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ORIGINAL RESEARCH

Venous thrombo-embolism (VTE) prevention of patients undergoing total hip and knee replacement: budget impact analysis of apixaban in Italy

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ABSTRACT

BACKGROUND: Venous thromboembolism (VTE) is a common and burdensome cardiovascular condition, frequently leading to severe complications and requiring high-cost healthcare interventions. New oral anticoagulants (nOACs) have demonstrated to be efficacious and safe in VTE prevention of patients undergoing total hip replacement (THR) and total knee replacement (TKR), a condition that is typically associated to cardiovascular disease. The Italian Healthcare Service (SSN) has recently approved the latest nOAC, apixaban. The present article aims to evaluate its economic impact in the perspective of the Italian SSN.

METHODS: We conducted a budget impact analysis to estimate clinical outcomes and economic consequences associated to the reimbursement of apixaban, in the prevention of VTE as a consequence of major orthopedic surgery, over a three-year time horizon. In our analysis we compared two alternative scenarios, with apixaban either reimbursed (Scenario B) or not reimbursed (Scenario A) by the Italian SSN, and estimated the difference of healthcare costs between the two scenarios. Only direct healthcare costs have been considered.

RESULTS: According to market assumptions, it is estimated that 1.2%, 3.7%, and 6.5% of THR patients, and 1.2%, 3.8% and 6.7% of TKR patients, would be treated with apixaban over the first three years since launch. At the estimated daily cost of apixaban (€2.48/die), this would translate into a budget impact of €14.3 mln, €45.5 mln, and €81.4 mln at years 1, 2 and 3 since launch, respectively. This expenditure would be more than offset by savings, due to: i) reduction of prescriptions of alternative treatment options (other nOACs, low-molecular weight heparins, fondaparinux); ii) reduction of the economic burden attributable of CV complications of VTE. Finally, Scenario B resulted slightly favourable compared to Scenario A, leading to economic savings for about €50 thousands over three years. Sensitivity analyses confirmed findings of the base-case analysis.

CONCLUSIONS: Reimbursement of apixaban does not determine a budget impact increase for Italian SSN. Its usage may be considered fully sustainable from a pharmaco-economic viewpoint.

Keywords

Apixaban, New oral anticoagulants, Venous thromboembolism

INTRODUCTION

Venous thromboembolism (VTE) is the third most common cardiovascular illness after acute coronary syndrome and stroke [1], affecting more than 1 million patients each year [2]. It includes two different conditions, pulmonary embolism (PE) and deep vein thrombosis (DVT), which are relevant reasons of mortality and morbidity worldwide [3,4]. Without an efficacious prophylaxis, risk of developing VTE is estimated around 42-57% in patients undergoing total hip replacement (THP), and around 41-85% in patients undergoing total knee replacement (TKR) [5], with substantial implications in terms of healthcare costs and patients' productivity for recurrent and prolonged inpatient stay [6-8].

In the last few years several studies have evaluated the economic impact of VTE. Recent estimates confirm that thromboembolism-attributable costs are more than $1.5 billion/year in the US [9]. In the same review, the authors highlighted that costs of acute venous episodes exceed $20,000 in certain patients' categories. In a recent US study on Medicare beneficiaries [3], THR or THK patients developing VTE were found to have statistically

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significant higher costs, mortality and risk of rehospitalisation at one year after hospital discharge, compared to matched non-VTE patients. In a recent paper, Rupert et al. [10] reviewed ten economic studies carried out in the US and Europe, analyzing costs of THR and TKR patients developing VTE in the US and Europe. Evidence in this review pointed out that orthopaedic patients having PE and DVT costs up to more than twice than similar patients (controls) without any cardiovascular complications. Moreover, results from US administrative databases showed cost variability, with economic burden between US$3,000-9,500 for an initial episode. These costs seem higher than costs in the European Union, where VTE hospital management costs were €1,800 and €3,200 after 3 months and 1 year since diagnosis, respectively. Longer permanence in intensive coronary units, longer length stay, increasing usage of drug and outpatient services significantly increase direct healthcare costs of these patients [11]. Moreover, adopting a longer time horizon should take into account long-term clinical consequences of DVT such as recurrent DVT [12], post-thrombotic syndrome (PTS) [13] and thromboembolic pulmonary hypertension (PH) [14].

New oral anticoagulants (nOACs), apixaban, rivaroxaban and dabigatran, have demonstrated to reduce the risk of VTE after TKR and THR surgery, and to be as safe as low-molecular weight heparins (LMWH), enoxaparin in particular [15-22]. Although these new treatments have significantly improved patients' outcomes in the last years, some concerns have been raised on their cost-effectiveness profile, due to the high daily costs. In particular, healthcare payers have expressed the need of evaluating the inclusion of nOACs in formularies in the light of the budget implications of their possible increasing usage. The present study aims to analyze the economic impact of reimbursing and funding apixaban for prevention of VTE after THR or TKR, from the perspective of the Italian healthcare system.

MATERIAL AND METHODS

The present analysis evaluates the economic and clinical implications of reimbursing apixaban in Italy for VTE prevention in patients undergoing THR and TKR interventions, over the first three years after market authorization and reimbursement.

Model design and key analysis parameters

To perform this analysis, a decision-analytical budget impact model (BIM) running in Microsoft Excel® was developed. The model estimates financial impact (healthcare costs and investments) and clinical benefits (number of avoided VTE episodes) of alternative treatment scenarios which would likely reflect future trends of VTE prevention in Italy. Costs and outcomes for each hypothetical scenario have been evaluated on a short-time horizon (90 days). Figure 1 illustrates the decision tree built to run the analysis.

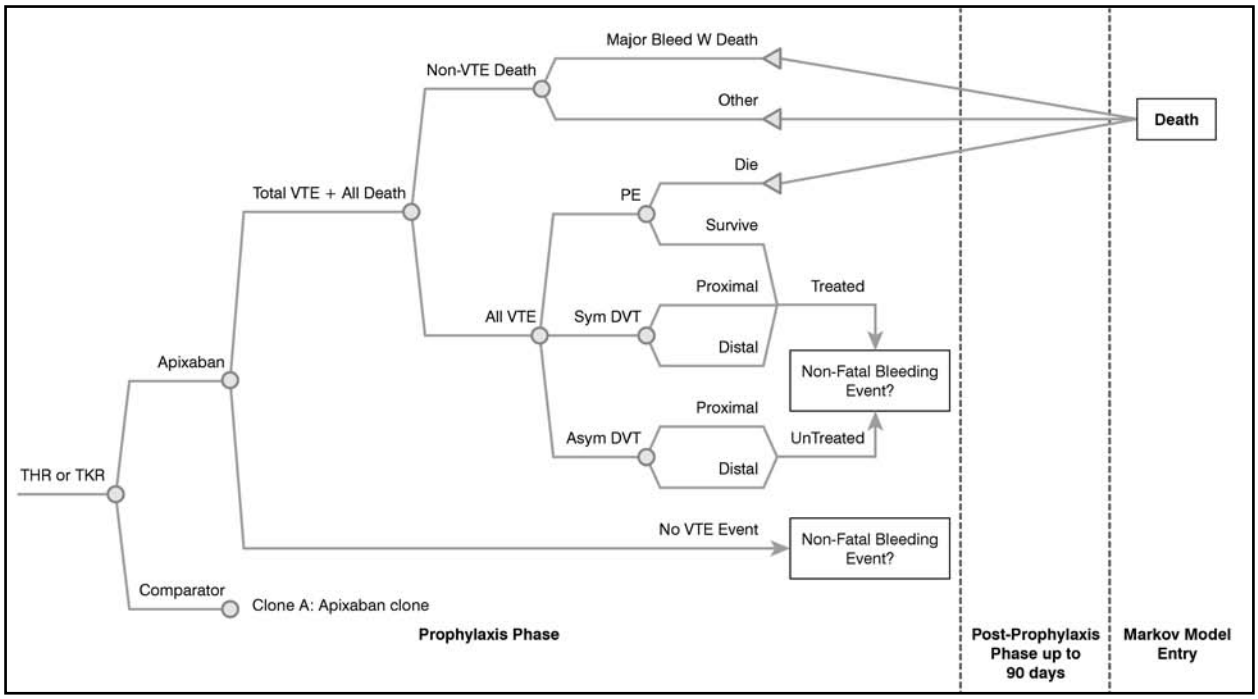

Figure 1. *Graphical representation of the decision tree adopted in the budget impact analysis*

A patient undergoing THR or TKR is treated to prevent VTE events. During the follow-up period the patient could have a certain likelihood to develop different forms of fatal or non-fatal VTE (PE or DVT), as well as bleeding events with different severity. Distribution of patients within the flow, as well as overall management costs, depends on the drug received. In the budget impact analysis, two different scenarios were defined and compared to each other:

- "Apixaban not reimbursed" scenario (defined "Scenario A"), assuming that apixaban would not be reimbursed and funded by Italian National Healthcare Service (SSN);
- "Apixaban reimbursed" scenario (defined "Scenario B"), assuming that apixaban would be reimbursed and funded by Italian SSN.

Assumptions on patients distribution for both scenarios, in terms of drug prescription, were built using current data of patients' treatment as reference, from updated market data [23]. According to current data, low molecular weight heparins represent the standard treatment for VTE prevention (administered to almost 90% of THR and TKR receiving VTE prevention, with enoxaparin being the most prescribed therapy). Fondaparinux and nOACs (rivaroxaban and dabigatran) are used in selected cases only. Table I shows the expected patients' treatment distribution in the next three years after apixaban market authorization, according to scenario (apixaban reimbursed vs. apixaban not reimbursed) and indication (VTE prevention in THR and TKR).

For the present analysis, the perspective of the Italian SSN was adopted. The healthcare direct costs were measured over a 3-years period (with results split by year). Costs after the first year since apixaban market authorization in Italy were discounted at an annual rate of 3.5%, while clinical outcomes were not discounted. Costs were measured in Euro (€) 2012.

Patient population

In order to calculate the overall budget impact of VTE prevention in Italy, we estimated the annual number of patients receiving VTE pharmacological prevention due to THR and TKR interventions. Italian population at December 31st, 2010 (60.62 million inhabitants) and expected annual percentage increase in population (0.47%) were retrieved from the National Statistics Institute (ISTAT) [24]. A recent report, published in 2009 by the Superior Health Institute (ISS) [25], estimated that annual incidence of TKR and THR is 0.12% and 0.10% respectively. According to 2010 internal market research data [26], 96% of THR patients and 93% TKR patients would receive VTE pharmacological prevention. Assuming that percentage of treated patients would not change over time, the estimated annual number of treated patients at years 1, 2 and 3 (after apixaban market authorization) is 71.16, 75.08, 79.21 thousands for THR, and 63.37, 66.60 and 69.99 thousands for TKR.

Therapy duration and hospital length of stay data

Duration of therapy for apixaban and the other drugs indicated in VTE prevention has

Treatment	Relative frequency, THR (%)			Relative frequency, TKR (%)		
	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3
Scenario A: apixaban not reimbursed by Italian SSN						
Apixaban	0.0	0.0	0.0	0.0	0.0	0.0
Low molecular weight heparins	89.1	84.1	81.3	89.1	84.2	81.5
Rivaroxaban	3.9	6.8	8.5	3.8	6.7	8.4
Dabigatran	3.0	5.0	5.9	3.0	4.9	5.8
Fondaparinux	4.0	4.2	4.3	4.0	4.2	4.3
Total	100.0	100.0	100.0	100.0	100.0	100.0
Scenario B: apixaban reimbursed by Italian SSN						
Apixaban	1.2	3.7	6.5	1.2	3.8	6.7
Low molecular weight heparins	88.0	81.0	76.0	88.0	81.0	76.0
Rivaroxaban	3.8	6.4	8.0	3.8	6.4	7.8
Dabigatran	3.0	4.8	5.5	3.0	4.8	5.4
Fondaparinux	4.0	4.0	4.0	4.0	4.0	4.0
Total	100.0	100.0	100.0	100.0	100.0	100.0

Table I. *Distribution of patients, by indication and treatment: expected trends after apixaban market authorization*

Treatment	Duration of treatment, THR (days)			Duration of treatment, TKR (days)		
	Hospital inpatient	After discharge	Total	Hospital inpatient	After discharge	Total
Apixaban	10.0	25.0	35.0	9.0	5.0	14.0
Low molecular weight heparins	10.0	25.0	35.0	9.0	5.0	14.0
Rivaroxaban	10.0	25.0	35.0	9.0	5.0	14.0
Dabigatran	10.0	21.5	31.5	8.0	0.0	8.0
Fondaparinux	10.0	25.0	35.0	9.0	5.0	14.0

Table II. *Duration of treatment, by indication and therapy setting*

been estimated in order to calculate treatment costs. Table II shows treatment duration assumptions, by therapy, treatment setting, and type of replacement surgery.

In this budget impact model it was assumed that overall treatment duration for each drug was the same as in clinical trials submitted for EMA approval. According to clinical trials data, overall duration of treatment is similar for all drugs except dabigatran, which is shorter. It is assumed that treatment is initiated during inpatient stay (for the orthopaedic replacement intervention) and then continued at home after discharge. Distinction between hospital and domiciliary treatment was necessary, as cost of pharmacological treatments in Italy could be different in the two settings (cfr "Economic Data"). Assumptions on length of stay (by type of replacement surgery) were obtained from a study measuring resource consumption and economic burden of hip and knee replacement interventions in Italy [27].

Treatment	THR		TKR	
	Total VTE + all cause death rate (%)	Bleeding events rate (%)	Total VTE + all cause death rate (%)	Bleeding events rate (%)
a) Incidence of VTE and bleeding events				
Apixaban	1.9	8.7	17.4	5.6
Low molecular weight heparins	5.4	9.4	27.4	7.2
Rivaroxaban	1.6	9.4	14.2	7.6
Dabigatran	4.8	10.0	26.3	7.0
Fondaparinux	1.7	8.7	11.3	6.2
	THR		**TKR**	
b) Distributions of VTE events and bleeding by severity/type				
PE events (% of total events)	**3.6**		**3.6**	
Fatal (% of PE events)	12.5		25.0	
Non-fatal (% of PE events)	87.5		75.0	
Symptomatic DVT events (% of total events)	**2.6**		**4.5**	
Distal (% of symptomatic DVT events)	16.7		80.0	
Proximal (% of symptomatic DVT events)	83.3		20.0	
Asymptomatic DVT events (% of total events)	**93.8**		**91.4**	
Distal (% of asymptomatic DVT events)	73.8		91.2	
Proximal (% of asymptomatic DVT events)	26.2		8.8	
Non-VTE death events (% of total events)	**3.5**		**3.5**	
All VTE events + non-VTE deaths (% of total events)	**100.0**		**100.0**	
Major bleedings (% of total bleeding events)	7.5		7.5	
Non major bleedings (% of total bleeding events)	34.1		34.1	
Minor bleedings(% of total bleeding events)	58.3		58.3	
All bleeding events (% of total events)	**100.0**		**100.0**	

Table III. *Efficacy data used in the model: a) adverse events and death incidence rates; b) conditional distribution of post-event rates*

Clinical data

Efficacy data for this analysis were derived from a mixed-treatment comparison evaluating evidence from clinical trials on VTE prevention in people undergoing elective THR and TKR surgery [28]. In absence of head-to-head clinical trials this metanalysis allowed to establish an indirect comparison of main clinical outcomes among VTE prevention treatments. This metanalysis was carried out according to NICE (National Institute of Clinical Excellence) requirements, and used as basis to build the economic evaluation of NICE single technology appraisal (STA) [29] Data for this metanalysis were selected through a systematic review, including the following clinical studies: double-blind randomised controlled trials (RCTs) of pharmacological prophylaxis of VTE in patients undergoing elective THR and TKR; trials enrolling mixed hip and knee populations, provided that patients undergoing hip surgery were randomised separately from patients undergoing knee surgery and patient numbers and results were stratified by surgery population; phase II trials, provided these were double-blind randomised controlled trials. Clinical evidence regarded LMWH, fondaparinux, rivaroxaban, dabigatran and apixaban, which could have been compared with either placebo or any of the treatments indicated in VTE prevention. Metanalysis measured two main clinical indicators: occurrence of VTE events (including pulmonary embolism, PE: symptomatic and asymptomatic deep vein thrombosis, DVT); occurrence of a bleeding events (major, non-major, minor events). In case of absence of calculated data for a certain drug, the rate of adverse events was assumed to be the lowest among compared treatments. Finally, rate of adverse events was stratified by distal vs. proximal DVT and fatal vs. non-fatal PE, using a conditional post-event distribution [28]. According to our assumptions, fatal events occurred in 12.5% and 25.0% of PE cases, for THR and TKR, respectively. Major bleedings represented 7.5% of all total bleeding events, for both THR and TKR patients. Table IIIa and Table IIIb illustrate, respectively, adverse events and death incidence rates (by drug and indication) and conditional distribution of post-event rates.

Economic data and assumptions on resource consumption

As the Italian SSN perspective was adopted in the analysis, only direct healthcare costs were measured. Overall VTE prevention therapy costs, inpatient costs for THR and TKR surgery, costs of VTE complications and bleedings were identified in our research. Figure 2 shows daily costs for pharmacological treatment.

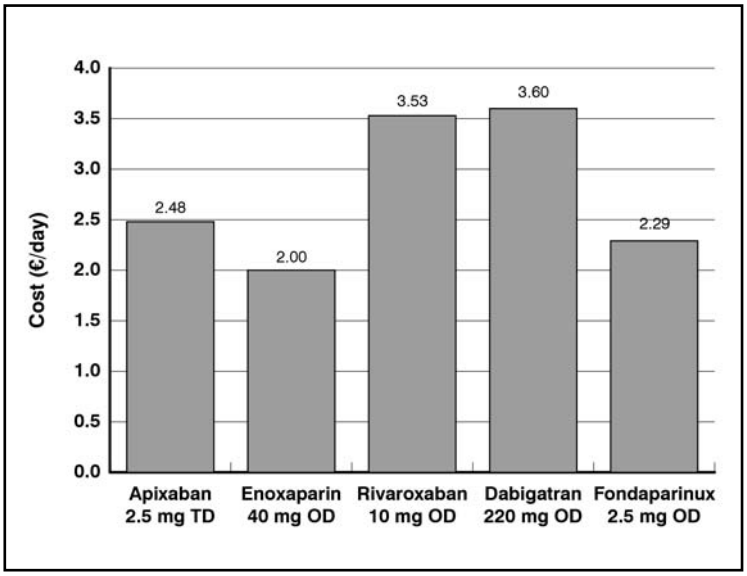

Figure 2. *Daily treatment costs of therapies indicated in VTE prevention (enoxaparin 40 mg: 4,000 International Units – IU)*
OD = once daily; TD = twice daily

With regard to apixaban, daily cost was calculated applying SSN rebates to the official ex-manufacturer price, published in the Official Gazette [30]. For the other therapies, a weighted average of inpatient and outpatient costs was used. Distinction between inpatient and outpatient costs was necessary as patients receiving initial treatment during hospitalization could continue therapy after discharge, if duration of treatment was longer than length of hospital stay (Table II). In our research, it was found that price of each marketed drug substantially varied among regions. Two main reasons determined this variability. First, Italian hospitals (or groups of hospitals) can negotiate prices with manufacturers through tenders, thus resulting in potentially different tender prices. Second, regions and local health units can discretionarily decide customized strategies to distribute heparins for outpatient use (i.e. direct distribution via hospitals, direct distribution via public pharmacies, standard retail distribution via public pharmacies), resulting again in different final prices for the SSN.

In order to obtain daily treatment costs being representative of the whole regional variability, we calculated average prices weighting regional prices by frequency of usage of a distribution channel and regional population. Regional prices and frequency of adoption of a certain distribution model were retrieved using multiple sources (internal market research data, official documentation on hospital tenders, etc.) Regional population data were finally extracted from Italian National Statistics sources (ISTAT data, December 31st 2010 [31]).

Costs for complications (VTE events and bleedings) requiring hospitalization are shown in Table III. In our model, only symptomatic VTE events determined healthcare costs for SSN. It was assumed that 100% of bleedings and 68.9% of symptomatic VTE events occurred at the time of hospital stay during the surgical replacement procedure [32]. In these cases an additional cost (40% of the DRG 78 tariff for PE events [33]; attributable DVT cost from PATHOS study [27]) was summed up to the standard hospital cost for THR or TKR (without complications) to take into account the higher burden for hospitals. A similar approach was used to estimate additional costs due to bleeding, by grade of severity. The remaining VTE events (31.1% of all cases) were assumed to occur after hospital discharge and to require hospital admission, according to costs and tariffs reported in Table IV.

SENSITIVITY ANALYSIS

A range of one-way deterministic sensitivity analyses was carried out to test robustness of base-case results. Specifically, variation of the following parameters was tested:

- Drug administration costs during THR/TKR hospitalization were included;
- Drug acquisition costs of nOACs were reduced of -40%, compared to base-case analysis;
- Discount rates for costs after year 1 were varied from 0% to 7% (discount in the base-case: 3.5%);
- Additional costs of VTE inpatient complications were varied of +10%, compared to base-case analysis;
- Percentage of patients receiving apixaban was varied of +10%, compared to apixaban patient share in the base-case.

RESULTS

According to patient population and treatment assumptions, the estimated number of patients (THR and TKR) is 134,533 at Year 1, 141,672 at Year 2 and 149,190 at Year 3. In Scenario B, the estimated number of patients treated with apixaban would be 1,613 at Year 1, 5,309 at Year 2 and 9,839 at Year 3. Main results of the budget impact analysis are illustrated in Table V.

In Scenario A (i.e. apixaban not reimbursed by the SSN) the increasing number of THR and TKR interventions over time translates into a budget impact increase for the SSN (+1.81%: Year 2 vs. Year 1; +1.71%: Year 3 vs. Year 2); index hospitalizations represents the budget impact driver for the SSN, accounting for 98.83% of overall costs, considering the 3-year time horizon of the analysis. The budget impact associated to Scenario B (introduction of apixaban in the Italian market) and Scenario A (non-reimbursement scenario) would be similar: €3,641,168,854 and €3,641,223,204, respectively. Therefore Scenario B would determine cumulative cost savings for €54,350 vs. Scenario A in the first three years, with a cost-saving profile achieved in each of the three years analyzed. Also,

		THR	TKR	Sources and assumptions
a) Hospital costs for replacement surgery and complications				
Hospital costs (without complications)		8,765	8,759	PATHOS study [27], average cost per intervention (without complications)
Symptomatic VTE	PE	1,510	1,510	40% of DRG 78 tariff (pulmonary embolism); TUC 2009 [34]
	Distal VTE	1,023	529	PATHOS study [27], additional costs due to distal VTE
	Proximal VTE	1,023	529	PATHOS study [27], additional costs due to proximal VTE
Bleedings	Major	1,267	1,267	40% of DRG 174 (gastro-intestinal hemorrhage with complications); TUC 2009 [34]
	Non major	754	754	40% of DRG 175 (gastro-intestinal hemorrhage with complications); TUC 2009 [34]
	Minor	41	41	National formulary of ambulatory specialist interventions, year 2009 [34]
b) Cost of complications (after hospital discharge)				
Symptomatic VTE	PE	3,773	3,773	DRG 78 tariff (pulmonary embolism); TUC 2009 [34]
	Distal/proximal DVT, requiring hospitalization	2,310	2,310	DRG 128 tariff (deep vein thrombo-phlebitis); TUC 2009 [34]
	Distal/proximal DVT, NOT requiring hospitalization	232	232	Nuijten MJC et al [35]

Table IV. *Hospital costs for a) replacement surgery and in-hospital VTE complications; b) after hospital discharge*
*DRG: diagnosis related group. **TUC: unified conventional tariff.

Time horizon	Scenarios	Overall direct healthcare costs (€)					
		Apixaban 2.5 mg TD	Enoxaparin 40 mg OD	Rivaroxaban 10 mg OD	Dabigatran 220 mg OD	Fondaparinux 2.5 mg OD	Total
Year 1	Scenario A	0	1,061,917,884	46,115,222	36,201,725	48,230,524	1,192,465,356
	Scenario B	14,297,284	1,049,183,674	45,562,267	35,767,641	47,652,169	1,192,463,036
	Difference (B-A)	**14,297,284**	**-12,734,210**	**-552,955**	**-434,084**	**-578,355**	**-2,320**
Year 2	Scenario A	0	1,021,322,981	81,844,878	60,453,713	50,381,598	1,214,003,171
	Scenario B	45,471,602	983,050,448	78,778,249	58,188,587	48,493,671	1,213,982,557
	Difference (B-A)	**45,471,602**	**-38,272,533**	**-3,066,629**	**-2,265,126**	**-1,887,927**	**-20,614**
Year 3	Scenario A	0	1,004,262,729	104,867,596	72,810,347	52,814,005	1,234,754,677
	Scenario B	81,400,279	938,030,298	97,952,558	68,009,203	49,330,923	1,234,723,261
	Difference (B-A)	**81,400,279**	**-66,232,431**	**-6,915,038**	**-4,801,144**	**-3,483,082**	**-31,416**
All Years	Scenario A	0	3,087,503,594	232,827,696	169,465,785	151,426,127	3,641,223,204
	Scenario B	141,169,165	2,970,264,420	222,293,074	161,965,431	145,476,763	3,641,168,854
	Difference (B-A)	**141,169,165**	**-117,239,174**	**-10,534,622**	**-7,500,354**	**-5,949,364**	**-54,350**

Table V. *Results of the budget impact analysis: scenarios comparison*

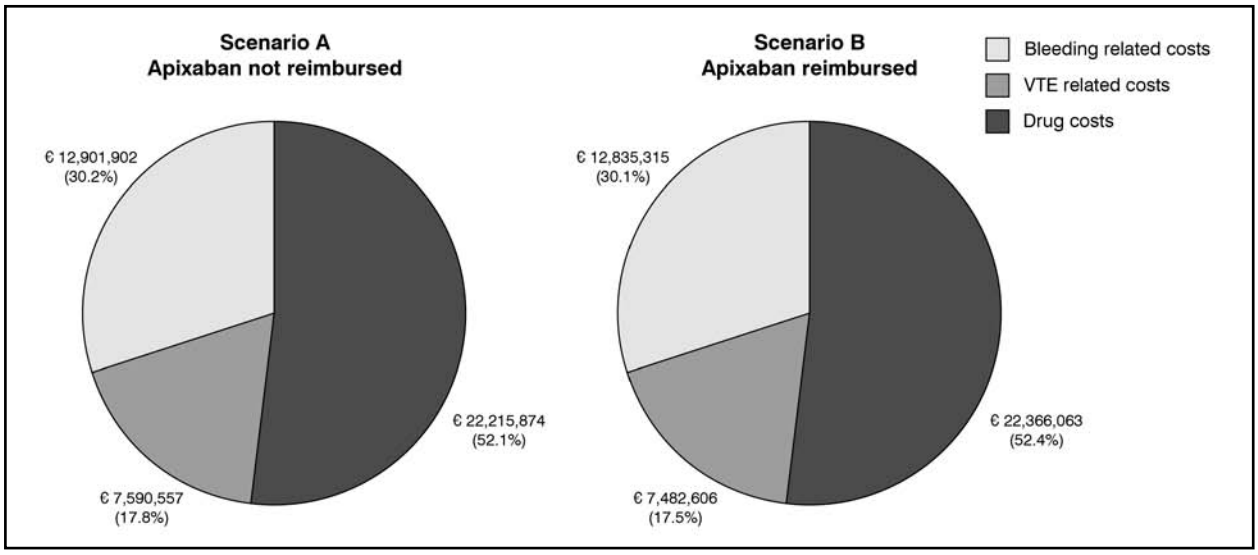

Figure 3. *Composition of direct healthcare costs*

the amount of cost savings sharply increases over time, as a consequence of the progressive replacement of LMWHs with nOACs.

Index hospitalizations represents the cost driver in the SSN perspective, being 98.83% of total direct healthcare costs. Excluding index hospitalization costs (for THR or TKR), drug costs account for 52.1% and 52.4% of total costs in Scenario B (apixaban reimbursed) and in Scenario A (apixaban not reimbursed), respectively (Figure 3). As a matter of fact, these costs (€22.24 million for Scenario A and €22.37 million for Scenario B) are relatively negligible, compared to inpatient costs for surgery replacement (€3.60 billion), which are the most relevant budget impact contributor of the analysis.

In Figure 4, the evolution of drug costs and VTE (inpatient and outpatient) costs in the

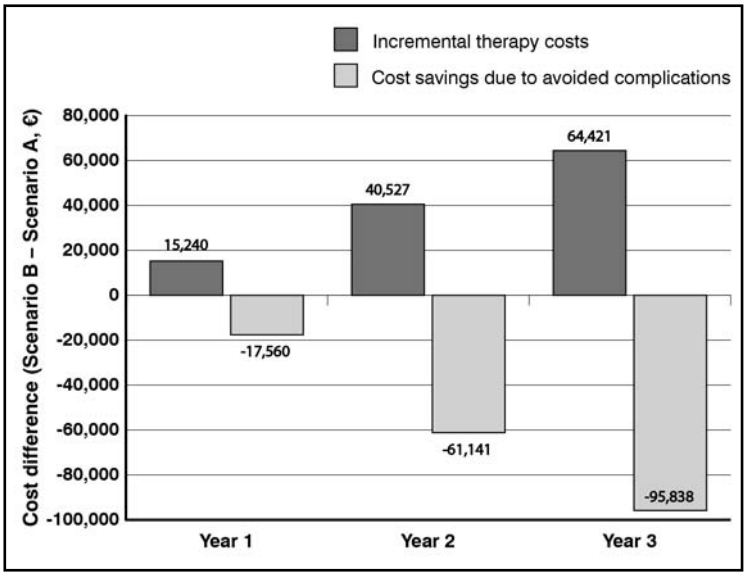

Figure 4. *Drug therapy and complications costs: scenario B vs. scenario A*

N.	Description of the analysis	Direct healthcare costs differences (€) – Scenario B-A				Overall direct healthcare costs with Scenario B All Years (€)
		Year 1	Year 2	Year 3	All years	
1	Base-case	-2,320	-20,614	-31,417	-54,351	3,641,168,854
2	Inclusion of drug administration costs	-18,840	-70,431	-117,942	-207,213	3,645,038,210
3	40% reduction of nOACs daily costs	-38,618	-127,999	-215,692	-382,309	3,639,346,360
4	Costs not discounted	-2,320	-21,336	-33,654	-57,310	3,771,601,407
5	Costs discounted at 7% rate	-2,320	-19,940	-29,395	-51,655	3,522,003,963
6	10% increase of VTE complications during THR/TKR hospitalization	-3,497	-24,301	-37,950	-65,747	3,642,770,443
7	10% decrease of VTE complications during THR/TKR hospitalization	-1,143	-16,929	-24,886	-42,958	3,639,567,445
8	100% increase of apixaban patient share	-5,147	-41,184	-62,981	-109,312	3,641,113,891

Table VI. *Results of sensitivity analysis*

first three years after apixaban reimbursement is illustrated. Drug investment with apixaban is fully set off by cost savings for avoided VTE episodes.

Based on clinical assumptions, Scenario B would be also associated to a reduction of VTE and bleeding events. In particular, over the entire period (3 years) apixaban introduction would be associated to the reduction of: symptomatic VTE and pulmonary embolism incidence (-106 non-fatal cases and -7 fatal cases vs. Scenario A); asymptomatic VTE incidence (-1,645 non-fatal cases vs. Scenario A); bleedings incidence (-186 cases vs. Scenario).

Results of sensitivity analysis, shown in Table VI, confirm that findings of the base-case study are robust.

In all scenarios tested, the inclusion of apixaban in the Italian market remains favourable. Inclusion of administration costs during index hospitalization, -40% reduction of drug costs, and +100% increase of apixaban usage would be the most beneficial scenarios, although the net benefit remains quite limited, if cost savings are compared with the overall budget impact of THR and TKR management, which is almost exclusively driven by hospital costs (+10% of hospital costs determines a +9.88% of overall budget impact for the SSN). The other scenarios included in the sensitivity analysis are affected by negligible fluctuations.

DISCUSSION

In a few years, nOACs have become an important alternative to previous and well established pharmacological treatments indicated in VTE prevention after orthopaedic surgery. Currently LMWHs remain the standard of care/prevention in this indication, but the usage of nOACs has been rapidly increasing, due to the good risk-benefit profile, the mode of administration, and the daily costs, which are comparable with LMWHs and fondaparinux. This analysis highlights two important aspects regarding VTE prevention. First, the introduction of the new oral anti-coagulant apixaban would not determine a budget impact increase for the SSN. More precisely, the analysis shows that a net economic benefit, even if small, will be achieved in the next years with apixaban reimbursement and usage. Second, the economic impact of pharmacological prevention of VTE is relatively low, compared to the annual amount of hospital costs for THR and TKR interventions. VTE prevention is prescribed for about 15-30 days, according to type of prevention, type of drug and patients' characteristics, and this sporadic usage makes the treatment affordable for the SSN. Our model estimates that only 1.7% of healthcare resources is allocated in VTE prevention, and that the introduction of new agents will not modify (increase) the number of treated patients, as almost all patients already receive a pharmacological VTE prevention.

In our analysis, we adopted a conservative approach for our base-case analysis. Drug administration costs (for parenteral treatments) were not included in the base-case analysis, assuming that these costs would be covered within the DRG (i.e. no extra-costs for hospitals). Also, we intentionally decided to focus on direct healthcare costs only, although the inclusion of indirect costs and the adoption of a societal perspective would have been favourable for apixaban and nOACs in general. Finally, and most importantly, apixaban daily cost only includes rebates granted to the official ex-manufacturer price, as the final result of government negotiations. Unlike the other treatments included in the analysis,

further rebates granted to hospitals have not been estimated/included, due to the very recent decision of reimbursement. Reasonably, an additional reduction of apixaban costs would reflect into additional cost savings for the SSN.

The selection of alternative scenarios to test with sensitivity analysis was performed adopting different points of view. For assumptions affected by uncertainty (positive/negative), we evaluated standard sensitivity analysis. This was the case of discount rates and additional inpatient costs due to VTE complications. With regard of apixaban usage, the effect of a limit-case analysis, assuming to double apixaban patients' share, was analyzed. Although this case may seem unlikely, it was tested to assess whether large, unexpected variations of the market could determine substantial budget impact increase, which would not be affordable, considering this period of economic constraints. Finally, the -40% reduction was chosen to take into account the future price erosion for nOACs at the time of launch of the second indication: prevention of stroke in patients with atrial fibrillation (SPAF). If the Italian Drug Agency (AIFA) will grant approval of nOACs in this new indication, a price reduction is likely to expect, and will be triggered by the following reasons: i) these drugs would be prescribed to a much larger number of patients, compared to the current situation; ii) pharmacological treatment SPAF is chronic; iii) likely, nOACs will be also distributed by public pharmacies, with additional costs for the SSN. All these reasons would lead to a substantial increase of economic resources to fund this class of agents, which will likely have to be offset by a price reduction of nOACs daily cost. Since the level of price discount for apixaban, rivaroxaban and dabigatran is hard to predict, we decided to apply a -40% reduction, which is the average final price rebate for enoxaparin (from ex-manufacturer price to the distribution price). This analysis shows that further discounts applied to nOACs would allow an additional slightly reduction of the budget impact, although majority of costs always depend on index hospitalizations.

The expected price reduction of nOACs in the next few years represents a definitive confirmation of affordability of nOACs usage in VTE prevention. On the other side, the possible approval and market authorization of these promising therapies in SPAF raise relevant questions on their cost-effectiveness, requiring further economic studies aimed to evaluate sustainability and comparative cost-effectiveness vs. available treatment options.

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