Journal of Medical Economics

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ijme20

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To cite this article: Andrés J. Muñoz, Laura Ortega, Ana Gutiérrez, Enrique Gallardo, Darío Rubio-Rodríguez, Carlos Rubio-Terrés, Blanca Morón, Pilar García-Alfonso & José Manuel Soria (2023) Cost-effectiveness of apixaban and rivaroxaban in thromboprophylaxis of cancer patients treated with chemotherapy in Spain, Journal of Medical Economics, 26:1, 1145-1154, DOI: 10.1080/13696998.2023.2248839

To link to this article: https://doi.org/10.1080/13696998.2023.2248839

JOURNAL OF MEDICAL ECONOMICS
2023, VOL. 26, NO. 1, 1145–1154
https://doi.org/10.1080/13696998.2023.2248839
Article 0050-RT/2248839

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ORIGINAL RESEARCH

Cost-effectiveness of apixaban and rivaroxaban in thromboprophylaxis of cancer patients treated with chemotherapy in Spain

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ABSTRACT

Background: Apixaban and rivaroxaban are two direct-acting oral anticoagulants (DOACs) recommended for thromboprophylaxis in cancer patients treated with chemotherapy in an ambulatory setting. We aimed to assess the cost-utility of thromboprophylaxis with apixaban and rivaroxaban vs no thromboprophylaxis in ambulatory cancer patients starting chemotherapy with an intermediate-to-high risk of venous thromboembolism (VTE), Khorana score $\geq$ 2 points.

Methods: A cost-effectiveness analysis was performed from the perspective of Spain's National Health System (NHS) using an analytical decision model in the short-term (180 days) and a Markov model in the long-term (5 years). Transition probabilities were obtained from randomized, double-blind, placebo-controlled clinical trials of apixaban and rivaroxaban in adult ambulatory patients with cancer at risk for VTE, treated with chemotherapy (AVERT and CASSINI trials). The costs (€2,021) were taken from Spanish sources. The utilities of the model were obtained through the EQ-5D questionnaire. Deterministic (base case) and probabilistic (second-order Monte Carlo simulation) analyses were conducted.

Results: In the probabilistic sensitivity analysis, apixaban generated a cost per patient of €1,082 ± 187, with a 95% confidence interval (CI) of €713–1,442, while no prophylaxis produced a cost per patient of €1,146 ± 218, with a 95% CI of €700–1,491, with a saving of €64 per patient and a gain of 0.008 QALYs. Likewise, rivaroxaban provided a cost per patient of €993 ± 133, with a 95% CI of €748–1,310, while no prophylaxis produced a cost per patient of €872 ± 152, with a 95% CI of €602–1,250, with an additional expense of €121 per patient and a gain of 0.008 QALYs.

Conclusions: In thromboprophylaxis of cancer patients, the use of apixaban and rivaroxaban generated similar costs compared to non-prophylaxis, without the difference found being statistically significant, with a clinically insignificant QALY gain.

ARTICLE HISTORY
Received 7 December 2022
Revised 9 August 2023
Accepted 14 August 2023

KEYWORDS
Cost-effectiveness; thromboprophylaxis; cancer; direct-acting oral anticoagulants; venous thromboembolism

JEL CLASSIFICATION CODES
D61; D6; D; I10; I1; I; C63; C6; C

Introduction

Venous thromboembolism (VTE) is a frequent complication in cancer patients and has been progressively increasing in the last two decades[1]. Cancer-associated thrombosis (CAT) has been associated with a higher mortality, morbidity, healthcare costs, and, more recently, with a significantly negative impact on the quality-of-life of cancer patients[2].

CAT rates vary widely among cancer patients[3]. The estimated CAT rate for average-risk patients is 13 per 1,000 person-years, while patients with metastatic disease or receiving thrombogenic therapies have a VTE rate of 68 per 1,000 person-years, with the highest risk reported in lung, pancreatic, and brain cancers (200 per 1,000 person-years). Currently, most venous thromboembolic events occur in the outpatient setting[4]. Different randomized clinical trials[5,6] and meta-analyses[7] have shown that ambulatory thromboprophylaxis is effective with an acceptable bleeding risk profile in this population.

Apixaban (APIX) and rivaroxaban (RIV) are the only direct oral anticoagulants (DOAC) recommended by the *American Society of Clinical Oncology* (ASCO)[8] and the *International Initiative on Thrombosis and Cancer* (ITAC)[9] in ambulatory cancer patients receiving systemic chemotherapy. These recommendations are based on two phase III randomized clinical trials: CASSINI[10] and AVERT[11] trials, that included a wide spectrum of prothrombotic cancers (gastrointestinal, genitourinary, lung, brain tumors and hematological neoplasms such as lymphoma and myeloma) in adult patients. Both studies have a similar design, they compared up to 6 months

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/13696998.2023.2248839.

thromboprophylaxis with RIV (10 mg daily) or APIX (2.5 mg twice daily) to placebo in ambulatory cancer patients initiating systemic anti-cancer therapy with a Khorana score of 2 points or higher. Patient populations share similar clinical features (Supplementary Table S1 and S2). In the AVERT trial, apixaban was associated with a significantly lower incidence of VTE compared to placebo in the primary modified intention-to-treat analysis (mITT), 4.2% versus 10.2%, respectively (hazard ratio = 0.41; 95% confidence interval [CI] = 0.26–0.65; $p < 0.001$). The rate of major bleeding was significantly higher with apixaban than with placebo in the mITT (3.5% and 1.8%, respectively; HR = 2.00; 95% CI = 1.01–3.95), but not during the treatment period. In the CASSINI trial, VTE incidence was lower with rivaroxaban compared to placebo in the per-protocol analysis, 2.6% versus 6.4% (HR = 0.40; 95% CI = 0.20–0.80), but not in the primary intention-to-treat analysis. Major bleeding occurred in 2% of patients receiving rivaroxaban and 1% receiving placebo (HR = 1.96; 95% CI = 0.59–6.49). This indication is not yet authorized in Spain, but, on the contrary, it is recommended by the Spanish Society of Medical Oncology (SEOM)[12]. Despite the availability of several validated risk assessment models for VTE in cancer patients and guideline recommendations, rates of VTE prophylaxis in high-risk patients are low in routine clinical practice. A recent survey by the Association of Community Cancer Centers reported that only 9% of oncologists use a risk assessment tool to identify high-risk patients in the outpatient setting and more than 90% of patients with very high-risk do not receive pharmacological thromboprophylaxis[13].

Two recently published economic analyses[14,15] assessed cost-effectiveness of thromboprophylaxis with DOAC in cancer patients treated with chemotherapy in ambulatory patients with an intermediate to high risk of suffering VTE (Khorana score $\geq$ 2). In these studies thromboprophylaxis refers to the pharmacological thromboprophylaxis for patients with cancer with high risk of VTE based on Khorana risk score. However, neither of the two studies performed a single drug-based analysis and no formal drug–drug comparison was provided (Supplementary Table S3).

The main hypothesis of this study is that APIX and RIV may have a different cost-effectiveness profile. The aim of this analysis is to know if the use of APIX or RIV is a cost-effective alternative in thromboprophylaxis for ambulatory cancer patients with intermediate-high risk of VTE (Khorana score $\geq$ 2) in Spain, based on the different results obtained in efficacy and safety with these drugs in placebo-controlled randomized clinical trials[9,10] and on different pharmacokinetic and pharmacodynamic profiles[16].

Methods

This cost-effectiveness analysis was performed from the perspective of the Spanish National Health Service, so only healthcare costs (direct medical costs) were included. A discount rate of 3% per year was applied to costs and outcomes. The primary outputs of the model included costs, quality-adjusted life years (QALYs), and incremental cost-effectiveness ratio (ICER). The model was constructed *via* TreeAge Pro 2018 (TreeAge Software, Inc, Williamston, MA).

Model structure and analysis type

The structure of the model was based on previously published models[17–20]. Figure 1 shows the structure of the economic model. It consists of a short-term (with a 180-day time horizon) decision analysis (DA) and subsequent long-term Markov model (with a 5-year time horizon) and a cycle length of 1 year. The short-term DA includes the following health states: (i) actively treated cancer; (ii) minor bleeding events (MIBE); (iii) major bleeding events (MABE); (iv) deep venous thrombosis (DVT); (v) pulmonary embolism (PE); or (vi) death from any cause. Patients with DVT were expected to evolve in the long-term (Markov model) to the following states: (i) actively treated cancer; (ii) post-thrombotic syndrome (PTS); or (iii) death from any cause. Similarly, the patient with PE was assumed to evolve (Markov) to the following states: (i) actively treated cancer; (ii) chronic thromboembolic pulmonary hypertension (CTPH); or (iii) death from any cause (Figure 1). Deterministic and probabilistic analysis (through 1.000 second-order Monte Carlo simulations) were performed. Probabilistic analyses allow the assessment of the uncertainty of the variables[21]. One-way (tornado) deterministic sensitivity analyses were also performed, modifying probabilities, costs, and utilities. A willingness-to-pay in Spain of EUR 25,000 per QALY gained was considered.

Probabilities of the model

Table 1 shows the short- and long-term probabilities considered in the model. The short-term probabilities were mainly obtained from the economic studies of Du et al.[14] and Li et al.[15], who, in turn, had taken them from phase III, randomized, placebo-controlled, double-blind clinical trials of APIX (AVERT study)[10], and RIV (CASSINI study)[11] in cancer, as well as from another previously published analysis[22]. The design and results of the AVERT and CASSINI trials, as well as the baseline demographic and clinical characteristics of the patients, are detailed in Supplementary Tables S1 and S2. The probabilities considered in the long-term Markov model (with 1 year cycles) were obtained from clinical and economic studies published earlier[14,17,21–25]. Transition probabilities of the model were calculated according to the formula $Pt = 1 - e^{-rt}$, r being the event rate and t the time in which such rate takes place[26].

Costs of the model

The costs of the model are presented in Table 2. For the calculation of the mean cost of prophylaxis with DOAC, the mean duration of prophylaxis (in days) was calculated using the medians from the AVERT study[10] according to the formula from Pudar et al.[27]. Thus, a mean duration of prophylaxis of 140 days was considered, between a minimum of 70 and a maximum of 150 days.

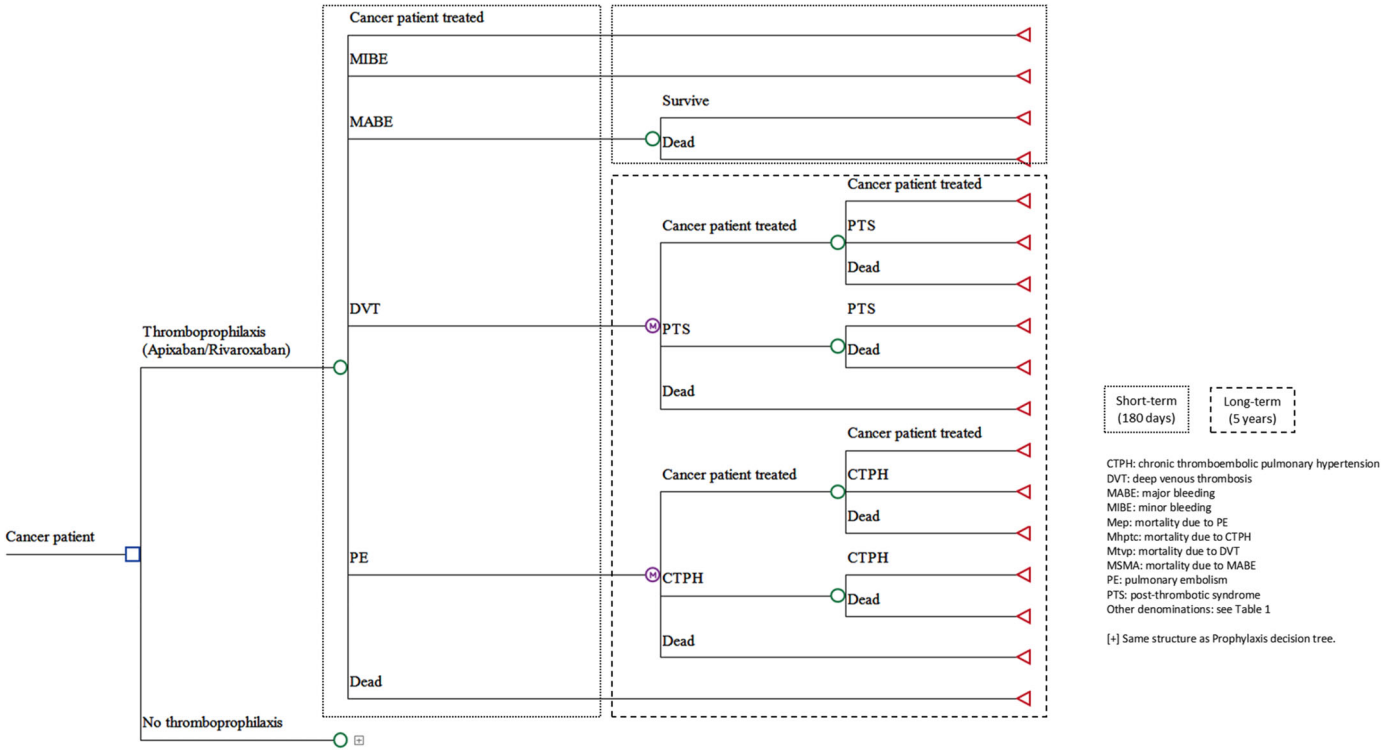

Figure 1. Economic model structure.

Table 1. Probabilities of the economic model in the short- and long-term.

Decision analysis model (180 days)	Average	Minimum	Maximum	SD	References
MIBE					
MIBE probability with apixaban	0.0606	0.0485	0.0727	0.0062	11,17
MIBE probability with placebo (vs apixaban)	0.0496	0.0397	0.0596	0.0051	11,17
MIBE probability with rivaroxaban	0.0268	0.0215	0.0322	0.0027	11,18
MIBE probability with placebo (vs rivaroxaban)	0.0196	0.0157	0.0235	0.0020	11,18
MABE					
MABE probability with apixaban	0.0206	0.0165	0.0247	0.0021	11,17
MABE probability with placebo (vs apixaban)	0.0108	0.0087	0.0130	0.0011	11,17
MABE probability with rivaroxaban	0.0196	0.0157	0.0235	0.0020	11,18
MABE probability with placebo (vs rivaroxaban)	0.0099	0.0079	0.0118	0.0010	11,18
DVT					
DVT probability with apixaban	0.0238	0.0190	0.0286	0.0024	11,17
DVT probability with placebo (vs apixaban)	0.0415	0.0332	0.0498	0.0042	11,17
DVT probability with rivaroxaban	0.0305	0.0244	0.0366	0.0031	11,18
DVT probability with placebo (vs rivaroxaban)	0.0441	0.0353	0.0529	0.0045	11,18
PE					
PE probability with apixaban	0.0171	0.0136	0.0205	0.0017	11,17
PE probability with placebo (vs apixaban)	0.0549	0.0439	0.0659	0.0056	11,17
PE probability with rivaroxaban	0.0282	0.0226	0.0338	0.0029	11,18
PE probability with placebo (vs rivaroxaban)	0.0419	0.0335	0.0503	0.0043	11,18
Mortality					
Mortality in cancer patients under thromboprophylaxis	0.1674	0.0715	0.2761	0.0522	10,19
Mortality in cancer patients without thromboprophylaxis	0.1820	0.0980	0.2380	0.0357	10,19
Mortality due to MABE	0.0465	0.0372	0.0558	0.0047	11

Markov model (5 years) (annual probabilities)	Average	Minimum	Maximum	SD	References
PTS					
If DVT, PTS probability	0.0564	0.0342	0.0786	0.0113	10,22
CTPH					
If PE, CTPH probability	0.0076	0.0046	0.0106	0.0015	10,21
Mortality					
Mortality due to DVT/PTS	0.1681	0.1345	0.2017	0.0172	10,19
Mortality due to PE	0.1875	0.1500	0.2250	0.0191	12
Mortality due to CTPH	0.1410	0.1110	0.1750	0.0163	20

Abbreviations. CTPH, chronic thromboembolic pulmonary hypertension; DVT, deep venous thrombosis; MIBE, minor bleeding events; MABE, major bleeding events; PE, pulmonary embolism; PTS, post-thrombotic syndrome; SD, standard deviation.

Table 2. Economic model costs (2020 €).

Item	Average (€)	Minimum (€)	Maximum (€)	SD (€)	References
	(140 days)	(70 days)	(150 days)		10,17
Apixaban (5 mg/day)	251.23	125.62	269.18	36.62	SmPC; Public prices
Rivaroxaban (10 mg/day)	251.23	125.62	269.18	36.62	SmPC; Public prices
DVT (DRG 197)*	5,867.50	2,504.00	12,293.00	2,497.19	25
PE (DRG 134)*	6,551.75	3,469.00	11,656.00	2,088.52	25
MABE (DRG 44)*	7,585.50	4,069.00	13,561.00	2,421.43	25
MIBE clinically relevant (DRG 253)*	5,898.50	2,702.00	11,955.00	2,360.46	25
PTS (DRG 197)*	5,867.50	2,504.00	12,293.00	2,497.19	25
CTPH (DRG 207)*	5,388.25	2,591.00	12,293.00	2,475.00	25

Abbreviations. CTPH, chronic thromboembolic pulmonary hypertension; DVT, deep venous thrombosis; MIBE, minor bleeding events; MABE, major bleeding events; PE, pulmonary embolism; PTS, post-thrombotic syndrome; SmPC, summary of product characteristics; SD, standard deviation. * Cost per event.

Table 3. Economic model utilities.

		Average	Minimum	Maximum	SD	References
Cancer without complications		0.645	0.616	0.672	0.014	10,26
Cancer with DVT		0.605	0.514	0.678	0.042	10,26
	Utilities loss	−0.040	−0.102	0.006	0.028	
Cancer with PE		0.621	0.477	0.725	0.063	10,26
	Utilities loss	−0.024	−0.139	0.053	0.049	
Cancer with MABE		0.593	0.461	0.693	0.059	10,26
	Utilities loss	−0.052	−0.155	0.021	0.045	
Cancer with clinically relevant MIBE		0.622	0.568	0.669	0.026	26
	Utilities loss	−0.023	−0.048	−0.003	0.011	
Cancer with PTS		0.500	0.320	0.650	0.084	10,26
	Utilities loss	−0.145	−0.296	−0.022	0.070	
CTPH		0.630	0.520	0.730	0.054	10,27
	Utilities loss	−0.015	−0.096	0.058	0.039	

Abbreviations. CTPH, chronic thromboembolic pulmonary hypertension; DVT, deep venous thrombosis; MIBE, minor bleeding events; MABE, major bleeding events; PE, pulmonary embolism; PTS, post-thrombotic syndrome; SD, standard deviation.

The cost of the events (DVP, PE, MABE, MIBE, PTS, and CTPH) in Spain were obtained from the public prices of health services of the Basque Health Service for the year 2020[28]. The costs of the following diagnostic-related groups (DRG): were considered: DVP (197); PE (134); MABE (44); MIBE (253); PTS (197), and CTPH (207).

Utilities of the model

The utilities considered in the model were the ones used in the recent economic analysis of Du et al.[13] (Table 3). These utilities derive from a study conducted in the United Kingdom using the EQ-5D instrument[29], excluding the CTPH utility, that was obtained from a study performed in the USA[30].

Clinical validation of the model

The economic model was clinically validated by two Spanish clinical experts with experience in thromboprophylaxis in cancer patients (Dr. Enrique Gallardo, Oncology Department, Hospital Universitario Parc Taulí, Sabadell, Spain; Dr. Andrés J. Muñoz, Medical Oncology Department, Hospital General Universitario Gregorio Marañón, Madrid, Spain).

Sensitivity analysis

A univariable and probabilistic sensitivity analyses were performed to assess the robustness of the model and the uncertainty in parameter estimation. In this study, a probabilistic deterministic sensitivity analysis (PDSA) expressed in incremental net benefit was performed instead of a normal univariant sensitivity analysis, because PDSA offers advantages versus a classic deterministic sensitivity analysis for providing insight on the effect of uncertainty in individual parameters on the estimate cost-effectiveness[31].

Results

Base-case analysis

APIX vs no prophylaxis

APIX would be dominant (greater effectiveness with lower costs) compared to no prophylaxis, with a gain of 0.005 quality adjusted life years (QALY) and a cost difference of –€59.49 (Table 4). It is estimated that for every 1,000 patients treated with APIX instead of RIV, seven episodes of DVT and 11 episodes of PE would be prevented (Supplementary Table S4).

RIV vs no prophylaxis

RIV would not be dominant compared with no prophylaxis. However, it would be cost-effective. The cost of gaining a QALY with RIV would be €18,746.77 (below a willingness to pay of €25,000–60,000 per QALY gained)[32]. If one considered that the QALY gain was not clinically relevant, with RIV, an additional cost of €116.23 per patient would be generated versus no thromboprophylaxis (Table 4).

Table 4. Base-case analysis.

Prophylaxis	Cost per patient (€)	Costs differences (€)	QALY per patient	QALY differences	Cost per QALY gained
Apixaban	1,077.10	−59.49	0.5380	0.0052	Apixaban is dominant*
No prophylaxis	1,136.58		0.5328		
Rivaroxaban	1,001.14	116.23	0.5400	0.0062	18,746.77 €
No prophylaxis	884.91 €		0.5338		

* With apixaban, QALYs are gained and savings are generated compared to no prophylaxis.
Abbreviation. QALYs, quality-adjusted life years.

Table 5. Probabilistic analysis results.

Prophylaxis	**Cost per patient (€) (95% CI)**	Costs differences (€)	**QALY per patient (€) (95% CI)**	QALY differences	Cost-effectiveness probability*
Apixaban	1,082 ± 187	−64	0.539 ± 0.034	0.008	62.6%
No prophylaxis	(713–1,442)		(0.465–0.734)		
	1,146 ± 218		0.531 ± 0.026		
	(700–1,491)		(0.430–0.695)		
Rivaroxaban	993 ± 133	121	0.541 ± 0.035	0.008	51.9%
No prophylaxis	(748–1,310)		(0.445–0.741)		
	872 ± 152		0.533 ± 0.027		
	(602–1,250)		(0.442–0.702)		

* Of prophylaxis versus no prophylaxis, for a willingness to pay of €25,000 per QALY gained. If all iteration with less QALY as negatives are taken into account, the probability API versus No prophylaxis will be 49.1%, and the probability RIV versus No prophylaxis will be 41.2%.
Abbreviations: QALYs, quality-adjusted life years.

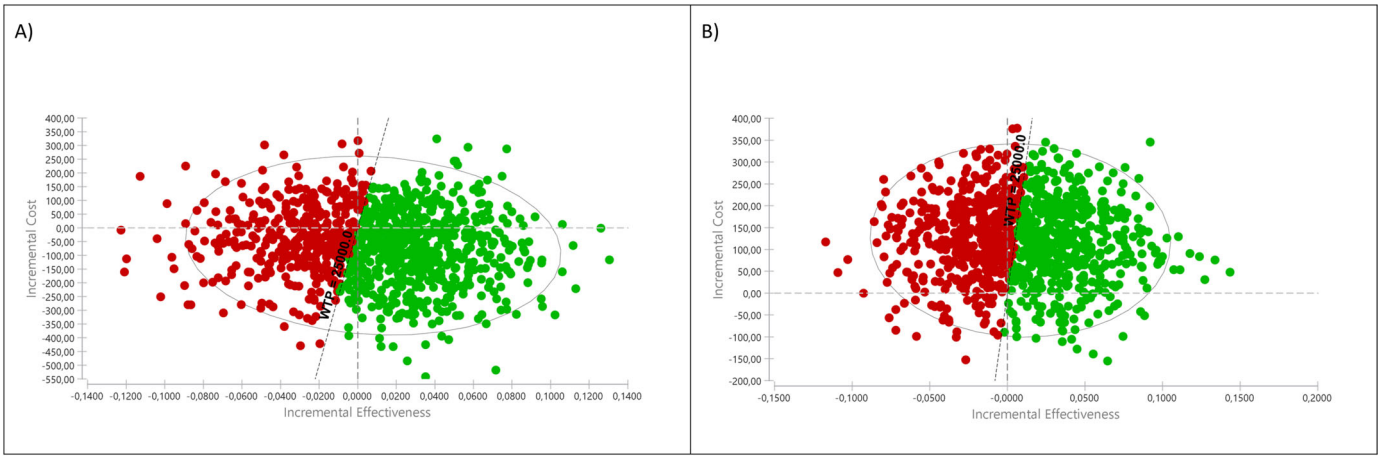

Figure 2. Incremental cost-effectiveness of APIX (a) and RIV (b) versus no prophylaxis.

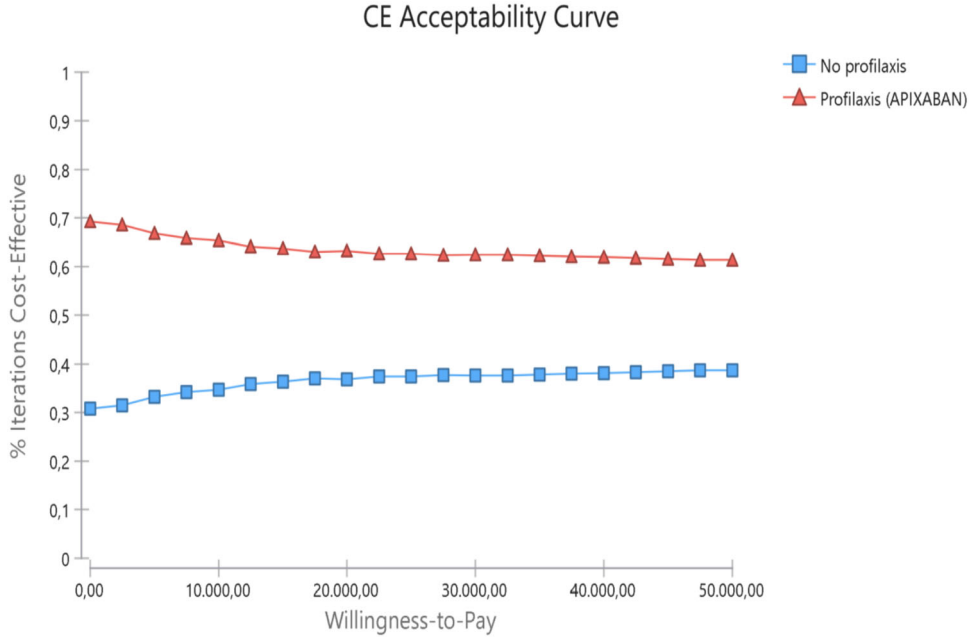

Figure 3. Cost-effectiveness acceptability curve of APIX versus no prophylaxis.

Probabilistic sensitivity analyses

APIX vs no prophylaxis

As shown in Table 5 and Figure 2a, the probabilistic analysis revealed savings of around €64 per patient treated with APIX and a gain of 0.008 QALY per patient treated with APIX compared to no prophylaxis. The probability of APIX being cost-effective, for a willingness-to-pay of €25,000 per QALY gained, was 62.2%. Figure 3 shows the cost-effectiveness acceptability curve (CEAC) of APIX vs no prophylaxis.

RIV vs no prophylaxis

As noted in Table 5 and Figure 2b, the probabilistic analysis showed an additional cost per patient treated with RIV of around €121 and a gain of 0.008 QALY per patient treated with RIV in comparison with no prophylaxis. The probability of RIV being cost-effective, for a willingness to pay of €25,000 per QALY gained, was 51.9%. Figure 4 shows the CEAC of RIV vs no prophylaxis.

Probabilistic deterministic sensitivity analyses

Incremental net monetary benefit (INMB) was positive (cost-effective) for a willingness to pay of €25,000 per QALY gained for all variables in the case of RIV, with two exceptions: the probability of cancer mortality with or without prophylaxis, in which case the risk of a negative IBNM (not cost-effective) would be 60.9% and 36.2%, respectively. In the case of APIX, the risk of a negative IBNM for the probability of cancer mortality with or without prophylaxis would be 64.0% and 30.8%, respectively. One-way deterministic sensitivity analyses are described in detailed for APIX and RIV in Table 6.

Discussion

In the last three decades the overall incidence of VTE has increased by 3-fold. It's estimated the risk of VTE in cancer patients is 12-fold higher than in the overall population, and in patients receiving systemic anti-cancer therapy reaches 23-fold[1]. VTE in cancer patients provokes a significant increase in VTE recurrence and major bleeding during anticoagulant therapy compared to non-cancer patients[33]. Furthermore, VTE is associated with temporary or definitive interruption of anticancer therapy with a potential impact on cancer prognosis. These data suggest that prevention of VTE in patients with cancer who receive systemic therapy in an ambulatory setting has a potentially high clinical value. Despite all these facts and available evidence from placebo-controlled randomized clinical trials showing outpatient thromboprophylaxis in cancer patients is effective and safe, it is still seldom used in clinical practice, and the cost-effectiveness relationship has not been well established yet.

In the present economic analysis thromboprophylaxis in cancer patients treated with systemic therapy would be more efficient with APIX than with RIV. APIX is dominant (greater effectiveness with lower costs) compared to no prophylaxis. Nevertheless, the gain of 0.005 QALY per patient might not be clinically relevant, since clinical relevance in utility gain (the smallest difference in quality-of-life that a patient can perceive) is generally considered to be between 0.03 and 0.04 QALY gained[34,35]. If this premise is accepted, one would save up to €59.49 per patient with APIX compared to no thromboprophylaxis. This fact shows that in addition to the clinical value derived from the use of APIX and RIV as thromboprophylaxis, the use of these alternatives will generate resource savings for the National Health System in the case of APIX and will be a cost-effective option in the case of RIV. It should be taken into account that there are no

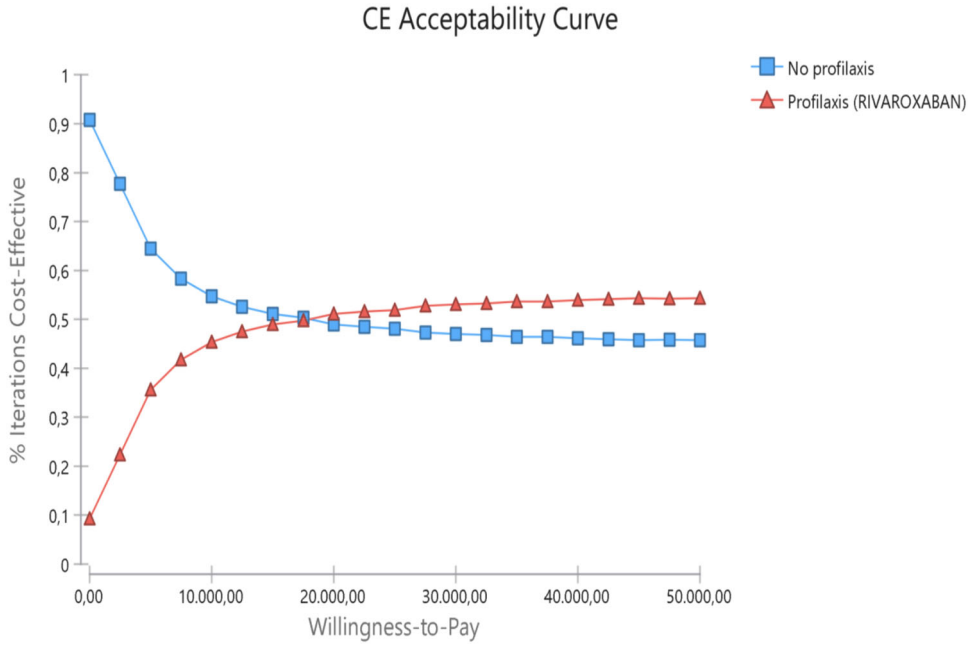

Figure 4. Cost-effectiveness acceptability curve of RIV versus no prophylaxis.

Table 6. One-way deterministic sensitivity analyses.

Variable Name	Variable Description	Variable Low	Variable Base	Variable High	Impact	Low	High	Risk %
Apixaban								
Mcon	Cancer mortality prob with prophylaxis	0.0715	0.1674	0.2761	Decrease	−1,167	2,618	0.6398
Msin	Cancer mortality prob without prophylaxis	0.098	0.182	0.238	Increase	−731	1,894	0.3078
Uep	Utility with PE	0.04	0.49	0.8	Increase	419	1,137	0.0230
EPpa	Placebo EP probability (vs apixaban)	0.0439	0.0549	0.0659	Increase	644	1,045	0.0072
Cep	PE cost	3,469	6,551.75	11,656	Increase	728	1,037	0.0043
Utvp	Utility with DVT	0.14	0.55	0.83	Increase	663	968	0.0042
TVPa	DVT probability with apixaban	0.019	0.0238	0.0366	Decrease	648	918	0.0032
TVPpa	DVT probability with placebo (vs apixaban)	0.0332	0.0415	0.0498	Increase	717	971	0.0029
Ctvp	DVT cost	2,504	5,867.5	12,293	Increase	785	958	0.0013
SMEa	MIBE probability with apixaban	0.0485	0.0606	0.0727	Decrease	761	928	0.0012
SMEpa	MIBE probability with placebo (vs apixaban)	0.0397	0.0496	0.0596	Increase	776	913	0.0008
Usma	Utility with MABE	0.32	0.65	0.89	Increase	767	900	0.0008
EPa	Apixaban PE probability	0.0136	0.0171	0.0205	Decrease	782	908	0.0007
Ca	Apixaban cost	125.62	251.23	269.18	Decrease	830	947	0.0006
Csme	MIBE cost	2,702	5,898.5	11,955	Decrease	778	879	0.0005
Csma	MABE cost	4,069	7,585.5	13,561	Decrease	786	879	0.0004
SMAa	MABE probability with apixaban	0.0165	0.0206	0.0247	Decrease	801	888	0.0003
Usme	Utility with MIBE	0.56	0.7	0.84	Increase	806	883	0.0003
Cspt	PTS cost	2,504	5,867.5	12,293	Increase	821	889	0.0002
SPT	PTS probability	0.0342	0.0564	0.0786	Decrease	817	873	0.0001
Uspt	Utility with PTS	0.53	0.67	0.81	Decrease	820	869	0.0001
Ucan	Utility with cancer	0.59	0.74	0.89	Decrease	821	868	0.0001
SMApa	MABE probability with placebo (vs apixaban)	0.0087	0.0108	0.013	Increase	822	868	0.0001
Chp	CTPH cost	2,591	5,388.25	12,293	Increase	838	859	0.0000
HPTC	CTPH probability	0.0046	0.0076	0.0106	Decrease	836	853	0.0000
Mtvp	DVT mortality pobability with cancer	0.1345	0.1681	0.2017	Increase	838	851	0.0000
Uhp	Utility with CTPH	0.52	0.63	0.73	Decrease	839	850	0.0000
MSMA	MABE mortality probability	0.0372	0.0465	0.0558	Decrease	843	846	0.0000
Mep	PE mortality with cancer	0.15	0.1875	0.225	Increase	843	845	0.0000
Mhptc	CTPH mortality with cancer	0.111	0.141	0.175	Increase	843	845	0.0000
SMEr	MIBE probability with rivaroxaban	0.0215	0.0268	0.0322	Increase	844	844	0.0000
SMEpr	MIBE probability with placebo (vs rivaroxaban)	0.0157	0.0196	0.0235	Increase	844	844	0.0000
SMAr	MABE probability with rivaroxaban	0.0157	0.0196	0.0235	Increase	844	844	0.0000
SMApr	MABE probability with placebo (vs rivaroxaban)	0.0079	0.0099	0.0118	Increase	844	844	0.0000
TVPr	DVT probability with rivaroxaban	0.0244	0.0305	0.0366	Increase	844	844	0.0000
TVPpr	DVT probability with placebo (vs rivaroxaban)	0.0353	0.0441	0.0529	Increase	844	844	0.0000
EPr	Rivaroxaban EP probability	0.0226	0.0282	0.0338	Increase	844	844	0.0000
EPpr	Placebo EP probability (vs rivaroxaban)	0.0335	0.0419	0.0503	Increase	844	844	0.0000
Cr	Rivaroxaban cost	125.62	251.23	269.18	Increase	844	844	0.0000

Variable Name	Variable Description	Variable Low	Variable Base	Variable High	Impact	Low	High	Risk %
Rivaroxaban								
Mcon	Cancer mortality prob with prophylaxis	0.0715	0.1674	0.2761	Decrease	−1,949	2,274	0.609
Msin	Cancer mortality prob without prophylaxis	0.098	0.182	0.238	Increase	−1,444	1,813	0.362
Uep	Utility with PE	0.04	0.49	0.8	Increase	244	662	0.006
EPpr	Placebo EP probability (vs rivaroxaban)	0.0335	0.0419	0.0503	Increase	282	690	0.006
TVPpr	DVT probability with placebo (vs rivaroxaban)	0.0353	0.0441	0.0529	Increase	290	640	0.004
EPr	Rivaroxaban EP probability	0.0226	0.0282	0.0338	Decrease	319	624	0.003
TVPr	DVT probability with rivaroxaban	0.0244	0.0305	0.0366	Decrease	364	635	0.003
Usma	Utility with MABE	0.32	0.65	0.89	Increase	367	581	0.002
Cep	PE cost	3,469	6,551.75	11,656	Increase	423	603	0.001
Utvp	Utility with DVT	0.14	0.55	0.83	Increase	399	554	0.001
Csma	MABE cost	4,069	7,585.5	13,561	Decrease	395	547	0.001
Cr	Rivaroxaban cost	125.62	251.23	269.18	Decrease	474	608	0.001
Mtvp	DVT mortality pobability with cancer	0.1345	0.1681	0.2017	Increase	435	558	0.001
SMAr	MABE probability with rivaroxaban	0.0157	0.0196	0.0235	Decrease	445	550	0.000
SPT	PTS probability	0.0342	0.0564	0.0786	Increase	471	571	0.000
Ctvp	DVT cost	2,504	5,867.5	12,293	Increase	461	549	0.000
SMEr	MIBE probability with rivaroxaban	0.0215	0.0268	0.0322	Decrease	463	519	0.000
Mep	PE mortality with cancer	0.15	0.1875	0.225	Decrease	461	504	0.000
SMEpr	MIBE probability with placebo (vs rivaroxaban)	0.0157	0.0196	0.0235	Increase	470	512	0.000
HPTC	CTPH probability	0.0046	0.0076	0.0106	Increase	491	530	0.000
SMApr	MABE probability with placebo (vs rivaroxaban)	0.0079	0.0099	0.0118	Increase	471	497	0.000
Ca	Apixaban cost	125.62	251.23	269.18	Increase	475	493	0.000
Csme	MIBE cost	2,702	5,898.5	11,955	Decrease	479	497	0.000
Ucan	Utility with cancer	0.59	0.74	0.89	Decrease	484	499	0.000
Usme	Utility with MIBE	0.56	0.7	0.84	Increase	484	498	0.000
Chp	CTPH cost	2591	5388.25	12293	Increase	488	500	0.000
Cspt	PTS cost	2504	5867.5	12293	Decrease	487	493	0.000
Uhp	Utility with CTPH	0.52	0.63	0.73	Decrease	488	495	0.000
Uspt	Utility with PTS	0.53	0.67	0.81	Increase	489	494	0.000
SMEa	MIBE probability with apixaban	0.0485	0.0606	0.0727	Increase	491	491	0.000
SMEpa	MIBE probability with placebo (vs apixaban)	0.0397	0.0496	0.0596	Increase	491	491	0.000

(*continued*)

Table 6. Continued.

Variable Name	Variable Description	Variable Low	Variable Base	Variable High	Impact	Low	High	Risk %
SMAa	MABE probability with apixaban	0.0165	0.0206	0.0247	Increase	491	491	0.000
SMApa	MABE probability with placebo (vs apixaban)	0.0087	0.0108	0.013	Increase	491	491	0.000
TVPa	DVT probability with apixaban	0.019	0.0238	0.0366	Increase	491	491	0.000
TVPpa	DVT probability with placebo (vs apixaban)	0.0332	0.0415	0.0498	Increase	491	491	0.000
EPa	Apixaban PE probability	0.0136	0.0171	0.0205	Increase	491	491	0.000
EPpa	Placebo EP probability (vs apixaban)	0.0439	0.0549	0.0659	Increase	491	491	0.000
MSMA	MABE mortality probability	0.0372	0.0465	0.0558	Increase	491	491	0.000
Mhptc	CTPH mortality with cancer	0.111	0.141	0.175	Increase	491	491	0.000

Abbreviations: CTPH, chronic thromboembolic pulmonary hypertension; DVT, deep venous thrombosis; MIBE, minor bleeding events; MABE, major bleeding events; PE, pulmonary embolism; PTS, post-thrombotic syndrome.
The risk percentages are expressed as a percentage of 1. For example, a risk percentage of 0.6398 is equivalent to a risk of 63.98%.

studies with this objective from the perspective of the Spanish National Health System.

Overall, data coming from cost-effectiveness analysis of ambulatory thromboprophylaxis of cancer patients (including DOAC, low-molecular-weight heparins, or vitamin K antagonists) from western European countries are scarce. These results are quite reassuring in order to expand outpatient thromboprophylaxis with low dose DOAC. In addition, it is expected to achieve a better cost-effectiveness result if other risk assessment models of VTE recently published, that have shown to significantly improve the capability of VTE risk prediction compared to Khorana score, are implemented in clinical practice[36,37]. Another significant finding of this analysis, and to our knowledge not described before in this setting, is the different cost-effectiveness profile of APIX and RIV. These results are in line with other clinical findings in cancer patients, mainly in safety, with a better bleeding risk profile for APIX compared to RIV (gastrointestinal tract bleeding and gastrointestinal cancers)[38,39], that suggest these drugs are not directly interchangeable. Lastly, these results have a direct local applicability from Spanish National Health System perspective and are in line with the recommendation of the Spanish National Guideline of Thrombosis and Cancer (Spanish Society of Medical Oncology, SEOM)[12].

This result should be assessed considering the strengths and weaknesses of the study. One of the main strengths would be the clinical validation of the model by two expert physicians with experience in thromboprophylaxis in cancer patients. Secondly, a second-order Monte Carlo simulation allowed us to analyze the uncertainty of the data (probabilities, costs, utilities) included in the analysis. This mathematical method allows the replication of simultaneous and random changes in the model parameters (probabilities, costs, utilities) in an attempt to simulate clinical evolution of patients in real life[40,41]. The confidence of the results was analyzed by the confidence intervals of 95%, with probabilities of cost-effectiveness of 62.2% and 51.9% in patients treated with APIX or RIV compared to no prophylaxis, respectively. In both cases, the probability of cost-effectiveness versus no thromboprophylaxis would be low (under 70%) for the indicated willingness to pay.

As far as the limitations of the study are concerned, first of all, it has to be taken into account that the theoretical model developed is, by definition, a simplified simulation of reality. The fact that there was no direct comparison between thromboprophylaxis with APIX and RIV can be considered a study limitation. Nonetheless, this was not possible for several reasons. Firstly, there are no clinical trials that compare these two drugs directly. The available clinical trials concerning DVT prophylaxis in cancer patients compared APIX (AVERT study)[10] and RIV (CASSINI study)[11] with a placebo control (no prophylaxis). Secondly, the results obtained in the placebo group of patients differed considerably between both studies, in particular, the probability to suffer symptomatic VTE, minor bleedings and VTE-related mortality, although this point did not invalidate the results of this study. However, the patients from both studies (AVERT and CASSINI) had similar baseline characteristics regarding age, gender, Khorana score, and previous thromboembolism rate[8,11]. The fact that only two clinical trials are available should be considered a major limitation of the study. Despite there not being any indications or signals that there would be subgroups of patients in which RIV was more cost-effective, we can't exclude that in certain subgroups RIV may be a better option. This type of subgroup analysis of cancer patients would require dedicated studies. Finally, quality-of-life studies in this setting are needed and should be performed to complement cost-effectiveness analysis.

Conclusions

From the present study the following conclusions can be drawn in ambulatory thromboprophylaxis of cancer patients receiving systemic anti-cancer therapy: (i) APIX is dominant (generating savings) compared to no prophylaxis; (ii) RIV is cost-effective (generating an additional cost) compared to no prophylaxis; (iii) QALY gains with both drugs are small and would probably not be clinically relevant (less than 0.03 QALY); (iv) the probability of prophylaxis with APIX being cost-effective (for a willingness to pay of 25,000€/QALY) is 62.6% and 51.9% with RIV (10.7% higher with APIX). However, the probability that both treatments are cost-effective vs. no prophylaxis was low (<70%).

Transparency

Declaration of funding

No funding was received to produce this article.

Declaration of financial/other relationships

AM:
Consultant or advisory role:

- Pfizer-BMS alliance, Sanofi, Celgene, Leo Pharma, Incyte, AstraZeneca, MSD, Lilly, Servier, Roche.

Research funding:

- Leo Pharma, Sanofi, Rovi, Celgene.

Speakers' bureau:

- Rovi, Bayer, Menarini, Stada, Daichii Sankyo.

Patents, Royalties, Other Intellectual Property:

- Risk assessment model in venous thromboembolism in cancer patients.

LO:
Speakers' bureau:

- Sanofi, Leo Pharma.

AG:

- No conflict of interests.

EG:
Consultant or advisory role:

- Sanofi, Janssen, Astellas, Bayer, Ipsen, Pfizer, Roche, Novartis, Eisai, EUSA Pharma, BMS, AstraZeneca, Merck, Rovi, Daiichi Sankyo, Techdow.

Speakers' bureau:

- Astellas, Janssen, Sanofi, Bayer, Ipsen, Pfizer, Roche, BMS, Rovi, Daiichi Sankyo, Leo Pharma, Menarini, Eisai, MSD, Boehringer Ingelheim, Merck, EUSA Pharma, Novartis.

Grant support (personal/institutional):

- Astellas, Janssen, Sanofi, Bayer, Ipsen, Ferrer, Pfizer, Roche, GSK, BMS, Novartis, Eisai, Pierre Fabre.

DRR:
Consultant for pharmaceutical companies Pfizer-BMS Alliance.
CRT:
Consultant for pharmaceutical companies Pfizer-BMS Alliance.
BM:
No conflict of interests.
PGA:
Consultant or advisory role:

- Roche, Lilly, Sanofi, Merck, Amgen, Servier, Piere Fabre.

Speakers' bureau:

- Roche, Lilly, Sanofi, Merck, Amgen, Servier, Piere Fabre.

JMS:
No conflict of interests.

Author contributions

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Data analysis: DRR, CRT, EG, AJM.
Interpretation of data: AJM, EG, DRR, CRT, JMS.
Paper drafting: AG, DRR, CRT, AJM, JMS
Revising it critically for intellectual content: AG, BM, PGA
Final approval: all authors.
No assistance in the preparation of this article is to be declared.

Acknowledgements

None stated.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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