-VASc scale ≥ 2 is used) and 58.4% with HAS-BLED ≥ 2. The mean prevalence of poor anticoagulant control was 48.3% (n = 287 089), between 39.4% (n = 234 373) and 57.2% (n = 340 257).

Table 2

<table>
<thead>
<tr>
<th>Costs (2018 euros)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ischemic stroke</strong></td>
<td></td>
</tr>
<tr>
<td>Direct health(^a)</td>
<td>9037.22</td>
</tr>
<tr>
<td>Direct nonhealth(^b)</td>
<td>19 259.83</td>
</tr>
<tr>
<td>Indirect(^c)</td>
<td>624.01</td>
</tr>
<tr>
<td><strong>Hemorrhagic stroke</strong></td>
<td></td>
</tr>
<tr>
<td>Direct health(^d)</td>
<td>7467.84</td>
</tr>
<tr>
<td>Direct nonhealth(^e)</td>
<td>21 389.60</td>
</tr>
<tr>
<td>Indirect(^f)</td>
<td>397.87</td>
</tr>
<tr>
<td><strong>Systemic embolism</strong></td>
<td></td>
</tr>
<tr>
<td>Direct health</td>
<td>3846.18</td>
</tr>
<tr>
<td><strong>Major bleeding</strong></td>
<td></td>
</tr>
<tr>
<td>Direct health</td>
<td>2982.61</td>
</tr>
</tbody>
</table>

DRG, diagnosis-related groups; MSCyBS, Ministry of Health, Consumer Affairs and Social Welfare.

\(^a\) Hospitalization cost for the first stroke episode, rehospitalizations during the entire follow-up period related to the stroke or new vascular events (1 year), medical visits, diagnostic procedures and tests, medical treatments, and rehabilitation.

\(^b\) Cost of social services (elderly home or other social and health services and home care), informal care, and other nonhealth costs, such as specialized medical transport services and refurbishments for physical adaptation of spaces.

\(^c\) Productivity loss costs according to the human-capital approach.
Table 3
Number of events per year (base case and sensitivity analysis)

<table>
<thead>
<tr>
<th></th>
<th>Poor control (range)</th>
<th>Adequate control (range)</th>
<th>Difference between poor control and adequate control (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhagic stroke</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>8699 (7101-10 310)</td>
<td>6463 (7570-5347)</td>
<td>2236 (~469 to 4963)</td>
</tr>
<tr>
<td>Deaths</td>
<td>33 360 (27 234-39 538)</td>
<td>18 897 (22 134-15 632)</td>
<td>14 463 (5101-23 906)</td>
</tr>
</tbody>
</table>

Sensitivity analysis

<table>
<thead>
<tr>
<th></th>
<th>Poor control (range)</th>
<th>Adequate control (range)</th>
<th>Difference between poor control and adequate control (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhagic stroke</td>
<td>574 (469-681)</td>
<td>185 (216-153)</td>
<td>390 (252-5287)</td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>201 (164-238)</td>
<td>0</td>
<td>201 (164-238)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>11 053 (9023-13 100)</td>
<td>4863 (5696-4023)</td>
<td>6190 (3128-9077)</td>
</tr>
<tr>
<td>Deaths</td>
<td>12 058 (9844-14 291)</td>
<td>5201 (6092-4303)</td>
<td>6856 (3752-9988)</td>
</tr>
</tbody>
</table>

ND, no data; TTR, time in therapeutic range.

a Poor control expressed as TTR < 65%.

b Adequate control expressed as TTR > 65%.

c The range expresses the results obtained if the lowest and highest prevalence of poor anticoagulant control are applied to studies carried out in Spain.

d All-cause mortality.

e Poor control expressed as TTR < 60%.

f Adequate control expressed as TTR ≥ 75%.

Compared with adequate control, poor anticoagulant control was associated with an increase of 4557 events per year (2321 ischemic strokes and 2236 major bleeds) and 14 463 all-cause deaths (table 3).

The annual cost of events due to poor anticoagulation control, considering only direct health costs, was €29 578 306 (€116/patient-year), mainly due to the cost associated with ischemic stroke (€20 979 365/year), which accounted for 70.9% of event costs.

When considering the societal perspective (including direct nonhealth costs and indirect costs), the impact of poor anticoagulant control was €75 737 451 (€293/patient-year), with ischemic stroke accounting for an even larger portion of the cost (€67 138 510/year; 88.6%)(table 4 and figure 3). The impact on mortality for the entire population analyzed was 170 502.05 PYLL (0.287 PYLL/patient-year).

Table 4
Costs of poor and adequate control of anticoagulant therapy (base case)

<table>
<thead>
<tr>
<th></th>
<th>Poor control (range)</th>
<th>Adequate control (range)</th>
<th>Difference between poor control and adequate control (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHS perspective</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>52 408 627 (42 785 212-62 114 571)</td>
<td>31 429 261 (36 812 657-25 999 698)</td>
<td>20 979 365 (5 972 555-36 114 873)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>33 457 172 (27 313 675-39 653 355)</td>
<td>24 858 231 (29 116 100-20 563 846)</td>
<td>8 598 941 (1 802 425-19 089 509)</td>
</tr>
<tr>
<td>Total</td>
<td>85 865 798 (70 098 887-101 767 927)</td>
<td>56 287 492.18 (65 928 757-46 536 544)</td>
<td>29 578 306 (4 170 130-55 204 382)</td>
</tr>
<tr>
<td>Societal perspective</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>167 718 948 (136 921 938-198 780 072)</td>
<td>100 580 439 (117 808 469-83 204 661)</td>
<td>67 138 510 (19 113 468-115 575 411)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>33 457 172 (27 313 675-39 653 355)</td>
<td>24 858 231 (29 116 100-20 563 846)</td>
<td>8 598 941 (~1 802 425 to 19 089 509)</td>
</tr>
<tr>
<td>Total</td>
<td>201 176 120 (164 235 613-238 433 428)</td>
<td>125 438 669 (146 924 569-103 768 508)</td>
<td>75 737 451 (17 311 043-134 664 920)</td>
</tr>
</tbody>
</table>

ND, National Health Service; TTR, time in therapeutic range.

a Poor control expressed as TTR < 65%.

b Adequate control expressed as TTR ≥ 65%.

c The range expresses the results obtained if the lowest and highest prevalence of poor anticoagulant control are applied to studies carried out in Spain.

DISCUSSION

The results of this study, the first in Spain to analyze the costs associated with oral anticoagulation quality, reveal the clinical and economic impact of poor control among patients receiving VKA therapy, a common clinical situation in Spain and a risk


discussed in the context of the current healthcare system.
factor for stroke in patients with NVAF. Another relevant finding of the analysis is the estimated mortality among these patients, expressed as PYLL.

The analysis started with the prevalence figures according to age bracket from the OFRECE, CARDIOTENS, PREV-ICTUS and AFABE studies, but the prevalence data from Gómez-Doval et al. were finally used because the study population was the most relevant. The percentage of VKA use was taken from the Val-FAAP study, which described a population receiving oral anticoagulants in a similar sample with similar characteristics to the cohort analyzed (population with CHADS2 ≥ 2, 74.4%). Although this study did not specify the type of anticoagulant therapy, it is assumed to be VKA in all patients because the study was conducted between 2009 and 2010, when direct-acting oral anticoagulants were rarely used. However, although the European PREFER registry has reported on VKA usage in Spain (80%), the present study was finally based on the levels from Barrios et al., because the patients in this study were at high cardioembolic risk (CHADS2 ≥ 2), similar to the cohort analyzed.

This analysis included studies evaluating the quality of anticoagulant therapy based on TTR according to the Rosendaal method using 65% as a cutoff point, as the method is considered most orthodox, is widely used in our field, and is recommended by health authorities. The PAULA and ESPARTA studies provided the extreme values for the analysis.

Despite the magnitude of the levels analyzed, the estimated impact of poor anticoagulant control could be lower than the real-world impact. According to the AFABE study results, 23.5% of patients with known AF and moderate-to-high cardioembolic risk (CHA2DS2-VASc ≥ 2) did not receive anticoagulant therapy and, therefore, a large patient population would not be included in the analysis. However, no cost was assigned to mortality, as no data were found on the amounts. In addition, the direct nonhealth and indirect costs of systemic embolism and major bleeding have not been identified and, therefore, these costs were not included in the analysis.

The limitations of this analysis include aspects related to calculating the target population (NVAF prevalence) and event rates. First, prevalences were applied to each age bracket (10-year intervals) from the OFRECE study to the population prevalences taken from the Spanish Statistics Institute (5-year intervals), which could underestimate the prevalences in the older groups of each bracket. Second, in the real-world study conducted in Spain by Rivera et al., event rates were limited to ischemic stroke, major bleeding, and all-cause mortality, unlike the study used in the sensitivity analysis (post hoc analysis of the SPORTIF III and V clinical trials performed in 23 countries in Europe, Asia and Oceania, United States, and Canada), which also included ischemic stroke and systemic embolism rates. Third, questions could be raised regarding the suitability of the White et al. study for the sensitivity analysis, as it was an international multicenter study with a different definition of poor anticoagulant control from ours (poor control, TTR < 60%; good control, TTR > 75%). However, the differences in rates used in the 2 studies were very similar between the groups (difference between adequate and poor control in ischemic stroke, 0.89% vs 0.82%; major bleeding, 0.93% vs 2.27%; mortality, 5.48% vs 2.51% in the base case and sensitivity analysis, respectively). Hence, it can be stated that the event and mortality rates used are valid in our model. Nevertheless, although the prevalence of NVAF has been applied by age bracket, the same exercise could not have been undertaken with the prevalence of poor control and the event rates because the information was not segregated by age. Furthermore, it would have been interesting to evaluate the clinical and economic impact of poor anticoagulant control according to possible differences between various regions of Spain, as mentioned in the PAULA study. Last, the analysis was limited to a 1-year time horizon, considering the 1-year unit costs of ischemic stroke and hemorrhage for these events (CONOCES study), which may not be representative of the entire natural course of the disease.

Despite the above-mentioned limitations, the study results underscore the high socioeconomic impact of poor control of VKA therapy in Spain, essentially based on acenocoumarol (although no differences were observed in the quality of anticoagulation control or events compared with warfarin). This poor control may have various causes: the presence of comorbidities (eg, kidney failure, type 2 diabetes mellitus, hypertension), factors such as labile international normalized ratio (INR), high bleeding risk, female sex, dietary habits, multidrug therapy, and prolonged use of antiplatelet agents. Obviously, nonadherence is a key factor (as with all long-term therapy), as observed in the REACT-AF study, which observed adherence > 80% in only 34.9% of patients. The last possible cause is therapeutic inertia, reported in studies such as ESPARTA, in which therapy was not switched to a direct-acting oral anticoagulant in 65.6% of NVAF patients at high risk of stroke (CHA2DS2-VASc ≥ 2) and treated with VKA who did not maintain INR within therapeutic range.

Irrespective of these considerations, poor anticoagulant control in Spain, in addition to affecting NVAF patients by compromising their clinical prognosis and producing higher mortality and disability, makes the NHS less efficient. The results of this study reveal the clinical and economic impact of poor anticoagulant control in NVAF patients treated with VKA, highlighting the potential importance of a change in clinical practice to lower the disease burden.

CONCLUSIONS

This study shows that higher rates of thrombotic, bleeding events, and mortality among patients with poor anticoagulant...
control treated with VKA represent a cost of more than €75 million per year (from the societal perspective) and a high impact of mortality, expressed in PYLL (up to 170 502 per year). Because this is a major issue for patients and the NHS, measures should be implemented to reduce the number of patients receiving VKA therapy who have poor anticoagulant control, thus minimizing the socioeconomic impact in our setting.

**FUNDING**

BMS and Pfizer provided unconditional funds for this project.

**CONFLICTS OF INTEREST**

V. Barrios, S. Cinza-Sanjurjo, O. Gavín, and I. Egocheaga declare no conflicts of interest. R. Burgos-Pol and M.A. Casado are employees of PORIB. C. Polanco and J. Suárez are employees of BMS. J. Soto is an employee of Pfizer.

**WHAT IS KNOWN ABOUT THE TOPIC?**

- VKA therapy is indicated in patients with NVAF and high cardioembolic risk.
- VKA therapy requires monitoring and dose titration. The time in therapeutic range, as measured by the Rosendaal method, evaluates the quality of monitoring of VKA anticoagulation and correlates with the appearance of thromboembolic or bleeding events.
- Numerous studies have shown that a high percentage of patients are not properly anticoagulated, a situation associated with a higher incidence of thromboembolic events, bleeds, and mortality.

**WHAT DOES THIS STUDY ADD?**

- This study is a cost-impact model based on real-world studies, providing clinical and economic information on the high impact of poor control of VKA anticoagulation in Spain.
- Clinical events could be as high as 4557, with a cost of €30 to 75 million per year, according to the perspective used.

**REFERENCES**


