



ORIGINAL
RESEARCH

Budget impact analysis resulting from the use of dabigatran etexilate in preventing stroke in patients with non-valvular atrial fibrillation in Italy

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ABSTRACT

Background: atrial fibrillation (AF) is the most common form of alteration in cardiac rhythm and associated with more severe episodes of stroke. Treatment with oral anticoagulants vitamin K antagonists (VKA) such as warfarin, is nowadays the therapy of choice for stroke prevention in patients with AF, but dabigatran etexilate (DE) 150 mg twice daily was more clinically effective than warfarin in reducing the risk of stroke or systemic embolism, ischaemic stroke and vascular mortality whereas DE 110 mg twice daily was non-inferior to warfarin.

Aim: to assess the affordability of the use of DE for the Italian NHS, in patients with non-valvular AF (NVAf) through a budget impact analysis (BIA).

Methods: the BIA in a timeframe of 5 years was divided into 3 scenarios (1: current management of patients with NVAf; 2: all patients with NVAf treated with VKA; 3: all patients with NVAf treated with DE). The population considered is the one with indication for anticoagulation. Analysis is from the NHS perspective: therefore, indirect costs are excluded.

Results: the underuse of oral anticoagulation, associated with the difficulty in keeping the patients treated with VKA within an acceptable therapeutic range, results in an enormous social and human cost, represented by a total of more than 63,000 strokes cumulated in the 5-year period considered. The cumulative cost for the scenario 1 over the 5-year period is over € 2.3 billion. In the scenario 2 the number of strokes avoided per year increases by -5,219 compared to no treatment (-2,368 compared to scenario 1), although the number of events remains high (about 10,000 events/year). In the 5-year observation period the scenario 2 would result in a reduction in the total number of strokes (-12,323 events vs. scenario 1), and savings for the NHS of around 95 million Euros compared to scenario 1. In the Scenario 3 there is a reduction of more than 38,600 of the total cumulative number of strokes vs. the scenario 1 and over 26,200 vs. scenario 2, and savings for the NHS at the fifth year of observation of circa 174 million Euros vs. scenario 1 and 123 million Euros vs. scenario 2.

Conclusion: DE in Italy is economically sustainable, as it allows savings for the NHS in the management of patients with NVAf from the second year vs. no treatment and vs. treatment with VKA.

Keywords

Dabigatran etexilate; Vitamin K antagonists; Non-valvular atrial fibrillation; Budget impact analysis

INTRODUCTION

Atrial fibrillation (AF) is the most common form of alteration in cardiac rhythm, with a prevalence of 1-2% in the general population [1]. AF, even in its non-valvular form (NVAf), is associated with more severe episodes of stroke, with a higher degree of residual disability, or associated with increased mortality, particularly in patients aged ≥ 75 years [2]. In Western countries, the annual cost of treatment for patient with AF is estimated to be about € 3,000 [3], which projected on the Italian population (543,000

subjects with NVAf in 2011) causes a potential expenditure of € 1,629,000,000 (about 2% of total public health expenditure). This expenditure is mainly due to the number of events caused by AF (stroke, intracranial and extracranial hemorrhages, transient ischemic attacks, myocardial infarction, etc.). Of these, the stroke is the most important event in terms of economic impact for the National Health Service (NHS), being the third leading cause of death (after cardiovascular diseases and cancer) and the leading cause of long-term serious disability [4].

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In Italy there are about 200,000 people affected by stroke every year: of these, 40,000 die shortly after and another 40,000 lose completely their self-sufficiency, completely changing their lives and those of their families [4]. It is estimated that 15% of total stroke is attributable to subjects with AF (about 30,000 strokes) [4]. Given these events, the cost to the NHS per stroke is about € 17,500, the annual total cost € 3,500,000,000 for all strokes and € 525,000,000 for those caused by AF [4]. Treatment with oral anticoagulants vitamin K antagonists (VKA) such as warfarin, is nowadays the therapy of choice for stroke prevention in patients with atrial fibrillation [5]. However, the difficulty in maintaining the anticoagulant effect in the therapeutic range greatly limits its effectiveness, increasing the probability of bleeding, as well as representing a contraindication to the prescription of therapy in patients with poor compliance or unable to perform the necessary laboratory checks. In addition, many patients who are administered this therapy, if not followed in specialized centers (TAO – anticoagulation therapy center) may suffer from inadequate anticoagulation [6]. In the RE-LY study (Randomized Evaluation of Long-Term Anticoagulation Therapy), dabigatran etexilate has proved effective as warfarin at the lowest dose (110 mg twice daily) and significantly more effective than warfarin at the highest dose (150 mg twice daily) in preventing stroke and systemic embolisms over a two-year period of treatment in patients with atrial fibrillation and risk of stroke [7].

AIM OF THE STUDY

The study aims to assess the affordability of the use of dabigatran etexilate (DE) for the Italian NHS, in patients with NVAF through a budget impact analysis in a timeframe of 5 years.

METHODS

Scenarios and reference population

The budget impact analysis in a timeframe of 5 years was divided into 3 scenarios:

- Scenario 1: current management of patients with NVAF.
- Scenario 2: all patients with NVAF treated with VKA.
- Scenario 3: all patients with NVAF treated with DE.

The population considered is the one with indication for anticoagulation. Therefore, also patients intolerant of VKA and patients with severe renal impairment are included.

Both types of patients are distributed evenly (VKA-treated patients and patients treated with dabigatran etexilate) among the various scenarios, avoiding biases regarding the comparison among the budget impacts.

Assumptions of the analysis

This was an analysis from the Italian NHS perspective: therefore, indirect costs are excluded, although they represent a major economic burden, in the case of warfarin use, both for families and society. Moreover, for estimating the target population of the analysis and the associated costs, the following assumptions are considered:

- In Italy, NVAF patients with indication for anticoagulation therapy are 335,000 (Appendix A).
- The risk of stroke is 4.5% per year in patients with untreated NVAF [8].
- The reduction in the risk of ischemic stroke associated with the treatment with warfarin, at adjusted dosage in order to achieve INR values between 2 and 3, is 65% [9].
- The incidence of hemorrhagic stroke with warfarin, well controlled, is equal to 0.38 x 100 patients/year [7,10].
- The average time in therapeutic range (TTR) in Italy for patients treated with VKA is equal to 56.3% [11].
- The odds of ischemic events is 43% in patients treated with warfarin with TTR < 60% [12].
- The average cost of management of acute stroke is equal to 17,500 €/year [4].
- The average cost of managing post-stroke period is equal to 7,600 €/year [13].
- The costs of management of stroke here considered may be conservative, since it is known that the atrial fibrillation-related strokes are generally more severe and disabling [4].
- The average cost of INR is equal to 355 €/year (LR Veneto data [14] updated to 2010, Istat index).
- The cost of warfarin is 0.05 €/day (16.2 €/year).
- The assumed cost of dabigatran etexilate is 2.10 €/day (current price in Spain; today, May 2012, the lowest price in Europe).
- Patients treated with dabigatran etexilate undergo creatinine clearance tests (kidney check-up). We assume once a year (cost = 1.80 €/service according to Regional Tariff).
- There is an increase in the number of patients with NVAF in the considered years of 2% per year [15], even after considering a 12% mortality of the

population (about twice the mortality of the general population in age-matched groups, as indicated in the 2010 ESC guidelines [16]).

- Dabigatran etexilate 150 mg causes a 75% reduction in stroke risk compared with no treatment (RR = 0.25; 95%CI: 0.12-0.51) [17].
- Dabigatran etexilate 110 mg results in a 65% reduction in stroke risk compared with no treatment (RR = 0.35; 95%CI: 0.17-0.71) [17].
- The incidence of hemorrhagic stroke with dabigatran etexilate is 0.11 x 100 patients/year in the RE-LY study [7,10]. In Europe, regulatory authorities recommend the use of dabigatran etexilate 150 mg twice daily for patients younger than 80 years (approximately 55,8% of the total population eligible to treatment) and 110 mg twice daily for patients aged ≥ 80 years (approximately 55,8% of the total population eligible to treatment).

In order to simplify the comparison, it was assumed that:

- In every scenario, all patients are treated from the first day of every year, to assess the maximum potential impact of the various costs.
- The adherence to the treatment for dabigatran etexilate and warfarin is 95% (728 €/year and 16,2 €/year, respectively) [7,10].
- The datum on the time in therapeutic range ($2 \leq \text{INR} \leq 3$) used is that for the patients treated for more than 1 year. This is justified by the fact that international and national studies show that, for patients treated for less than 1 year, the TTR is significantly lower than the TTR correlated with a longer duration of anticoagulant treatment, remaining below the average figure of 50% [4,11]. In fact, as widely recognized by the international scientific community [3], these patients are at significantly greater risk of developing a stroke than others. On the other hand, the inclusion of this parameter in scenarios 1 and 2 would have led to a considerable increase in the hypothetical cost of disease management or an advantage in the scenario where dabigatran etexilate is used. It was therefore decided to prefer the simplicity of analysis of the model and not to include this additional parameter.

Sensitivity analysis

Finally, a one-way sensitivity analysis was performed on the costs of monitoring patients on VKA therapy and on the costs of the drug; both parameters, taken into ac-

count, are those most affected by a high variability (heterogeneity of monitoring costs), uncertainty (the price of the drug will be determined by AIFA) and impact on the final budget impact result. The minimum (€ 212) and maximum (€ 446) value of the costs of treatment monitoring of patients on VKA therapy was extracted from a research done by ANMDO (2012) in collaboration with the Centro Interdipartimentale di Studi Internazionali sull'Economia e lo Sviluppo (CEIS) at the Faculty of Economics, University of Rome Tor Vergata, and the Centro di Ricerche e Studi in Management Sanitario (CERISMAS) at the Catholic University of Sacro Cuore in Rome. Variations of +/-10% were applied to the cost of the drug.

RESULTS

Scenario 1: current management of patients with NVAF

In the year 1 (2011), 335,000 individuals with NVAF have indication for oral anticoagulation, of whom approximately 183,000 are treated with VKA, while the remaining 152,000 aren't treated with oral anticoagulants. In Table I the current situation versus no treatment is analyzed in terms of events prevented by the current management of disease (year 1). Table II shows the 5-year prediction of ischemic and hemorrhagic strokes in the Italian situation.

From Table I it is clear how the current treatment of NVAF involves the reduction of only 2,851 strokes, in the first year of observation, compared with the total number of strokes developed in the scenario of total non-treatment (15,075). This confirms that, despite the enormous organizational effort, there is still a major unmet need in the management of NVAF. The underuse of oral anticoagulation, associated with the difficulty in keeping the patients treated with VKA within an acceptable therapeutic range, results in an enormous social and human cost, represented by a total of more than 63,000 strokes cumulated in the 5-year period considered (Table II).

Starting from the cost assumptions reported in the background when presenting the scenarios, Table III shows the current cost of management of NVAF. Table III shows that the cumulative cost over the 5-year period is over € 2.3 billions and the major cost generator in the management of NVAF is the cost of stroke management (€ 2.03 billions). Indirect costs, burdening families and society, were not considered in this analysis. According to the CENSIS survey, presented in 2011

No treatment		
Total patients with NVAF (nr.)		335,000
Risk of stroke (%/year)		4.50
Total strokes (nr./year)		15,075
Current situation		
	Pts treated with VKA	Pts not treated with VKA
Total patients with NVAF (nr.)	183,000	152,000
Number of strokes (nr./year)	8,235	6,840
VKA: risk reduction with "real life"-TTR of 56.3% (%)	-43	0
Ischemic strokes (nr./year)	4,694	6,840
Total ischemic strokes (nr./year)		11,534
Hemorrhagic strokes (nr./year)	690	0*
Total hemorrhagic strokes (nr./year)		690
Total ischemic/hemorrhagic strokes (nr./year)		12,224
Total ischemic/hemorrhagic strokes prevented vs. no treatment (nr./year)		2,851

Table I. Current situation vs. no treatment (year 1)

* The figure of hemorrhagic strokes (total per year), in the group of patients not treated with VKA, has been considered to be zero to simplify the calculation

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Events in no treatment (nr.)	15,075	15,377	15,684	15,998	16,318	78,452
Events in current situation (nr.)	12,224	12,468	12,718	12,972	13,232	63,614
Prevented events current situation vs. no treatment (nr.)	2,851	2,909	2,966	3,026	3,086	14,838

Table II. Prevented events (ischemic and hemorrhagic strokes), current situation vs. no treatment over 5 year

Cost item	Year 1	Year 2	Year 3	Year 4	Year 5	Total
INR monitoring (€ x 1,000)	64,965	6,264	67,590	68,941	70,320	338,080
VKA (€ x 1,000)	2,965	3,024	3,084	3,146	3,209	15,428
Management of ischemic/hemorrhagic stroke (€ x 1,000)	213,920	311,228	406,259	503,086	601,745	2,036,237
Total cost (€ x 1,000)	281,850	380,516	476,933	575,173	675,274	2,389,745

Table III. Current cost of management of NVAF in the scenario 1 (current situation)

at the World Day of stroke, every stroke patient costs about € 30,000 to the family per year [18].

No treatment	
Total patients with NVAF (nr.)	335,000
Risk of stroke (%/year)	4.50
Total strokes (nr./year)	15,075
Pts treated with VKA	
Total patients with NVAF (nr.)	335,000
VKA: risk reduction with "real life"-TTR of 56.3%	-43%
Total observed ischemic strokes (nr./year)	8,593
Total hemorrhagic strokes (nr./year)*	1,263
Total ischemic/hemorrhagic strokes (nr./year)	9,856
Total ischemic/hemorrhagic strokes prevented vs. no treatment (nr./year)	5,219

Table IV. Patients treated with VKA vs. no treatment (year 1)

* 0.38% per year

Scenario 2: all patients with NVAF treated with VKA

Scenario 2 was developed on the assumption that all patients with NVAF are treated with VKA. This is a hypothetical scenario, since there are both structural and therapeutic limitations. Structural limitations due to the uneven presence of anticoagulation therapy centers on the Italian territory, despite such therapy is available for over 50 years. Therapeutic limitations due to:

- Resistance to the use of VKA for fear of bleeding.
- Difficult management of this therapy, making more than 30% of patients treated with VKA discontinue therapy after one year.
- Difficulty in maintaining the patients treated with VKA within an acceptable TTR.

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Events in no treatment (nr.)	15,075	15,377	15,684	15,998	16,318	78,452
Events in VKA treatment (nr.)	9,856	10,053	10,254	10,459	10,668	51,290
Prevented events VKA vs. no treatment (nr.)	5,219	5,323	5,430	5,539	5,649	27,160

Table V. Prevented events (ischemic and hemorrhagic strokes) VKA treatment vs. no treatment over 5 year

Cost item	Year 1	Year 2	Year 3	Year 4	Year 5	Total
INR monitoring (€ x 1,000)	118,925	121,304	123,730	126,204	128,728	618,890
VKA (€ x 1,000)	5,427	5,536	5,646	5,759	5,874	28,242
Management of ischemic/hemorrhagic stroke (€ x 1,000)	172,479	250,928	329,447	408,035	486,696	1,647,585
Total cost (€ x 1,000)	296,831	377,767	458,823	539,999	621,298	2,294,718

Table VI. Cost of patients treated with VKA vs. no treatment over 5 years

Scenario 2 vs. scenario 1	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Ischemic strokes (nr.)	-2,941	-3,000	-3,060	-3,121	-3,184	-15,306
Hemorrhagic strokes (nr.)	573	585	596	608	620	2,983
Total ischemic/hemorrhagic strokes (nr.)	-2,368	-2,415	-2,464	-2,513	-2,563	-12,323
Cost of INR monitoring (€ x 1,000)	53,960	55,039	56,140	57,263	58,408	280,810
Drug cost (€ x 1,000)	2,462	2,512	2,562	2,613	2,665	12,814
Cost of management of ischemic/hemorrhagic stroke (€ x 1,000)	-41,441	-60,299	-76,812	-95,051	-115,049	-388,651
Total cost (€ x 1,000)	14,982	-2,748	-18,110	-35,175	-53,975	-95,027

Table VII. VKA treatment of all patients vs. current situation over 5 years

Table IV lists the number of ischemic and hemorrhagic strokes resulting from this scenario, and how many of them would be avoided in comparison with the current situation. Table V shows the prediction of the 5-year period of ischemic and hemorrhagic strokes after treatment with VKA of the entire Italian population with NVAF.

In this scenario (Table IV), the number of strokes avoided per year increases to -5,219 compared to no treatment (-2,368 compared to the current situation), although the number of events remains high (about 10,000 events/year; Table V). Starting from the cost assumptions reported in methods section, Table VI shows the cost of management of NVAF if all patients were treated with VKA. Again, as in the previous scenario, the cumulative cost over the 5-year period is over 2 billion Euros (2.294 billion Euros).

Although in the presence of a theoretical extensive use of the VKA on all patients, the difficulty of maintaining within an acceptable therapeutic range the patients treated with VKA imposes an enormous social and human cost, represented by a total of approximately

51,000 strokes cumulated in the 5-year period under analysis.

The Table VII shows that an extensive use of VKA, scenario 2, in the 5-year observation period would result in:

- A reduction in the total number of strokes (12,323 fewer events in scenario 2 than in scenario 1).
- Savings for the NHS of around 95 million Euros compared to scenario 1.

Scenario 3: all patients with NVAF treated with dabigatran etexilate

Scenario 3: all patients with NVAF treated with dabigatran etexilate Tables VIII-IX show the potential ischemic and hemorrhagic strokes when using dabigatran etexilate on the entire population with NVAF.

Tables VIII and IX show that:

- The total number of strokes per year is significantly reduced compared with no treatment (about 4,800 strokes compared with about 15,075 of no treatment);
- The number of strokes avoided per year is about 7,500 compared to scenario 1 and about 5,000 compared to scenario 2.

No treatment		
Total patients with NVAF (nr.)	335,000	
Risk of stroke (%/year)	4.50	
Total strokes (nr./year)	15,075	
Pts treated with DE		
	DE 150 mg (pts < 80 years)	DE 110 mg (pts ≥ 80 years)
Patients with NVAF (nr.)	187,000	148,000
DE: reduction in the risk of stroke (%)	-75	-65
Ischemic strokes (nr./year)	2,059	2,394
Total ischemic strokes (nr./year)		4,435
Hemorrhagic strokes (nr./year)	205	163
Total hemorrhagic strokes (nr./year)		368
Total ischemic/hemorrhagic strokes (nr./year)		4,803
Total ischemic/hemorrhagic strokes prevented vs. no treatment (nr./year)		10,272

Table VIII. Patients treated with dabigatran etexilate (DE) vs. no treatment (year 1)

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Events in no treatment (nr.)	15,075	15,377	15,684	15,998	16,318	78,452
Events in DE treatment (nr.)	4,803	4,899	4,997	5,097	5,199	24,995
Prevented events DE vs. no treatment (nr.)	10,272	10,478	10,687	10,901	11,119	53,457

Table IX. Prevented events (ischemic and hemorrhagic strokes): treatment with dabigatran etexilate (DE) over 5 years

Cost item	Year 1	Year 2	Year 3	Year 4	Year 5	Total
DE* (€ x 1,000)	244,542	249,432	254,421	259,510	264,700	1,272,604
Management cost of ischemic + hemorrhagic stroke (€ x 1,000)	84,047	122,153	160,289	198,458	236,658	801,605
Total cost (€ x 1,000)	328,589	371,585	414,710	457,967	501,358	2,074,209

Table X. Cost of patients treated with dabigatran etexilate (DE)

* Cost/day = € 2.10; Compliance rate 95%

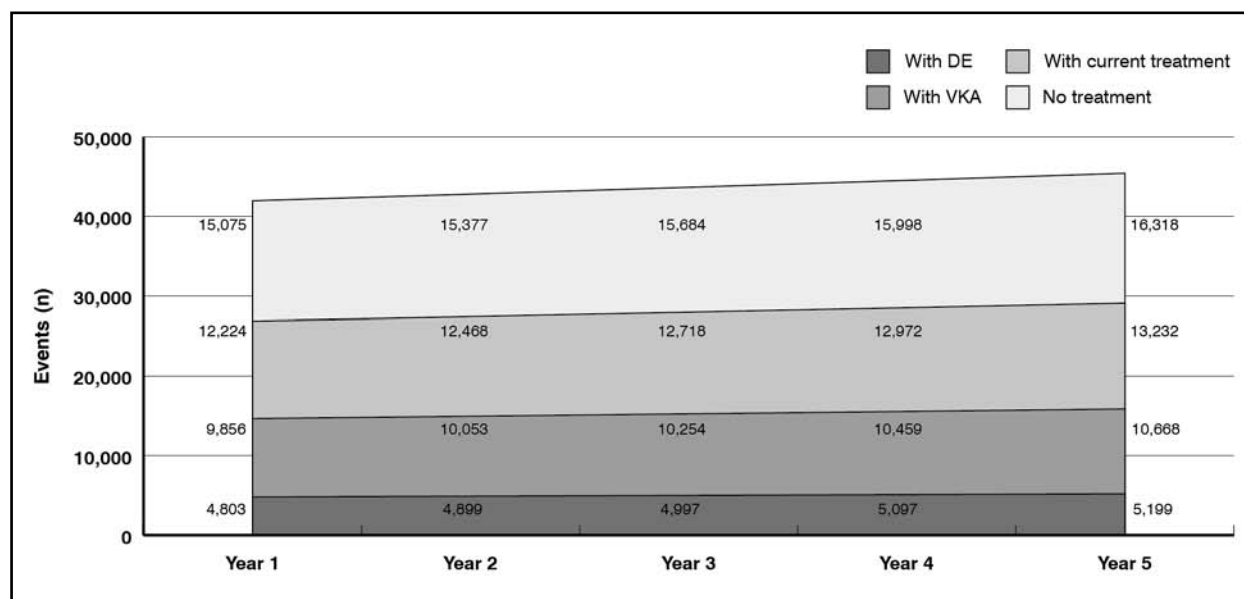


Figure 1. Number of events (hemorrhagic and ischemic strokes) in the various scenarios
DE = dabigatran etexilate

Similarly to the previous scenarios, starting from the cost assumptions reported in the background, and using a daily cost of dabigatran etexilate equal to € 2.10 (the lowest in Europe in May 2012: current price in Spain), Table X reports the management costs of NVAF. Figures 1, 2 and 3 show the comparison among the scenario 3 (all the patients treated with dabigatran etexilate) and other scenarios in terms of events and costs.

An extensive use of dabigatran etexilate would cause:

- A reduction of more than 38,500 of the total cumulative number of strokes vs. the current scenario and over 26,297 vs. the

treatment with VKA, with all the obvious social and health benefits in terms of health “saved”.

- An increase in the cost of drug treatment, which in this case must be considered as the potential maximal expenditure.
- Savings for the NHS at the fifth year of observation of 173 million Euros vs. the current treatment and 123 million Euros vs. treatment with VKA.

The savings from the reduction of indirect costs of both society and families of patients with NVAF should be added to all this, resulting in huge direct and indirect savings for the society.

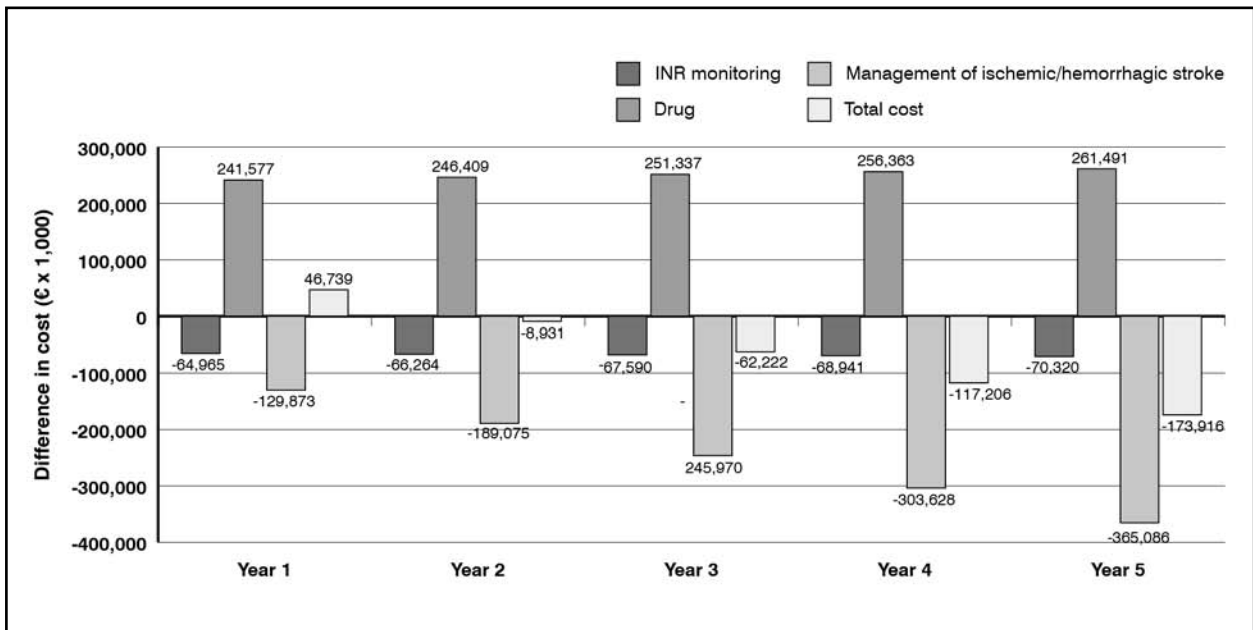


Figure 2. Differences in cost of dabigatran etexilate vs. current scenario

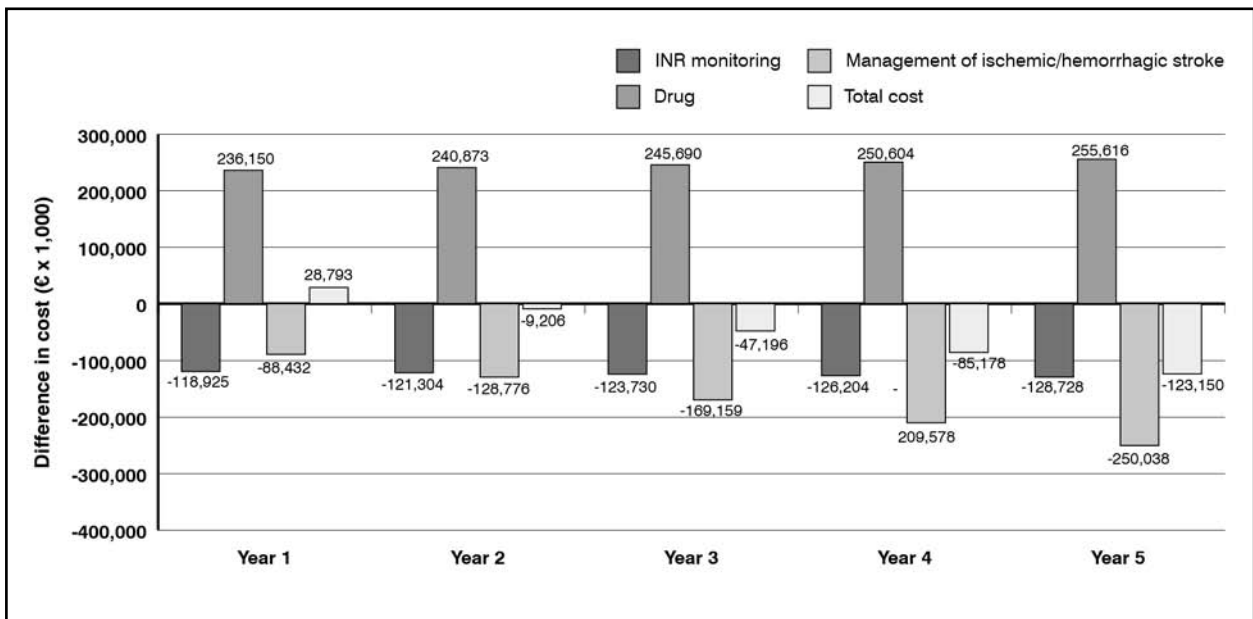


Figure 3. Differences in cost of dabigatran etexilate vs. treatment with VKA

Scenario 3 vs. scenario 2	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Ischemic strokes (nr.)	-4,158	-4,241	-4,326	-4,413	-4,501	-21,638
Hemorrhagic strokes (nr.)	-895	-913	-931	-950	-969	-4,659
Total ischemic/hemorrhagic strokes (nr.)	-5,053	-5,154	-5,257	-5,363	-5,470	-26,297
Cost of INR monitoring (€ x 1,000)	-71,020	-72,440	-73,889	-75,367	-76,874	-369,591
Drug cost (€ x 1,000)	236,150	240,873	245,690	250,604	255,616	1,228,934
Cost of management of ischemic/hemorrhagic stroke (€ x 1,000)	-88,432	-128,776	-169,157	-209,578	-250,038	-845,980
Total cost (€ x 1,000)	76,698	39,657	2,644	-34,341	-71,296	13,363

Table XI. Dabigatran etexilate vs. treatment with VKA (cost of monitoring = € 212)

Scenario 3 vs. scenario 2	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Ischemic strokes (nr.)	-4,158	-4,241	-4,326	-4,413	-4,501	-21,638
Hemorrhagic strokes (nr.)	-895	-913	-931	-950	-969	-4,659
Total ischemic/hemorrhagic strokes (nr.)	-5,053	-5,154	-5,257	-5,363	-5,470	-26,297
Cost of INR monitoring (€ x 1,000)	-149,410	-152,398	-155,446	-158,555	-161,726	-777,536
Drug cost (€ x 1,000)	236,150	240,873	245,690	250,604	255,616	1,228,934
Cost of management of ischemic/hemorrhagic stroke (€ x 1,000)	-88,432	-128,776	-169,157	-209,578	-250,038	-845,980
Total cost (€ x 1,000)	-1,692	-40,301	-78,913	-117,529	-156,148	-394,582

Table XII. Dabigatran etexilate vs. VKA treatment (cost of monitoring = € 446)

Scenario 3 vs. scenario 2	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Ischemic strokes (nr.)	-4,158	-4,241	-4,326	-4,413	-4,501	-21,638
Hemorrhagic strokes (nr.)	-895	-913	-931	-950	-969	-4,659
Total ischemic/hemorrhagic strokes (nr.)	-5,053	-5,154	-5,257	-5,363	-5,470	-26,297
Cost of INR monitoring (€ x 1,000)	-118,925	-121,304	-123,730	-126,204	-128,728	-618,890
Drug cost (€ x 1,000)	211,756	215,991	220,311	224,717	229,212	1,101,988
Cost of management of ischemic/hemorrhagic stroke (€ x 1,000)	-88,432	-128,776	-169,157	-209,578	-250,038	-845,980
Total cost (€ x 1,000)	4,399	-34,088	-72,576	-111,065	-149,554	-362,883

Table XIII. Dabigatran etexilate (1,89 €/die) vs. VKA treatment

Scenario 3 vs. scenario 2	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Ischemic strokes (nr.)	-4,158	-4,241	-4,326	-4,413	-4,501	-21,638
Hemorrhagic strokes (nr.)	-895	-913	-931	-950	-969	-4,659
Total ischemic/hemorrhagic strokes (nr.)	-5,053	-5,154	-5,257	-5,363	-5,470	-26,297
Cost of INR monitoring (€ x 1,000)	-118,925	-121,304	-123,730	-126,204	-128,728	-618,890
Drug cost (€ x 1,000)	260,544	265,755	271,070	276,491	282,021	1,355,881
Cost of management of ischemic/hemorrhagic stroke (€ x 1,000)	-88,432	-128,776	-169,157	-209,578	-250,038	-845,980
Total cost (€ x 1,000)	53,187	15,676	-21,817	-59,291	-96,745	-108,990

Table XIV. Dabigatran etexilate vs. VKA treatment

SENSITIVITY ANALYSIS

Cost of monitoring of the patient receiving VKA therapy = € 212

As showed in Table XI an extensive use of dabigatran etexilate would result in:

- Also in this situation, a saving for the NHS at the fifth year of observation of 71 million Euros vs. the treatment with VKA (-43% compared to the basal hypothesis).
- A reduction of 26,297 in the total number of cumulative strokes vs. the treatment with VKA, with all the obvious social and health benefits in terms of health “saved” (savings in terms of clinical benefit remain unchanged).

Cost of monitoring of the patient receiving VKA therapy € 446

As showed in Table XII, an extensive use of dabigatran etexilate would result in:

- A saving for the NHS at the fifth year of observation of 156 million Euros vs. the treatment with VKA (+27% compared to the basal hypothesis).
- A reduction of 26,297 in the total number of cumulative strokes vs. the treatment with VKA, with all the obvious social and health benefits in terms of health “saved” (savings in terms of clinical benefit remain unchanged).

Cost of dabigatran etexilate 1.89 €/day (-10% vs. basal hypothesis)

As showed in Table XIII an extensive use of dabigatran etexilate would result in:

- In this situation a saving for the NHS at the fifth year of observation of 149 million Euros vs. the treatment with VKA (+24,6% compared to the basal hypothesis).
- A reduction of 26,297 in the total number of cumulative strokes vs. the treatment with VKA, with all the obvious social and health benefits in terms of health “saved” (savings in terms of clinical benefit remain unchanged).

Cost of dabigatran etexilate 2.31 €/day (+10% vs. basal hypothesis)

As showed in Table XIV an extensive use of dabigatran etexilate would result in :

- Also in this situation a saving for the NHS at the fifth year of observation of 96 million Euros vs. the treatment with VKA (-21% compared to the basal hypothesis).
- A reduction of 26,297 in the total number of cumulative strokes vs. the treatment with VKA, with all the obvious social and health benefits in terms of health “saved” (savings in terms of clinical benefit remain unchanged).

DISCUSSION

The current treatment of NVAF involves the reduction of only 2,851 strokes, in the first year of observation, compared with the total number of strokes developed in the scenario of total non-treatment (15,075). This confirms that, despite the enormous organizational effort, there is still a major unmet need in the management of NVAF. The underuse of oral anticoagulation, associated with the difficulty in keeping the patients treated with VKA within an acceptable therapeutic range, results in an enormous social and human cost, represented by a total of more than 63,000 strokes cumulated in the 5-year period considered (Table II). The cumulative cost for the current treatment of NVAF over the 5-year period exceeds € 2.3 billions and the major cost generator in NVAF management is stroke management cost (2.03 billions). Indirect costs, burdening families and society, were not considered in this analysis. According to the CENSIS survey, presented in 2011 at the World Day of stroke, every stroke patient costs about € 30,000 to his/her family per year [18]. The number of avoided strokes per year, resulting from the scenario where all NVAF patients are treated with VKA, amounts to 5,219 compared to no treatment (-2,368 compared to the current situation), although the number of events remains high (about 10,000 events/year; Table V). Again, as in the previous scenario, the cumulative cost over the 5-year period is over 2 billion Euros (2.294 billion Euros). Similarly to the previous scenarios, starting from the cost assumptions reported in the background, and using a daily cost of dabigatran etexilate equal to 2.10 Euros (the lowest in Europe in May 2012: current price in Spain), an extensive use of dabigatran etexilate would cause:

- A reduction of more than 38,500 of the total cumulative number of strokes vs. the current scenario and over 26,297 vs. the treatment with VKA, with all the obvious social and health benefits in terms of health “saved”.
- An increase in the cost of drug treatment, which in this case must be considered as the potential maximal expenditure.
- Savings for the NHS at the fifth year of observation of 173 million Euros vs. the current treatment and 123 million Euros vs. treatment with VKA.

The savings from the reduction of indirect costs of both society and families of patients with NVAF should be added to all this, resulting in huge direct and indirect savings for the society.

CONCLUSIONS

According to the model used in the present study, which includes both epidemiologic and economic data, it is possible to affirm that marketing dabigatran etexilate in Italy with the new SPAF (stroke prevention in atrial fibrillation) indication is economically sustainable: it allows savings for the NHS in the management of patients with NVAf from the second year vs. no treatment and vs. treatment with VKA. Furthermore it appears socially and ethically convenient as it allows a significant overall increase in expectancy and quality of life of patients with NVAf, through the reduction of the total number of strokes.

Finally dabigatran etexilate allows significant savings in indirect costs for society and families involved in a debilitating disease such as stroke. These costs are inherently difficult to quantify, yet priceless when considering the socio-emotional impact caused by a stroke, not only for the patient but also for all the relatives involved in this important event.

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APPENDIX A

Figure 1A shows the basis for the calculation of patients with non-valvular atrial fibrillation (NVAF) eligible for treatment

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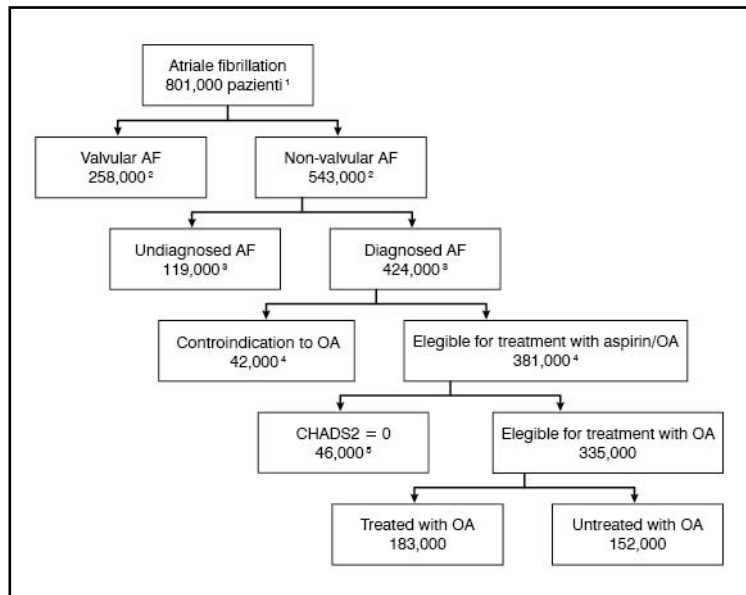


Figure 1A. Bases for the calculation of patients with (NVAF) eligible for treatment

¹ AF based on data from Osservatorio Epidemiologico Cardiovascolare [1] and Servizio Epidemiologico della Regione Veneto [2] applied to the Italian population, ISTAT 2011 [3]

² 32.2% cases of valvular AF; from ATA-AF study by ANMCO and FADOI 2011 [4]

³ 22% are undiagnosed; from market research IMS 2010 [5]

⁴ 10% with contraindication to OA; conservative estimate compared to 22% recorded in ATA-AF study by ANMCO and FADOI 2011 [4]

⁵ 12% CHADS = 0; from survey SIMG 2011 [6]