PCV23 - Clinical and economic impact of non-VKA anticoagulants increased use in the treatment of nonvalvular atrial fibrillation in Spain based on real-life data.

Carlos Escobar Cervantes[1], Julio Martí-Almor[2], Alejandro Pérez Cabeza[3], Miriam Prades Martí[4], Susana Aceituno Mata[4]

1 Departamento de Cardiología, Hospital La Paz, Madrid (Spain); 2 Servicio de Cardiología, Hospital del Mar, Barcelona (Spain); 3 Servicio de Cardiología, Hospital Costa del Sol, Marbella, Málaga (Spain); 4 Outcomes'10 S.L.U., Castellón (Spain)

Introduction

- Atrial fibrillation (AF) is a highly prevalent arrhythmia, affecting the 4.4% of adults older than 40 years of age [1] in Spain, being associated with increased rates of death, stroke, and other thrombo-embolic events [2,3]. Most cases of AF have a non-valvular origin (NVAF) and suppose the most frequent cardiac cause associated to stroke, about 50% [3,4].
- Stroke is associated with severe disability and dependence, involving significant increases in direct and indirect costs, approximately 67% of the total cost corresponds to direct non-medical and indirect costs [5].
- All reference clinical guidelines [6-10] recommend non-VKA anticoagulants (NOACs) over vitamin K antagonists (VKA) for preventing stroke and systemic embolism in NVAF patients. Despite this, in Spain, the local Therapeutic Positioning Report [9] positions NOACs as a second line therapy after VKA, in part, due to efficiency concerns.

Objectives

- Make an estimation, for a 10-year horizon, of the clinical and economic impact of NVAF and associated complications in patients receiving anticoagulant treatment, from the perspective of the Spanish National Health System (NHS).
- To estimate the clinical and economic impact of increasing the use of NOACs vs VKA through a reduction in current use restrictions, getting closer to the recommendations of all clinical practice guidelines.

Methods

Model structure

- A prevalence-based Markov model was developed in Excel to simulate the evolution of patients on the Spanish population with NVAF, ≥40 years of age, at high risk of stroke according to the CHA2-DS2-VASc score (≥ 2) and treated with anticoagulant treatment.
- The target population was estimated based on the prevalence, incidence and mortality data extracted from the literature (Figure 1).
- A Markov model (annual cycles and 10-year horizon) was used for each treatment cohort (Figure 2). Each patient could only experience 1 complication per cycle and only 1 recurrence of event was permitted. Population was distributed according to NOACs (rivaroxaban, dabigatran, apixaban) and VKA (acenocumarol) usage[13] (Figure 3).

Transition probabilities

- The transition probabilities of major non-fatal events (stroke, SE, ICH and MH) and all-cause death were calculated by applying the hazard ratios (HR) of NOACs[16,17] versus VKA[18,19] (Table 1). HR for major non-fatal events and all-cause death were obtained from the meta-analysis by Escobar et al. [16] and Coleman et al. [17] respectively, as Escobar et al. [16], did not provide mortality data. Both studies were based on real-life data.

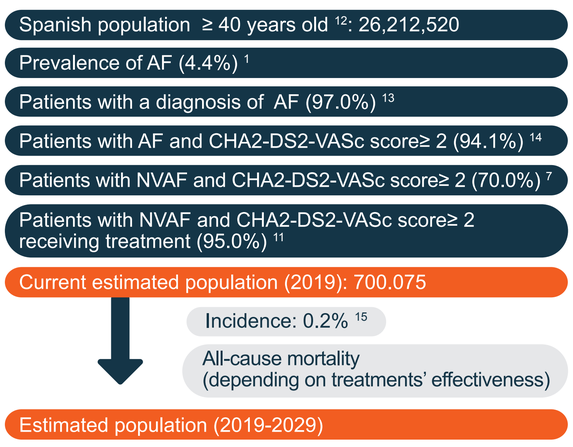
Costs

- Only direct health costs (€, 2,019) associated to pharmacological treatment, patient follow-up and major non-fatal events have been included. Costs were discounted at a rate of 3.0% [20].
- Pharmacological treatment (€32.78 per cycle for VKA and €654.99 for NOACs [ex-factory prices])[21] was calculated based on the recommendations of the Summary of Product Characteristics. A mandatory discount was applied according to the applicant law [22].
- Patient follow-up: an annual cost of €1,603.41 for VKA and €1,011.53 for NOACs was estimated. This cost includes International Normalized Ratio (INR) monitoring (€339.20 vs €0), primary care and specialists' visits (€768.97 vs €647.13) and laboratory tests (€495.24 vs €364.39). The resources use was based on experts' opinion. Unit costs were extracted from Spanish databases [21,23].
- Costs associated to events (acute phase and follow-up during first and subsequent years) were extracted from literature (Table 2) [24-26].

Analysis

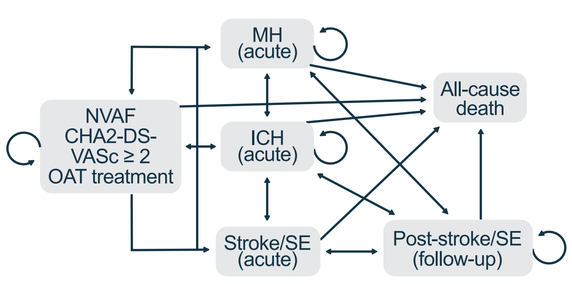
- The clinical and economic impact of NVAF and associated complications in patients receiving anticoagulant treatment (base case scenario) was estimated through the following outcome measures: cumulative (10-years) number and rate (per 1,000 patients/year) of major non-fatal events (stroke, systemic embolism, major and intracranial hemorrhage) and all-cause deaths, cumulative cost and annual cost per patient.
- In addition, the clinical and economic impact associated with the increased use of NOACs vs VKA has been assessed by calculating the difference in major non-fatal events, all-cause deaths and costs obtained in the base case and in four alternative scenarios (Figure 3).

Figure 1. Estimation of the target population



AF: atrial fibrillation; NVAF: non-valvular atrial fibrillation

Figure 2. Markov diagram: health states



NVAF: non-valvular atrial fibrillation; OAT: oral anticoagulant therapy; MH: major hemorrhage (extracraneal); ICH: intracranial hemorrhage; SE: systemic embolism.

Table 1. Effectiveness, safety and mortality data

	Rivaroxaban		Dabigatran		Apixaban	
Event	**HR (95% CI)**	**Pr**	**HR (95% CI)**	**Pr**	**HR (95% CI)**	**Pr**
Stroke /SE [16]	0.800 (0.690-0.930)	0.0100	0.920 (0.760-1.110)	0.0114	0.880 (0.640-1.210)	0.0109
Major hemorrhage [16]	1.020 (0.950-1.100)	0.0107	0.830 (0.700-0.970)	0.0087	0.660 (0.550-0.800)	0.0069
Intracranial hemorrhage [16]	0.660 (0.490-0.880)	0.0024	0.450 (0.390-0.510)	0.0016	0.560 (0.420-0.730)	0.0020
All-cause death [17]	0.50 (0.290-0.850)	0.016	0.650 (0.550-0.760)	0.020	0.650 (0.550-0.760)*	0.020*

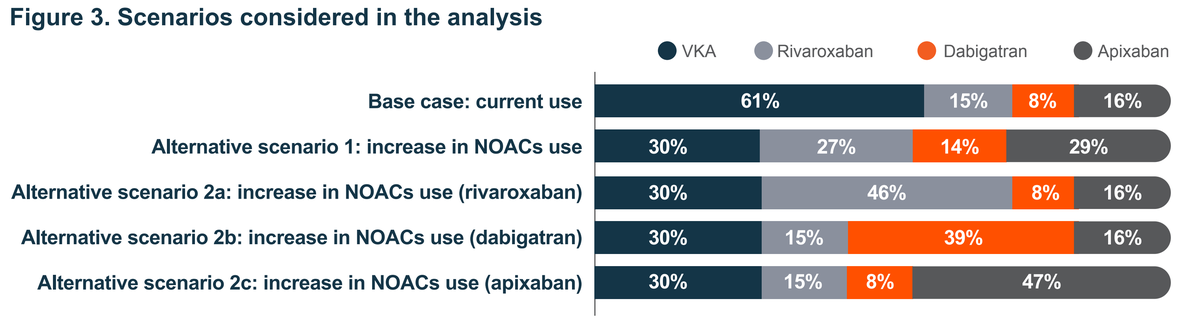
CI: confidence interval, HR: hazard ratio; Pr: Probability; SE: systemic embolism

** The original HR all-cause death for apixaban was 0.32 (95% IC: 0.05-2.08)[17]. Since HR is not statistically significant with a very wide 95% CI it was assumed the same probability of death from any cause of dabigatran. This assumption is considered conservative since according to the real-life data we cannot confirm that the probability of death from any cause is lower in the population receiving apixaban vs VKA.*

Table 2. Cost of major non-fatal events (first and subsequent years)

Major non-fatal event	Cost of 1st year (acute phase + follow-up)	Cost of subsequent years
Stroke	€15,535.35	€11,183.92
Systemic embolism	€5,393.74	€1,499.93
Major hemorrhage	€3,678.40	-
Intracranial hemorrhage	€6,209.26	-

Figure 3. Scenarios considered in the analysis



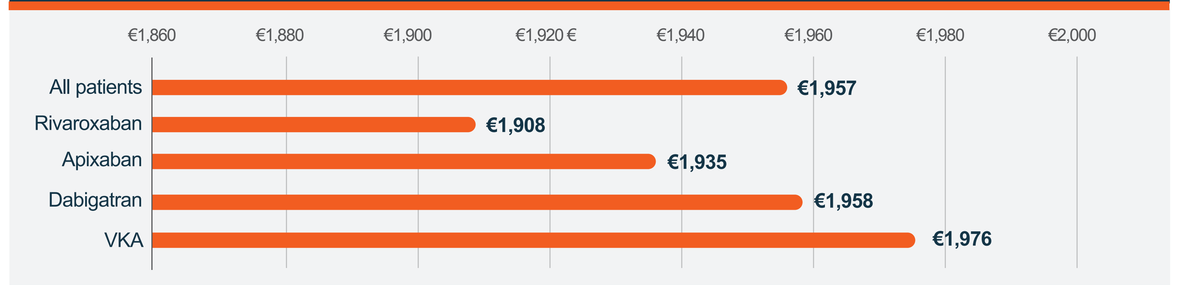
- One-way sensitivity analyses (OWSA) of all variables were included in the model over their plausible ranges derived from 95% CI or applying ±10%. OWSA analyses were performed for the base case results and for the impact results obtained through the comparison between base case and each alternative scenario.

Results

Base case

- The cumulative number of major non-fatal events and all-cause deaths over the time horizon was 192,197 (23.71 per 1,000 patients/year) and 206,944 (25.53 per 1,000 patients/year), respectively. The lower rates of stroke, SE and all-cause mortality were obtained in patients treated with rivaroxaban (7.98, 1.60 and 15.07 per 1,000 patients/year, respectively).
- The cumulative (10-years) cost was estimated at €15,864,100,618, resulting in a mean annual cost per patient of €1,957. Patients receiving rivaroxaban showed the lowest annual cost per patient (Figure 4).

Figure 4. Annual mean cost per patient with NVAF in anticoagulant treatment (base case) over the 10-year time horizon



Alternative scenarios

- The increase in use of NOACs compared with VKA reduced the number of major non-fatal events and all-cause deaths (-37,937) (Table 3).
- The preferential use of rivaroxaban could lead to a highest reduction in strokes and all-cause deaths (-3,584 and -35,536). The lowest number of hemorrhage was associated with increased use of apixaban (-11,173).
- The increase in use of NOACs compared with VKA (alternative scenario 1) reduced the cost per patient (-€17) (Table 4).
- The preferential use of rivaroxaban (alternative scenario 2a) could lead to a highest reduction in cost per patient (-€24) (Table 4). Considering that direct non-medical and indirect costs may represent 67% of the total cost of stroke [5], an increased use of rivaroxaban would result in even more savings compared to the other scenarios (base case, increase in dabigatran and increase in apixaban) if these costs were accounted for.

Table 3. Difference of events (n) between base case and alternative scenarios

Event	Base case	Alternative scenarios			
		1	2a	2b	2c
Stroke	76,734	-2,331	**-3,584**	-872	-1,886
Systemic embolism	15,347	-466	**-717**	-174	-377
Hemorrhage (major and intracranial)	100,116	-6,298	-325	-7,749	**-11,173**
All-cause deaths	206,944	-28,841	**-35,536**	-24,657	-24,657
Total (major non-fatal events and all-cause deaths)	399,141	-37,937	**-40,162**	-33,453	-38,093

Data in bold indicates the greatest events reduction

Table 4. Difference of annual costs per patient between base case and alternative scenarios

Type of cost	Base case	Alternative scenarios			
		1	2a	2b	2c
Pharmacological cost	**€242**	+€168	+€169	+€168	+€168
Monitoring cost	€1,191	**-€160**	**-€161**	**-€160**	**-€160**
Major non-fatal event cost	€524	-€25	**-€31**	-€16	-€23
Total cost	€1,957	-€17	**-€24**	-€8	-€15

Data in bold indicates the greatest savings

Sensitivity analysis

- Results obtained from the OWSA showed the robustness of the analysis. AF incidence was the parameter with greatest impact in the OWSA performed for the base case. Follow-up cost, effectiveness and mortality data were the main parameters influencing the results obtained in the comparisons between base case and alternative scenarios.

Conclusion

A less restrictive prescription scenario in Spain, with an increased NOACs use following the recommendations of all clinical practice guidelines, would translate in better health outcomes, lower all-cause mortality and a lower cost per patient, being rivaroxaban the NOAC associated with lower strokes, mortality and cost.

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Disclosures

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