Budget impact analysis of apixaban to treat and prevent venous thromboembolism in Italy

ORIGINAL RESEARCH

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ABSTRACT

BACKGROUND: Venous thromboembolism (VTE), a collective term for deep vein thrombosis (DVT) and pulmonary embolism (PE), is a serious vascular condition associated to high economic and clinical burden. Apixaban, a Novel Oral Anticoagulant (NOAC) has shown non-inferiority efficacy versus the current standard of care (low molecular weight heparin [LMWH]/vitamin K antagonist [VKA]) in the acute treatment and prevention of VTE and a significant reduction in the risk of bleeding.

AIM: Evaluate the economic impact of the use of apixaban for treatment and prevention of DVT and PE from the perspective of the Italian National Health System (NHS).

METHODS: A budget impact model was adapted in order to compare clinical outcomes and economic consequences associated to apixaban vs. LMWH/VKA and others NOACs over a three-year time horizon in the Italian setting. In the analysis two scenario were compared: status quo scenario without apixaban and an alternative scenario with apixaban. Only direct healthcare costs have been considered.

RESULTS: Assuming a population of patients receiving apixaban over the first 3 years equal to 20,957, the introduction of apixaban is associated to an incremental saving of € 821,748 in the first years, € 1,250,454 in the second year, and € 1,866,466 in the third year. The total net saving over the 3-year period is € 3,938,668, which is a 2.47% decrease from the total budget for the status quo scenario without apixaban. This saving is mainly due to reduced VTE events and bleeds by apixaban. Indeed apixaban is associated with less VTE events (both fatal and non-fatal), less major bleeding and less Clinical Relevant Non Major (CRNM) bleeding with a total of 52 fatal events avoided.

CONCLUSIONS: The listing of apixaban for the treatment of VTE (both DVT and PE) and the prevention of recurrent VTE provides both significant clinical advantages, in terms of deaths and events avoided, and economical advantages, consisting in a reduction in the total expenditure on the Italian NHS.

Keywords

Apixaban; Venous thromboembolism; Budget Impact; NOAC

INTRODUCTION

Venous Thromboembolism (VTE), including pulmonary embolism (PE) and deep vein thrombosis (DVT) is a clinical condition associated with a high morbidity and mortality rate [1]. VTE is the third cause of cardiovascular death, with PE constituting a greater risk than DVT; in fact, 30-day mortality for patients with DVT is around 6% while for patients with PE it is around 12%, rising to 17% within 3 months [2].

The incidence of VTE in the general population is around 70-120 cases/year/100,000 inhabitants (one third of which are cases of PE with or without DVT and two third are cases of DVT) [2-4]. It is estimated that in Italy the incidence rate is 9.6 cases/10,000 in men and 11.1 cases/10,000 in women, with a total of around 61,000 cases [5]. In addition to its clinical impact, VTE also involves a heavy financial burden for the NHS (National Health System) due not only to management of the acute episode, but also the management and prevention of long-term complications, such as recurrences of VTE, post-thrombotic syndrome and pulmonary hypertension [1]. The risk of recurrence is particularly high, with a recurrence rate of around 7% during the first 6 months and increasing to 25% during the 5 years following the acute episode [2,6]. Correct management of VTE must therefore provide not only appropriate, timely treatment of

the acute episode, but also effective prevention of recurrent events.

The standard treatment for VTE is an initial subcutaneous injection of low molecular weight heparin (LMWH) followed by oral therapy with vitamin K antagonists (VKA) [7]. The limitations of standard treatment relate to the parenteral administration of LMWH, which is potentially inconvenient in the case of treatment outside of hospital, and factors associated with VKA therapy, which could reduce patient compliance. These factors include interactions with drugs and food, the need for regular International Normalized Ratio (INR) monitoring, followed by the ne-

cessary dosage adjustments, and the risk of major bleeds [8].

In order to overcome the limitations associated with LMWH/VKA therapy, new anticoagulant drugs have been developed, which are capable of simplifying even long-term patient management [9]. The novel oral anticoagulants (NOACs) currently available (rivaroxaban, dabigatran, apixaban and edoxaban), indicated in the treatment and prevention of recurrent VTE, have demonstrated similar efficacy and greater safety than the standard treatment, without the need for INR monitoring [10].

In May 2015, apixaban, previously indicated for the prevention of VTE in patients undergoing major orthopaedic surgery and in prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation, obtained by the AIFA (*Agenzia Italiana del Farmaco*) approval and reimbursement also for the treatment and prevention of recurrent VTE [11]. Registration of the new indication was supported by the results of AMPLIFY (apixaban vs. enoxaparin/warfarin) [12] and AMPLIFY-EXT (apixaban vs. placebo) [13] multicentre, randomized, double blind, phase III studies.

The purpose of this analysis is to evaluate the impact on the Italian NHS budget of including apixaban in the current treatment mix (LMWH/VKA, rivaroxaban and dabigatran) for the treatment of acute episodes and the prevention of recurrent VTE in Italy.
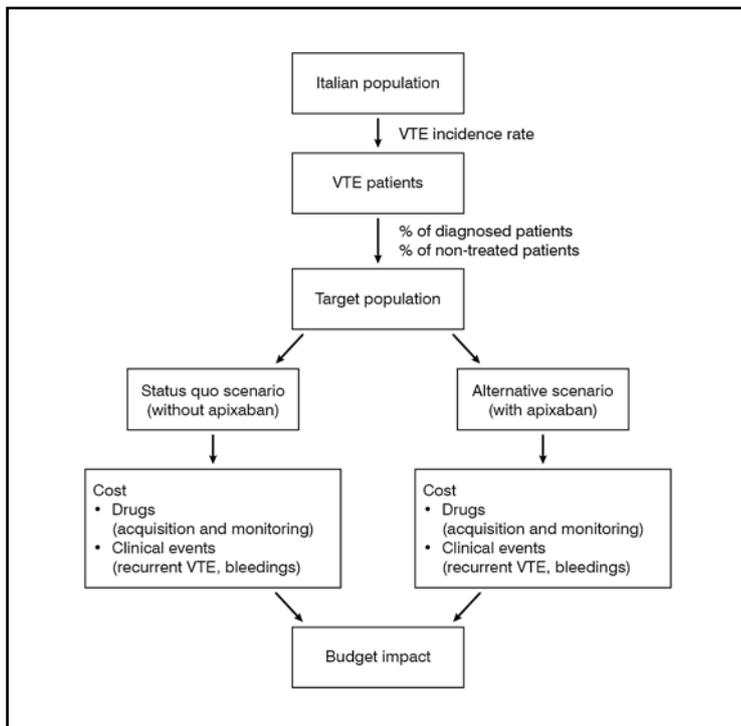
MATERIALS AND METHODS

A budget impact model, previously developed but not yet published, was adapted to simulate the economic impact of apixaban vs. LMWH/VKA and others NOACs for treatment and prevention of DVT and PE within an Italian cohort.

The budget impact analysis, performed using an analytical model developed in Microsoft Excel, was conducted from the perspective of the Italian NHS over a 3-year period according to guidelines from ISPOR [14,15].

The financial impact from introducing apixaban into the current prescribing pattern for the treatment and secondary prevention of VTE was estimated by analysing total costs in a cohort of patients with VTE eligible for treatment, and comparing a status quo scenario in which apixaban is not yet available with an alternative scenario following the introduction of apixaban (Figure 1). In particular, costs relating to the acquisition and monitoring of drugs, the treatment of episodes of recurrent VTE and the management of clinical bleeding events (fatal bleeding, intra-

Figure 1. *Scheme of the budget impact analysis*

	Year 1	Year 2	Year 3
Population (n.)	61,178,335	61,423,049	61,668,741
VTE incidence rate (%)		0.1	
Non-diagnosed patients (%)		30.6	
PE			
• Incidence (%)		33.3	
• Non-treated patients (%)		0	
• Treated patients (n.)	14,157	14,214	14,271
DVT			
• Incidence (%)		66.7	
• Non-treated patients (%)		2	
• Treated patients (n.)	27,748	27,859	27,971
Total treated patients (n.)	41,906	42,073	42,241

Table I. *Calculation of the target population over the 3 years of analysis*

cranial bleeding – IC, major non-IC and clinical relevant non-major – CRNM bleeding) were considered. Mortality associated with a recurrent VTE event or bleeding has also taken into account.

The estimated eligible population for treatment over the 3 years of analysis was calculated based on natural growth rates [16] using the population of Italy living there on 1st January 2013 and applying a VTE incidence rate of 0.1%, as reported by the study conducted by Cimminiello et al. [5], which retrospectively analysed the data of 372,000 patients of 400 general practitioners between 2001 and 2004. The percentage of patients that is undiagnosed, estimated at 30.6%, was excluded from the incident population. Finally, patients were subdivided based on the diagnosis of PE or DVT (33.3% and 66.7%, respectively according to epidemiological estimates) and patients thought not to be receiving treatment (0% of patients with PE and 2% of patients with DVT [Assumption] were excluded. The calculation of the target population is reported in Table I.

Treatment scenarios

Target patients were divided into the treatment regimens currently approved and prescribed in Italy for the treatment and prevention of VTE: NOACs (apixaban, dabigatran and rivaroxaban) and the standard treatment with LMWH/VKA (enoxaparin/warfarin). Edoxaban was not included as it was not yet available at the time of carrying out the analysis.

The percentage distribution of patients into the individual classes of available drugs derives from a simulation of prescription scenarios in which the market share of NOACs is 50%, 55% and 60% in years 1, 2 and 3, respectively, with the remaining percentages (50%, 45% and 40%) belonging to LMWH/VKA.

In the status quo scenario, in which apixaban is not available, the market shares of the NOACs are divided between dabigatran and rivaroxaban, with percentages of 25% and 75% of the total market shares of NOACs, respectively.

In the scenario in which apixaban is available, it is estimated that NOACs will represent a greater market share (60%, 65% and 70%) than LMWH-VKA (40%, 35% and 30%). In the case of apixaban, this is estimated to obtain 15%, 25% and 35% of prescriptions of NOACs over the three years of analysis. The remaining market shares of NOACs, i.e. 51%, 48.75% and 45.5%, are divided between dabigatran (25%) and rivaroxaban (75%). Table II shows the estimated distribution of the different treatment regimens over the three years of analysis for the two scenarios considered.

Clinical events

The clinical events considered in the analysis include recurrent VTE (including episodes of non-fatal PE, non-fatal DVT and fatal VTE), major bleeding (including fatal bleeding, IC and non-IC bleeding) and CRNM bleeding.

The clinical event onset rates for apixaban comes from the AMPLIFY pivotal trial [12] with regard to the first 6 months following the start of treatment, and the AMPLIFY-EXT pivotal trial [13] with regard to months 6-18 post initiation of treatment.

These trials were conducted in order to evaluate the efficacy and safety of apixaban in treating PE and DVT and in preventing recurrent VTE after 6-12 months of treatment. In particular, the AMPLIFY study [12] involved 5,395 patients with an acute episode of VTE who were randomized to receive apixaban 10 mg bid *per os* for 7 days, followed by 5 apixaban 5 mg bid *per os* for the next 6 months or enoxaparin 1 mg/kg bid administered subcutaneously for at least 5 days (until INR > 2) and warfarin *per os* for 6 months.

The study results demonstrated the non-inferiority of apixaban compared with enoxaparin/warfarin in terms of incidence of recurrent fatal and non-fatal VTE (RR: 0.84; CI95%: 0.60-1.18) and its superiority compared with enoxaparin/warfarin with regard to the primary safety endpoint (major bleeds RR: 0.31; CI95%: 0.17-0.55). Apixaban also significantly reduced the incidence of composite endpoints comprising major/CRNM

	Status quo scenario (without apixaban)			Alternative scenario (with apixaban)		
	Year 1	**Year 2**	**Year 3**	**Year 1**	**Year 2**	**Year 3**
LMWH-VKA (%)	50.00	45.00	40.00	40.00	35.00	30.00
NOACs (%)	50.00	55.00	60.00	60.00	65.00	70.00
• Apixaban	-	-	-	9.00	16.25	24.50
• Rivaroxaban	37.50	41.25	45.00	38.25	36.56	34.13
• LMWH-dabigatran	12.50	13.75	15.00	12.75	12.19	11.37

Table II. *Distribution of patient numbers in the scenario with and without apixaban*

	Package	Ex-factory price[1] (€)	Unit cost (€)	Induction daily dose	Prophylactic daily dose
Apixaban	60 tablets 2.5 or 5 mg	66.97	1.12	10 mg bid (7 days)	10/5 mg/die[2]
Rivaroxaban	42 tablets 15 mg	92.57	2.20	15 mg bid (21 days)	20 mg/die
	28 tablets 20 mg	61.71			
LMWH[3]	10000 UI AXA/1 ml solution for injection 10 prefilled syringes 1 ml	66.34	6.63	1 mg/kg bid (7,64 days)	-
Dabigatran	60 tablets 150 mg	66.97	1.12	-	150 mg bid
VKA (warfarin)	30 tablets 5 mg	2.17[4]	0.07	5 mg/die (7,64 days)	5 mg/die

Table III. *Daily cost and dosage of treatment with the various alternatives during the induction and prophylaxis phases*
[1] The drug acquisition costs were calculated based on hospital sales prices at the net of transitory legal price reductions (temporary reductions referred to AIFA Resolutions of 3/7/2006 and 27/09/2006) and mandatory discounts, estimates on the median of the tender prices
[2] Apixaban 5 mg bid is administered for the first 6 months after the induction phase and the dose of 2.5 mg bid is administered thereafter
[3] The cost of LMWH was estimated for a patient with an average weight of 84.6 kg treated with enoxaparin [12]
[4] Retail price

bleeding (RR: 0.44; CI95%: 0.36-0.55) and VTE/mortality from VTE/major bleeding (RR: 0.62; CI95%: 0.47-0.83) [12]. The AMPLIFY-EXT study [13] was designed to determine the efficacy and safety of apixaban in preventing the recurrence of DVT and PE. 2,482 patients were enrolled into the study, having completed 6 to 12 months of anticoagulant therapy. They were randomized to treatment with apixaban 2.5 mg bid, 5 mg bid or placebo for 12 months. Both dosages of apixaban proved superior to the placebo in terms of preventing the recurrence of VTE and in terms of total mortality (2.5 mg = RR: 0.33; CI95%: 0.22-0.48; 5 mg = RR: 0.36; CI95%: 0.25-0.53), while the incidence of major bleeding was similar in all three treatment groups [13].

In the absence of any study carrying out a direct comparison, the relative risks for the comparators derive from two network meta-analysis that were conducted to compare the efficacy and safety of anticoagulant for the initial, long-term and extended treatment of VTE [10,17]. The same risk of clinical event was taken into consideration for all patients who completed the treatment period, regardless of the treatment they received.

Costs

In order to reflect the NHS's perspective, the analysis only considered health costs directly relating to the acquisition and monitoring of drugs and to the inpatient or outpatient management of episodes of VTE and bleeding events. The cost for the first event of VTE was not taken into account, as it does not generate any differential cost between scenario with and without apixaban.

Drugs

The drug acquisition costs are drawn from the Italian Official Gazette (OG General Series No. 246 of 22-10-2014). In keeping with current legislation and what is stated by the OG, the direct distribution channel for apixaban, rivaroxaban, dabigatran and LMVH through hospitals (valued using the ex-factory price) and the territorial channel for warfarin (valued using the retail price) were considered.

Treatment costs for both induction and prophylactic phase were calculated based on the dosages shown in the SPCs of the drugs (Table III).

The duration of treatment was assumed to be the same for all alternatives in both scenarios

Resource	Unit cost (€)	Source	Frequency of use (n.) [23]	
			DVT	PE
Outpatient treatment				
Doppler ultrasound	43.90	Cod. 88.77.2 [24]	1	1
CT angiography	184.80	Cod. 88.92.2 [24]	0	1
Echocardiogram	11.62	Cod. 89.52 [24]	0	1
D-Dimer test	4.99	Cod. 90.61.5 [24]	1	1
Chest X-ray	15.49	Cod. 87.44.1 [24]	0	1
Emergency admission	270.00	Italian Ministry of Health [25]	1	1
Inpatient treatment				
Non-fatal PE	4,009.00	DRG 78 [22]	-	-
Non-fatal DVT	2,315.00	DRG 128 [22]	-	-
Fatal VTE	2,315.00	DRG 128 [22]	-	-
Bleeding events				
IC	25,812.00	DRG 528 [22]	-	-
Major non-IC	3,317.00	DRG 174 [22]	-	-
CRNM	2,091.00	DRG 175 [22]	-	-
Fatal	3,891.00	DRG 14 [22]	-	-

Table IV. *List of resources used to manage clinical events and the respective sources*

considered and it was estimated that 40% of patients remain under treatment for 3 months, 30% for 6 months, 20% for 12 months and 10% for 18 months. The cost of the LMWH injection was not taken into account as it was assumed to be self-administered by all patients.

INR monitoring is only counted in the case of warfarin, and as recommended by the guidelines of the Task Force on Pulmonary Embolism [18], 14 check-ups were taken into account during the first 3 months with 1 check-up/month thereafter. The cost of the check-up was calculated based on the annual cost reported by Mennini et al. [19] and the frequency of monitoring reported by Pengo et al. [20] and was estimated at € 23.75.

Management of clinical events

The costs associated with managing recurrent VTE were estimated taking into account both inpatient and outpatient treatment. From a prospective study based on data from the MASTER registry, which gathered the data on 25 Italian centres about 2,119 patients suffering an acute episode of VTE, we know that 90.8% of patients were admitted to hospital after a VTE episode and only the 68.1% after a DVT episode [21].

In an inpatient setting, the cost per patient for the management of an episode of PE is € 4,009, and it is € 2,315 for an episode of DVT.

The cost of managing an episode of non-fatal PE and DVT on an outpatient basis was estimated at € 530.80 and € 318.89 respectively. Table IV shows the resources and sources used to estimate the cost and frequency of use. The cost of hospitalization following an episode of VTE comes from the price list for hospital services for acute patients [22], and in particular DRG 78 was used for PE and DRG 128 was used for DVT. The cost of treating an episode of fatal VTE was assumed to be the same as inpatient treatment for DVT (Table IV).

The costs of managing bleeding events were calculated using the price list for hospital care for acute patients [22] (Table IV).

Scenario analysis

In order to test the robustness of the results obtained and the parameters used in the base-case, several scenario analyses were performed, in which the percentage of patients under treatment for 3, 6, 12 and 18 months was changed. In particular, two different alternative scenarios were examined:

1. All patients treated for 6 months;
2. 30% of patients treated for 3 months, 30% for 6 months, 30% for 12 months and 10% for 18 months;

Two different scenarios were also examined based on patient distribution:

3. One scenario in which the only NOAC available is apixaban, therefore in the scenario without apixaban all patients are reserved for LMWH-VKA. Following the introduction of apixaban there is an equal distribution of patients (base scenario: LMWH-VKA = 100%; alternative scenario: LMWH-VKA = 50%/Apixaban = 50%);
4. One scenario in which only NOACs are present, therefore in the scenario without apixaban, patients are divided equally between rivaroxaban and dabigatran. In the alternative scenario 100% of patients are equally divided between the three NOACs (status quo scenario: rivaroxaban/dabigatran = 50%/50%; alternative scenario: apixaban/rivaroxaban/dabigatran = 33.3%/33.3%/33.3%).

RESULTS

Table V shows the number of patients allocated to the different treatment strategies in the two scenarios analyzed in the base-case.

The results of the budget impact analysis show that for an estimated target population eligible for treatment and prevention of VTE of 41,905 patients for the first year, 42,073

| | Treated patients (n.) | | | | | |
| | Status quo scenario (without apixaban) | | | Alternative scenario (with apixaban) | | |
	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3
Apixaban	0	0	0	3,771	6,837	10,349
Rivaroxaban	15,714	17,355	19,009	16,029	15,382	14,417
LMWH-dabigatran	5,238	5,785	6,336	5,343	5,129	4,803
LMWH-VKA	20,953	18,933	16,896	16,762	14,726	12,672
Total	41,905	42,073	42,241	41,905	42,073	42,241

Table V. *Distribution of patients between the different treatment strategies in both scenarios*

	Costs (€)					
	Year 1		**Year 2**		**Year 3**	
	Status quo scenario[1]	**Alternative scenario[2]**	**Status quo scenario[1]**	**Alternative scenario[2]**	**Status quo scenario[1]**	**Alternative scenario[2]**
Pharmaceutical	8,988,034	10,599,151	10,503,633	12,335,721	11,381,600	13,310,314
INR monitoring	8,746,631	6,997,305	8,198,914	6,383,498	7,320,371	5,497,694
Recurrent VTE events	7,946,260	7,924,638	16,077,039	16,044,535	24,501,867	24,453,720
Bleeding events	14,668,311	14,006,394	18,946,554	17,711,932	22,345,958	20,421,602
Total	40,349,236	39,527,488	53,726,140	52,475,686	65,549,796	63,683,330
Budget impact	- 821,748		- 1,250,454		- 1,866,466	

Table VI. *Results of the budget impact analysis over three years*
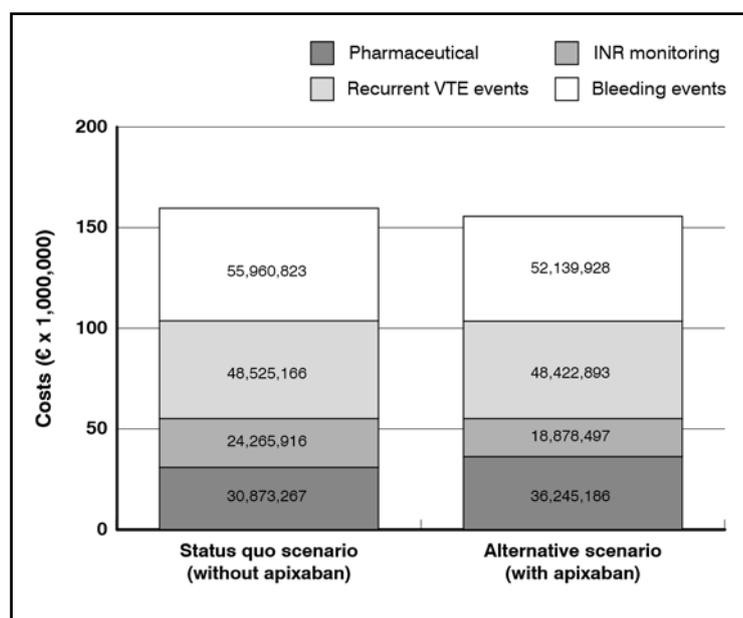[1] Without apixaban
[2] With apixaban

Figure 2. *Results of the cumulative budget impact analysis over three years*

for the second year and 42,241 patients for the third year, the introduction of apixaban into the current combination therapy for VTE, with annually increasing percentages of use, would mean a potential saving for the Italian NHS of € 821,748, € 1,250,454 and € 1,866,466 in the course of the first, second and third year of treatment, respectively (Table VI).

Figure 2 shows the cumulative results of the budget impact analysis for 3 year, resulting in a total saving for the Italian NHS of € 3,938,668, due to the use of apixaban over a three-year period.

Table VII shows the annual cost per patient for the various treatment options considered in the analysis.

Table VIII shows the clinical events (episodes of recurrent fatal and non-fatal VTE) and major bleedings in both treatment scenarios

	Costs (€/pts)				
	Pharmaceutical	**INR monitoring**	**Recurrent VTE events**	**Bleeding events**	**Total**
Year 1					
Apixaban	418.96	0.00	183.96	176.43	3,137.25
Rivaroxaban	389.38	0.00	187.54	380.81	3,315.63
LMWH-dabigatran	418.64	0.00	195.64	251.50	3,223.70
LMWH-VKA	32.27	417.44	189.68	351.59	3,348.88
Year 2					
Apixaban	439.16	0.00	291.22	220.50	3,308.75
Rivaroxaban	422.34	0.00	389.54	501.39	3,671.18
LMWH-dabigatran	456.32	0.00	396.92	340.71	3,551.84
LMWH-VKA	33.71	433.50	409.22	458.02	3,692.37
Year 3					
Apixaban	443.16	0.00	385.30	257.98	3,444.32
Rivaroxaban	423.13	0.00	616.08	591.79	3,988.89
LMWH-dabigatran	457.23	0.00	623.71	430.46	3,869.29
LMWH-VKA	33.74	433.83	677.72	564.41	4,067.59

Table VII. *Annual costs per patient for the various treatment options considered*

over the three years of analysis. The introduction of apixaban make it possible to avoid 36 new episodes of VTE (including 11 fatal episodes), 302 major bleeding events (including 41 fatal events) and 944 CRNM bleeding events, making a total of 1,282 fewer events over the course of three years.

Scenario analysis

Tables IX and X and Figure 3 show the results of the scenario analysis.

DISCUSSION

In recent years NOACs have become an important alternative to the standard therapy employed to treat acute episodes and prevent recurrent VTE. Although LMWH/VKA is still widely used in this setting, their good efficacy and safety profile and practicality have enabled the NOACs to gain large numbers of patients. Apixaban, a reversible, direct selective factor Xa inhibitor is an oral anticoagulant indicated in the treatment and prevention of recurrent DVT and PE. Like the other drugs in its class it presents some benefits with regard to standard treatment: no INR monitoring is necessary, the use of a fixed dosage, the lack of significant interactions with food and infrequent drug interactions. Moreover, like rivaroxaban, but unlike dabigatran, it does not require initial treatment with LMWH. The AMPLIFY study demonstrated the non-inferiority of apixaban to LMWH/VKA with regard to the primary endpoint of efficacy, and its superiority with regard to the primary endpoint of safety; the AMPLIFY-EXT study demonstrated that apixaban has a favourable profile in preventing the recurrence of VTE compared with placebo, with a similar major bleeding rate [12,13]. In the absence of direct comparative studies, some network meta-analyses have shown that apixaban is associated with a lower incidence

	Clinical events (n.)		
	Status quo scenario[1]	Alternative scenario[2]	Avoided
VTE	20,747	20,711	36
• Non-fatal PE	5,862	5,844	17
• Non-fatal DVT	11,878	11,870	8
• Fatal VTE	3,007	2,997	11
Major bleeding	4,189	3,887	302
• IC	506	470	37
• Non-IC	3,119	2,894	225
• Fatal	564	523	41
CRNM	14,514	13,570	944

Table VIII. *Clinical events over the three-year period in both treatment scenarios*
[1] Without apixaban
[2] With apixaban

Costs (€)			
Status quo scenario[1]	Alternative scenario[2]	Budget impact	Difference in budget impact: vs. base-case
Base-case			
159,625,170	155,686,505	-3,938,665	-
Scenario (a) – All patients treated for 6 months			
143,562,978	139,858,168	-3,704,810	+233,855
Scenario (b) – Treatment 3-6-12-18 months: 30%/30%/30%/10%			
164,783,102	160,736,028	-4,047,074	-108,406

Table IX. *Results of the scenario analysis relating to duration of treatment*
[1] Without apixaban
[2] With apixaban

Costs (€)			
Status quo scenario[1]	Alternative scenario[2]	Budget impact	Budget impact/ patient
Scenario (c) – LMWH-VKA = 100% - LMWH-VKA/apixaban = 50%/50%			
162,083,429	149,129,222	-12,954,207	-103
Scenario (d) – NOACs = 50%/50% - NOACs = 33.3%/33.3%/33.3%			
154,291,017	148,250,867	-6,040,150	-48

Table X. *Results of the scenario analysis relating to patient distribution*
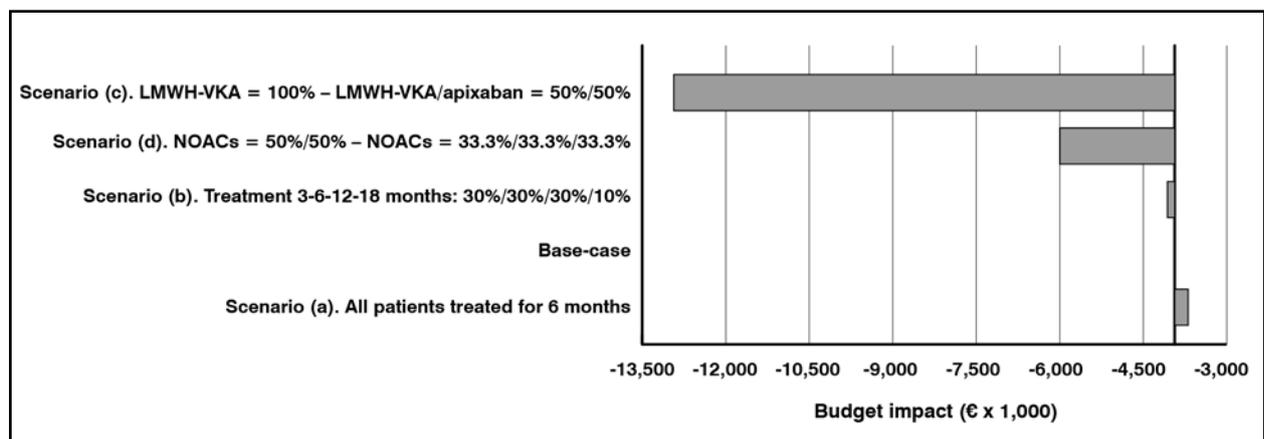[1] Without apixaban
[2] With apixaban

Figure 3. *Results of the scenario analysis*

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of major bleeding than the other NOACs in the acute treatment of VTE [10,26].

The current guidelines of the American College of Chest Physicians (ACCP), published in 2016, suggest that the NOACs (dabigatran, rivaroxaban, apixaban and edoxaban) be given preference over conventional therapy in the acute treatment of VTE in non-neoplastic patients [9]. A Technology Appraisal published in June 2015 by the National Institute for Health and Clinical Excellence (NICE) recommends apixaban among the options for the treatment and secondary prevention of PE and DVT, also due to the favorable cost-efficacy ratio that it has demonstrated compared with warfarin in the UK setting [27].

The financial benefit of apixaban has been confirmed by the results of this budget impact analysis, in which the introduction of apixaban in the current mix of treatments for VTE is associated with a saving for the Italian NHS in terms of direct health costs relating to the treatment of recurrent VTE and bleeding episodes. In particular, if apixaban were to acquire 15%, 25% and 35% of the market shares of the NOACs, the saving for the NHS would amount to € 821,748, € 1,250,454 and € 1,866,466 in the first, second and third year following its introduction, respectively, meaning a total saving of € 3,938,668 during the first three years of its use. The use of apixaban has also been associated with a reduction in the number of episodes of fatal and non-fatal recurrent VTE, major bleeding and CRNM bleeding, with a total of 52 fatal events avoided in three years.

As for all the economic evaluations, also in this analysis there are some limitations resulting from the assumptions adopted in the development of the model, which may be affected by uncertainty. In the absence of RCTs that directly compare apixaban with other NOACs, relative risks derive from network meta-analysis [10,17], which is a type of analysis widely used in pharmacoeconomics evaluation [28] for overcoming the lack of head-to-head trials. Some credibility intervals of RRs obtained from the Bayesian fixed-effect network meta-analysis cross 1: in the classic interpretation of frequentist statistics they would be considered as not significant. However, the classical interpretation of statistical significance may not be applied directly to the Bayesian credibility interval, which indicates a plausible range of values [29]. Nevertheless, a sensitivity analysis in

which these RR values are put equal to 1 (apixaban and comparators have the same event risk) has been performed, showing a 10% reduction of the savings at the year 3. However, the base-case analysis is to be considered conservative owing to the prudence of the assumptions made by the Authors: specifically, the inclusion of apixaban in the therapeutic arsenal for managing VTE determines an increase in treatment with NOACs compared with standard treatment (as assumed in the scenario with apixaban, in which the category of NOACs gains +10% of patients compared with the status quo scenario), which at the same time favors the entire category, also allowing dabigatran and rivaroxaban to gain patient numbers compared with the scenario without apixaban. This dynamic, known in microeconomics as the "knock-on benefit", according to which the distribution of one product favors an increase in sales of the entire category, influences savings during the first year of analysis: specifically, patients treated with rivaroxaban and dabigatran are associated with higher VTE management costs than they would have been if all the patients gained in the category of NOACs had been under treatment with apixaban.

Finally, the results of the scenario analyses confirmed the results of the budget impact analysis, suggesting the potentially greater benefit of apixaban when treatment is extended beyond 6 months. The scenario in which the percentages of patients under treatment for 3, 6, 12 and 18 months are equal to 30%, 30%, 30% and 10%, respectively, actually further increased the saving achieved in the base-case by € 108,406. Finally, the scenario analyses performed by modifying patient distribution also confirmed the benefit associated with apixaban, both in the case where patient numbers were shared only between the NOACs (BI = -6,040,150 €) and in the case where numbers were shared equally with LMWH/VKA (BI = -12,954,207 €).

CONCLUSIONS

The inclusion of apixaban in the current mix of available treatments for acute episodes of VTA and the prevention of recurrent VTE is associated with clinical benefits in terms of reducing recurrent fatal and non-fatal VTE events and bleeding episodes, and financial benefits in terms of impact on the budget of the Italian NHS.

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