Economic Analysis of Rivaroxaban for the Treatment and Long-Term Prevention of Venous Thromboembolism in Portugal

Estudo de Avaliação Económica de Rivaroxabano para Tratamento e Prevenção a Longo-Prazo de Tromboembolismo em Portugal

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ABSTRACT

Introduction: Venous thromboembolism is a burden on healthcare systems. The aim of this analysis was to project the long-term costs and outcomes for rivaroxaban compared to standard of care (enoxaparin/warfarin) in Portugal for the treatment and secondary prevention of venous thromboembolism.

Material and Methods: A Markov model was developed using event rates extracted from the EINSTEIN trials supplemented with literature-based estimates of longer-term outcomes. Core outcomes included per patient costs and quality-adjusted life years reported separately per treatment arm and incrementally, as well as cost per quality-adjusted life years gained. The deep vein thrombosis and pulmonary embolism indications were analysed separately. The analyses were conducted from the Portuguese societal perspective and over a 5-year time horizon. Costs and outcomes were discounted at a 5% annual rate. Several scenario analyses were undertaken to explore the impact on results of varying key modeling assumptions.

Results: Rivaroxaban treatment was associated with cost-savings for the treatment of deep vein thrombosis and was both cost-saving and more effective for the treatment of pulmonary embolism, compared with enoxaparin/warfarin.

Discussion: The results of the sensitivity and scenario analyses further supported that rivaroxaban is a cost-effective alternative to standard of care treatment. The use of an expert panel to derive some input values and the lack of Portuguese specific utilities were the main limitations.

Conclusion: Rivaroxaban represents an efficient alternative to using enoxaparin/warfarin in Portugal, as it's associated with lower costs (for both indications) and greater quality adjusted life years (for the pulmonary embolism indication).

Keywords: Cost-Benefit Analysis; Venous Thrombosis; Pulmonary Embolism; Rivaroxaban; Venous Thromboembolism.

RESUMO

Introdução: O tromboembolismo venoso representa uma carga substancial para os sistemas de saúde. O objectivo foi estimar os resultados clínicos e económicos a longo-prazo associados a rivaroxabano relativamente à prática clínica (enoxaparina/varfarina) no tratamento e prevenção secundária de tromboembolismo venoso em Portugal.

Material e Métodos: Foi desenvolvido um modelo de Markov baseado nos ensaios clínicos EINSTEIN e dados da literatura para complicações a longo-prazo. Foram avaliados custos e anos de vida ajustados pela qualidade de vida totais e incrementais e rácio custo-efectividade incremental. As indicações trombose venosa profunda e embolismo pulmonar foram analisados separadamente. Adoptou-se a perspectiva da sociedade portuguesa e um horizonte temporal de cinco anos. Aplicou-se uma taxa de actualização de cinco por cento para custos e consequências. Foram desenvolvidas análises de sensibilidade e diversas análises de cenário para avaliação da variação dos resultados em função de determinados pressupostos.

Resultados: Rivaroxabano está associado a menores custos na trombose venosa profunda e constitui uma alternativa associada a menores custos e a maior eficácia no tratamento de embolismo pulmonar, relativamente a enoxaparina/varfarina.

Discussão: O recurso a um painel de peritos para identificação de alguns recursos e a ausência de utilidades específicas para Portugal constituem as principais limitações.

Conclusão: Rivaroxabano constitui uma alternativa eficaz, estando associado a menores custos (para ambas as indicações) e a mais anos de vida ajustados pela qualidade de vida (para embolismo pulmonar) relativamente a enoxaparina/varfarina em Portugal.

Palavras-chave: Análise Custo-Benefício; Trombose Venosa; Embolismo Pulmonar; Rivaroxabano; Tromboembolismo Venoso.

INTRODUCTION

Venous thromboembolism (VTE), in its most frequent manifestations, deep vein thrombosis (DVT) and pulmonary embolism (PE), is an important public health issue due its impact on society in terms of morbidity, mortality, costs and resource consumption.[1] Approximately one-third of patients with symptomatic VTE has a pulmonary embolism, while two-thirds experience a DVT alone.[2] Morbidity and healthcare costs result from associated complications of VTE, such as post-thrombotic syndrome (PTS), which affects approximately one-third of DVT patients,[2] and chronic thromboembolic pulmonary hypertension (CTEPH), which has a cumulative incidence of 1% to 5% within 2 years after the initial PE event.[3-5] VTE affects more than 600,000 people each year in the United States (US)[1] and more than 1 million individuals each year across the European Union (EU).[2] The number of annual VTE-related deaths is also substantial, of approximately 300000 and 540000 in the US and EU, respectively.[6]

In Portugal, the Portuguese Society of Internal Medicine (Sociedade Portuguesa de Medicina Interna - SPMI) published guidelines for the prevention, diagnosis

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and treatment of VTE in medically ill patients. These guidelines present recommendations for the treatment of VTE that are in line with other national or European guidelines, emphasising that anticoagulants should be used as the standard of care.[7-11] In clinical practice, VTE patients are usually initiated with a course of parenteral unfractionated heparin or low molecular weight heparin (LMWH).[12,13] Vitamin K antagonist (VKA) treatment should be commenced together with parenteral agents during the initial days of treatment and parenteral treatment discontinued when the international normalised ratio (INR) is stable and above 2.0 for at least 24 hours.[13] The duration of anticoagulation is determined by the trade-off between the risk of recurrent VTE and the risk of treatment-induced hemorrhage.[14] Individualisation of treatment duration has been recommended in several treatment guidelines. [7,10]

Although the current treatment options for VTE are effective, they have several disadvantages. Heparins and fondaparinux require parenteral administration, and heparin may be associated with the development of rare but potentially life-threatening heparin-induced thrombocytopenia.[15] In addition, treatment with VKA is associated with large variability in dose response among patients, with multiple food-drug and drug-drug interactions, and requires regular INR monitoring and dose adjustment.[16]

Rivaroxaban is a highly selective, oral, direct factor Xa inhibitor that has predictable pharmacokinetics and pharmacodynamics with few relevant interactions. Rivaroxaban provides a single-drug approach for the acute and continued treatment of VTE, and does not require routine INR monitoring.

The EINSTEIN-DVT and the EINSTEIN-PE trials were designed to explore the efficacy and safety of rivaroxaban in the treatment of patients with acute symptomatic DVT and acute symptomatic PE (with or without previous/simultaneous DVT), respectively. In both trials, patients were randomised in an open-label, event-driven, non-inferiority study that compared rivaroxaban to standard dual-drug therapy (LMWH followed by VKA) for a total duration of either 3, 6 or 12 months.[17,18] Duration of therapy was defined by the treating clinician based on patients' baseline characteristics and on risk of recurrent VTE or bleeding. Results of both studies showed non-inferiority for the primary composite efficacy outcome of recurrent VTE, compared with LMWH/VKA.[17,18] Rivaroxaban also showed non-inferiority for the primary safety outcome of major and non-major clinically relevant bleeding, although there was a trend towards a reduced risk of major bleeding, which was significant in EINSTEIN-PE (HR = 0.49; 95% CI 0.31–0.79; p = 0.003).

In Portugal, several policy changes have affected the uptake of pharmaceutical over the last decade, including new pricing regulations, the introduction of generic substitution, the reduction of distribution margins and more restrictive prescribing patterns by physicians.[1] In this context, health economic evaluations such as cost-effectiveness analyses (CEA) may be useful tools to inform resource allocation decisions in a systematic, transparent and efficient manner. The primary outcomes of a CEA are estimations of costs and effects associated with the technology at hand, and its comparator(s). These provide an indication to the healthcare payer of whether the new treatment provides 'good value for money' compared to existing treatments. Therefore, a cost-effectiveness model based on the findings of the EINSTEIN trials was developed to project the long-term costs and outcomes for rivaroxaban compared to standard of care (enoxaparin/warfarin) in the treatment of VTE patients in the Portuguese healthcare setting.

MATERIAL AND METHODS

Analyses overview: Published cost-effectiveness models[20-24] were used, in combination with expert opinion, to inform the structure of the model. The analyses were conducted from the societal perspective and only direct costs were included. Indirect costs were not included due to the lack of data regarding productivity losses caused by the disease (DVT or PE) in the Portuguese population. The model timeframe was designed to capture the impact of VTE events from the initial or 'index' VTE event (either DVT or PE) to development of longer term complications, with a time horizon of 5-years. Costs and outcomes were discounted at a 5% annual rate, as recommended by Portuguese guidelines.[25]

Patient population and treatment regimens: The DVT and PE patient populations considered in the model reflect those recruited in EINSTEIN-DVT and EINSTEIN-PE, with cohort starting ages of 56 and 58 years, respectively.[17,18] The Committee for Medicinal Products for Human Use of European Medicines Agency considered that the study populations of EINSTEIN-DVT and EINSTEIN-PE were representative of the targeted European VTE population.[2,26] Therefore, patient populations considered in the present study are likely to be representative of the Portuguese population. Patients were assumed to be treated either with an enoxaparin/warfarin combination therapy or with rivaroxaban. Patients in the enoxaparin/warfarin arm were treated with enoxaparin, the LMWH therapy most frequently prescribed in Portugal for this patient population (based on an expert panel opinion) and at the recommended dose (1 mg/kg twice-day - BID). Based upon findings from an expert panel and in line with typical Portuguese clinical practice, patients were assumed to receive enoxaparin for 6 days. This duration, which is shorter than that observed in the EINSTEIN trials, was deemed a conservative estimate. Warfarin 5 mg once-daily (OD) was administered for the remainder of anticoagulation treatment. In line with its licensed dose for this indication, rivaroxaban was given at 15 mg BID for the initial 21 days, followed by 20 mg OD for the remaining treatment duration.

Model structure: A Markov model was developed that included health states describing the management and complications of VTE, including: on-treatment for index event, off-treatment, recurrent VTE (ipsilateral DVT, contralateral DVT and PE), bleeding events and long-term

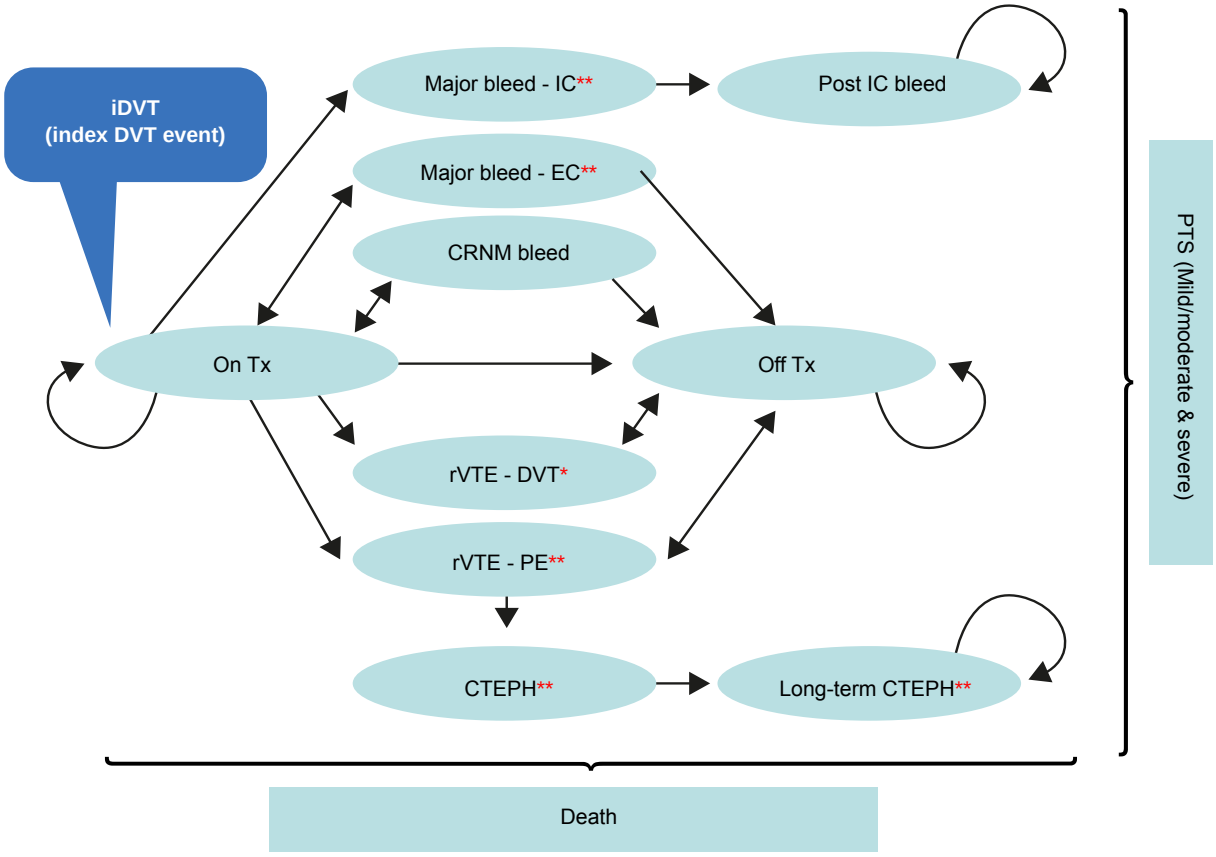

Figure 1 – DVT model structure

*DVT split into contralateral and ipsilateral. ** Additional mortality

On Tx: On treatment; **Off Tx:** Off treatment; **rVTE:** recurrent VTE event; **DVT:** Deep vein thrombosis (ipsileteral and contralateral); **PE:** Pulmonary embolism; **PTS:** Post thrombotic syndrome; **CTEPH:** Chronic thromboembolic pulmonary hypertension.

complications (Fig. 1). Bleeding events were categorised as major (extracranial (EC) or intracranial (IC)) or clinically relevant non-major (CRNM). Definitions of these bleeding events are according to literature.[17,18] A post-IC bleed state was incorporated to account for long-term morbidity. The risk of PTS was captured by application of a pay-off to patients with a history of DVT and therefore risk of PTS. For patients with an index PE additional states were included to track patients' history of DVT and associated risk of PTS (off-treatment post-DVT and PE experienced post-DVT). The model's cycle length was 3 months, reflecting EINSTEIN trials' design. Each health state was associated with a resource and utility weighting. Patients entered the model following diagnosis of an acute VTE event (either DVT or PE) and were administered treatment. Duration of treatment was determined according to patients' risk profile (3, 6 or 12 months) and model results weighted by the patient stratification in the EINSTEIN trials. Following active treatment, all patients transferred to a 'no treatment' option and were subsequently at risk of additional events for the post treatment period, based on population estimates derived from an observational study.[27] Expected costs and outcomes were calculated across the cohorts according to the chosen treatment.

Model inputs: The model was based on the results of the EINSTEIN-DVT[17] and EINSTEIN-PE[18] clinical trials, with long-term complications of treatment and utility values derived from published literature.

Treatment efficacy and safety: Treatment effect was modeled through application of hazard ratio (HR) to the underlying risk of events (VTE or bleed) for VKA treatment (Table 1). The probability of a recurrent VTE event being characterised as a DVT was based on observations from the EINSTEIN trials: 48.3% and 37.2% after an index DVT or PE, respectively. In the PE analyses, it was further assumed that 3.4% of patients with an index PE also experienced a DVT event and were at risk of PTS. The probability that a major bleeding event was an IC bleed was 12.5% for the DVT analyses and 20.6% for the PE analyses, based on EINSTEIN-DVT[17] and EINSTEIN-PE,[18] respectively. Consistent with the non-inferiority finding of EINSTEIN-DVT[17] and Portuguese health economic modeling guidance, it was assumed that rivaroxaban and enoxaparin/warfarin were equivalent for efficacy and safety. Consequently, a cost-minimisation analysis was conducted for the DVT analyses. EINSTEIN-PE[18] was also a non-inferiority study, however, rivaroxaban was associated with a significant reduction in the risk of major bleeds (HR = 0.49; 95% CI,

Table 1 - Clinical parameters values

Event/outcome	Index VTE		Source
	DVT	PE	
Recurrent VTE (Baseline risk) (%)			
0-3 months	2.6 (1.9-3.4)	1.6%	
3-6 months	0.4 (0.2-0.8)	0.2%	EINSTEIN-DVT/PE[17,18]
6-12 months	0.3 (0.0-0.9)	0.1%	
CRNM Bleeding (Baseline risk) (%)			
0-3 months	4.9 (3.9-4.9)	6.5%	
3-6 months	1.6 (0.9-2.3)	2.5%	EINSTEIN-DVT/PE[17,18]
6-12 months	2.7 (1.3-4.1)	2.2%	
Major bleeding (Baseline risk) (%)			
0-3 months	0.9 (0.5-1.3)	1.3%	
3-6 months	0.3 (0.01-0.6)	0.6%	EINSTEIN-DVT/PE[17,18]
6-12 months	0.0	0.4%	
Other efficacy inputs (%)			
Probability that a recurrent VTE is a DVT	48.3	37.2	
Probability that a major bleeding event is an IC bleed	12.5	20.6	EINSTEIN-DVT/PE[17,18]
Long-term complications (%)			
Recurrent VTE	1.26 (1.09-1.46)		Prandoni 2007[27]
PTS (severe): 1 year/ 5 years	2.7 (1.3-4.1) / 8.1 (5.8-10.4)		Prandoni 1997[28]
PTS (mild/moderate): 1 year/ 5 years	18.0 (14.7-21.3) / 29.6 (25.7-33.5)		Prandoni 1997[28]
CTEPH	1.25 (0.03-2.46)		Miniati 2006[29]
Mortality associated with model events (%)			
PE	25.0 (17.0-33.0)		EINSTEIN-DVT/PE[17,18]
Major IC bleeding	43.6 (36.5-50.7)		Linkins 2010[31]
Major EC bleeding	3.9 (2.5-5.4)		Linkins 2010[31]
CTEPH (per 3-month cycle)	2.48 (2.05-2.93)		Condliffe 2008[32]
Treatment effect for rivaroxaban versus dual LMWH/VKA therapy (HR) Incidence of major bleeding	N/A	0.493	EINSTEIN-PE[18]

0.31 to 0.79, p = 0.003). Therefore, the major bleed risk reduction associated with rivaroxaban was modeled in the base-case analysis for the PE indication.

Long-term complications: Both models captured common VTE long-term complications such as PTS, CTEPH and recurrent VTE. Given that no trial-based evidence is currently available to support a difference following treatment with either rivaroxaban or warfarin, the risks of these complications were derived from published observational studies: Prandoni[27] 2007 for recurrent VTE, Prandoni[28] 1997 for PTS and Miniati[29] 2006 for CTEPH (Table 1).

Mortality: The model distinguished between background mortality, reflecting mortality rates in the general Portuguese population (adjusted for age),[30] and disease-specific mortality associated with particular events. Event-specific mortality rates were estimated for the following model health states: PE, major IC bleed, major EC bleed, and CTEPH (Table 1). These risks were retrieved from publications[31,32] identified by a systematic literature review. Each mortality risk was applied once in the model, following the event, except for mortality associated with CTEPH, which was modelled as an ongoing risk per cycle.

Utility: The term 'utility' refers to the preferences individuals or society may have for any particular set of health outcomes. Utility analysis is viewed as a particular useful technique in health economic evaluations as it provides a generic outcome measure for comparisons across different treatments and pathologies. The generic outcome is usually expressed using Quality-adjusted life years (QALYs). QALYs are derived by adjusting the length of time affected through the health outcome by the utility value of the associated health status.[33] Due the lack of Portuguese-specific utility values, this analysis incorporated utility values from a combination of studies from the international published literature. All base-case utility assumptions were made independent of treatment arm. The starting point in the modelling of utility was the population norm value of 0.825 (SD 0.17, n = 3395) established in the landmark UK EQ-5D survey,[34] which was used as an anchor point in this evaluation. The values used in the analysis were applied either as multipliers to the population norm value (DVT, PE,

PTS, EC bleed and IC bleed)[35,36] or as straight values when derived using the EQ-5D or comparable methods (post-IC bleed and CTEPH)[37,38] (Table 2). A disutility associated with warfarin was not applied in the base-case, but was tested in a sensitivity analysis (0.988).[23]

Costs and resource inputs: Only direct costs were considered in the model. Unit costs were obtained from published Portuguese official sources, namely, Acts of the Parliament (Portaria n.º 139/2009 and Portaria n.º 220/2011)[39,40] and reports issued by the Central Administration of the Health System (Report of Analytical Accountability of National Health System Hospitals).[41] A panel composed by qualified experts from several medical specialties (internal medicine, general surgery, vascular surgery and general practice) was convened using the Delbecq technique to advise on estimates for cost or resource data unavailable from established sources. All costs were expressed in 2012 Euros. For costs identified for years prior to 2012, an annual inflation rate was applied based on data from Portuguese Statistical office (Instituto Nacional de Estatística). Drug acquisition costs were obtained from INFOMED (INFARMED's database) and combined with doses estimated by the expert panel (Table 3). The monitoring costs relating to warfarin treatment included physician monitoring costs and the cost of INR testing. Although rivaroxaban does not require blood monitoring, based upon advice from the expert panel, it was conservatively assumed that two physician visits were required per year. Monitoring costs were weighted to include the differences in setting of care. It was assumed that 30% of patients were monitored by general practitioners (GP) and that the remaining 70% were managed by specialists. For warfarin, it was assumed that 7 monitoring visits were required during the initial cycle based on the expert panel's opinion; 3.5 visits were applied for subsequent 3-month model cycles based on Macedo et al.[42]

Analyses conducted: Base-case analyses were undertaken separately for patients with either an index-DVT or an index-PE. In addition, extensive sensitivity analyses were performed to assess the uncertainty around outputs and several scenario analyses were conducted to explore the impact on the results of varying key assumptions.

Base-case: The duration of VTE treatment (3, 6 or 12 months) varied across patients according to their risk profile. In order to provide results reflective of the overall population, cost and outcomes for each of the treatment durations were weighted by the distribution of patients by treatment durations in the EINSTEIN trials. For the DVT indication, a cost-minimisation (*i.e.* equivalence*)* analysis was conducted to reflect the non-inferior efficacy (risk of VTE) and safety (risk of bleed) reported for rivaroxaban and enoxaparin/warfarin in the EINSTEIN-DVT trial. For the PE indication, equivalence was also assumed for efficacy, however inclusion of rivaroxaban's safety benefit observed in EINSTEIN-PE permitted cost-effectiveness analyses to be undertaken.

Sensitivity analyses: Although models are useful tools for simulating real-world situations, uncertainties still remain around assumptions that are applied.[43] Therefore, one-way sensitivity analysis (OWSA) was carried out in order

Table 2 - Utility values

Model state	Mean	Sensitivity analyses		Source
		Lower	Upper	
Population norm	0.825	0.819	0.831	Kind[34]
Post-IC bleed	0.71	0.7	0.72	Rivero Arias[37]
CTEPH	0.56	0.53	0.59	Meads[38]
Adjustments to baseline utility due to modelled events				
DVT	0.84	0.64	0.98	Locadia[35]
PE	0.63	0.36	0.86	Locadia[35]
EC bleed (GI bleeding was the disease state valued)	0.65	0.49	0.86	Locadia[35]
IC bleed (Haemorrhagic stroke was the disease state valued)	0.33	0.14	0.53	Locadia[35]
PTS (Serious PTS was the disease state valued)	0.93	0.91	1	Lenert[36]

CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; EC, extracranial; GI, gastrointestinal; IC, intracranial; PE, pulmonary embolism; PTS, post-thrombotic syndrome.

Notes to table:

- Locadia et al[35] quoted a population norm (own health) as 0.95 (95% confidence interval [CI] 0.81–1.00)
- Lower and upper values are estimates of 95% CIs from data presented (e.g. sample population size, *n*, and standard deviation) in the source literature.
- The 95% CIs for DVT, PE, EC bleeding and IC bleeding adjustments to utility norms have been assumed to equal the interquartile range because of the absence of further information and the size of the sample in Locadia et al.[35] For the PSA, the parameters above were modelled as arising from independent beta distributions with alpha and beta parameters set such that the mean is the point estimate and the lower and upper values represent the 95% CI.

Table 3 - Unit costs and resource use

Model input			Value
Drug acquisition cost (per day) (€)			
Warfarin – 5 mg OD			0.06
Rivaroxaban – first 3 weeks: 15 mg BID; after: 20 mg OD			2.65
Enoxaparin (acute) - 80 mg BID			12.60
Monitoring costs (€)			
Rivaroxaban	GP		33.87
	Specialist		156.60
	First visit		161.74
Warfarin	Following visits	GP	33.89
		Specialist	97.09
DVT management (€)			
Cost in inpatient setting (40%)			1884.50
Cost in outpatient setting (60%)			2068.35
PE management (€)			
Cost in inpatient setting*(100%)			4477.30
PTS management (3 month cost) (€)			
Mild/moderate			110.47
Severe			527.88
Cost of CTEPH (€)			
Diagnosis			3314.78
Acute treatment			22507.15
CTEPH ongoing costs (annual cost)			44755.97
Cost per additional day of hospitalisation (€)			
DVT			224.34
PE			231.22

* PE not treated in outpatient setting

to identify the key drivers of cost-effectiveness. Several parameters were varied, such as time horizon, discount rates, probability of clinical events, treatment effects in relation to efficacy and safety variables and utility values. Probabilistic sensitivity analysis (PSA) was performed with the intention of testing the overall robustness of the model. The PSA was run for 1000 iterations with repeated sampling of mean parameter values from a series of assigned distribution types, based on the point estimates and standard error statistics for each mean parameter value. In order to make full use of the information available, the PSA was sampled from observed differences in treatment effect, regardless of statistical significance. The distribution type that was applied to a given parameter was dependent on the nature of each parameter and supporting data.

Scenario analyses: Additional analyses were performed to explore the variation in results when including cost-savings related to a length of stay reduction for hospitalised rivaroxaban patients. Furthermore, for the PE indication, two additional scenarios were performed in which the following assumptions were made: i) equal efficacy and equal safety (cost-minimisation analysis); ii) equal efficacy and equal safety, and a length of stay reduction for patients treated with rivaroxaban. The cost-saving associated with early discharge achieved in patients hospitalised and treated with rivaroxaban was based on the reduction in length of stay associated with rivaroxaban (21% for DVT and 12% for PE),[44] the proportion of VTE events treated as inpatients (40% for DVT and 100% for PE) and on a cost per additional day of hospitalisation (€224.34 for DVT and €231.22 for PE)

(Table 3). A further analysis was undertaken to estimate the cost-effectiveness of rivaroxaban compared to enoxaparin/warfarin for the overall VTE indication, in which results for the individual indications were weighted by the proportion of VTE patients experiencing either an index DVT or an index PE. The VTE population was considered to consist of 2/3 of patients with index DVT and 1/3 of patients with index PE based on Cohen et al[2] 2007.

RESULTS

Base-case analyses: In the DVT base-case cost-minimisation analysis, rivaroxaban was found to be cost saving (- € 322 per patient) compared to enoxaparin/warfarin over a 5-year time horizon (Table 4). Treatment with rivaroxaban incurred additional drug costs; however these were offset by reduced monitoring costs. Rivaroxaban was also associated with lower additional costs for bleeding events. The slightly higher cost of bleeding in the enoxaparin/warfarin arm compared with the rivaroxaban arm resulted from the fact that the monitoring costs for re-initiation of therapy were included during that 3-month cycle, which were greater with enoxaparin/warfarin. In the PE base-case cost-effectiveness analysis rivaroxaban 'dominated' enoxaparin/warfarin, as it was associated with greater health benefit (QALY gain of 0.005 per patient) and cost saving (incremental costs: - € 293 per patient) (Table 4). Similarly to the DVT indication, treatment with rivaroxaban generated additional drug costs, which were offset by reduced monitoring costs. The bleed benefit associated with rivaroxaban translated into both increased cost savings for the management of bleeds and into a QALY gain. Rivaroxaban was however associated with very low additional costs for recurrent VTE events and complications (CTEPH and PTS). This can be attributed to the survival paradox, whereby patients treated with rivaroxaban experienced a reduced risk of major bleeds which resulted in longer survival compared to enoxaparin/warfarin patients and therefore greater exposure to the risk of VTE and associated complications.

Sensitivity analyses: The OWSA conducted for DVT patients demonstrated that rivaroxaban remained cost-saving or cost-effective when varying the value of key model inputs. The results were most sensitive to the following parameters: distribution of patients across the clinic and the GP settings for VKA monitoring, disutility associated with warfarin and cost of ambulatory visits in the outpatient setting, irrespective of treatment duration. Similarly, the OWSA undertaken for the PE population demonstrated that rivaroxaban remained cost-effective when varying the value of key model inputs, and the same parameters were identified to drive the results. The PSA further supported the dominance of rivaroxaban over treatment with enoxaparin/warfarin for VTE as greater than 95% of all simulations indicated that rivaroxaban was both less costly and more effective compared to enoxaparin/warfarin.

Scenarios analyses: Results obtained showed greater savings with rivaroxaban compared to enoxaparin/warfarin for all the scenarios performed (Table 5).

DISCUSSION

VTE continues to be a burden on healthcare systems, affecting both hospitalised patients and those managed

Table 4 - Base-case results

	Rivaroxaban	LMWH/VKA	Difference
DVT indication			
Total cost (€)	**4406**	**4728**	**-322**
Drug cost (€)	597	87	509
Monitoring cost (€)	133	953	-820
Event costs (€)	2814	2814	0
Bleed cost (€)	63	74	-11
PST/CTEPH (€)	799	799	0
QALY	3.637	3.637	0.000
PE indication			
Total cost (€)	**8311**	**8604**	**-293**
Drug cost (€)	670	89	581
Monitoring cost (€)	151	972	-822
Event costs (€)	5360	5358	2
Bleed cost (€)	73	131	-58
PST/CTEPH (€)	2057	2053	4
QALY	**3.585**	**3.581**	**0.005**
ICER (€/QALY)	**---**	**---**	**Dominant**

Note: all values have been rounded.

Table 5 -Scenario analyses results

	Rivaroxaban	LMWH/VKA	Difference
DVT – cost-minimisation analysis with length of stay reduction			
Total cost (€)	4253	4728	-475
QALY	3.637	3.637	0.000
PE – cost-minimisation analysis without length of stay reduction			
Total cost (€)	8344	8604	-260
QALY	3.581	3.581	0.000
PE – cost-effectiveness analysis with length of stay reduction			
Total cost (€)	8102	8604	-502
QALY	3.585	3.581	0.005
ICER (€/QALY)	---	---	Dominant
PE – cost-minimisation analysis with length of stay reduction			
Total cost (€)	8135	8604	-469
QALY	3.581	3.581	0.000
VTE cross-indication analysis*			
Total cost (€)	5708	6020	-312
QALY	3.620	3.619	0.002
ICER (€/QALY)	---	---	Dominant

* without cost-savings associated with early discharge

Note all values have been rounded.

in the outpatient or ambulatory setting.[45,46] Although VKAs and LMWHs are well established and widely used for the prevention of thromboembolic disease in Portugal, these agents are associated with a number of limitations.[16,46] Rivaroxaban is the first novel oral anticoagulant to be approved for the treatment and prevention of recurrent VTE. Its efficacy and safety was explored for this patient population in the EINSTEIN clinical trial programme. Beyond the promising results of the EINSTEIN trials[17,18] rivaroxaban represents an attractive and convenient alternative treatment option to both patient and physician for several reasons.

In the current economic evaluation, rivaroxaban was compared to the standard of care (enoxaparin/warfarin) for the treatment of VTE in the Portuguese setting over a 5-year time horizon. Analyses were undertaken independently for the DVT and PE patient groups. In the base-case analysis for the DVT population, the same efficacy and the same safety were assumed across the two treatment arms, in line with the findings of the EINSTEIN DVT trial. The results of the analysis showed that rivaroxaban was cost-saving compared to enoxaparin/warfarin. In the base-case analysis for the PE population, it was assumed, based on results of the EINSTEIN PE trial, that patients treated with rivaroxaban were exposed to a lower risk of major bleed compared with those receiving enoxaparin/warfarin. The results demonstrated that rivaroxaban was both more effective and cost-saving compared to enoxaparin/warfarin. Results from the PSAs conducted around the results of both the DVT and PE base-case analyses supported this finding. OWSAs performed indicated that distribution of patients across the different settings for VKA monitoring, disutility associated with warfarin and cost of ambulatory visits in the outpatient setting were the main drivers of the cost-effectiveness analysis for both DVT and PE indications.

As with any economic evaluation, the current analysis encompasses a number of strengths and limitations. The main strength of this study lies in the comprehensive model structure and in the robust sources used to inform the values of the model inputs. For example clinical input values were derived from the EINSTEIN phase III pivotal trials and a systematic literature review was conducted to identify relevant publications to populate specific model inputs. Given the scarcity of Portuguese-specific resource

use data, an expert panel was also necessary to derive input values that best represented clinical practice in Portugal. Sensitivity analyses identified that this was of particular importance given that INR monitoring frequency was a key driver. Another limitation of the model is that no Portuguese-specific utilities could be identified; consequently,utilities from other European countries and the US were used. Base-case analyses for both DVT and PE indications did not capture the full range of benefits offered by rivaroxaban, such as reduced patient training burden, shorter hospital length of stay (assessed in an additional analysis), as well as greater convenience for patients and healthcare professionals. Discussion with clinical experts around the findings of the EINSTEIN clinical trials[17,18] suggested that, in clinical practice, rivaroxaban is likely to reduce the length of hospital stay for VTE patients.[44] Therefore, scenario analyses were performed to explore the impact on results of including cost-savings due to a reduced length of stay for patients treated with rivaroxaban. As expected, the results of these analyses showed greater cost savings with rivaroxaban irrespective of whether a DVT or PE was treated. Reduced length of hospital stay may also lead, in clinical practice, to additional gains in health-related quality of life for patients receiving rivaroxaban. However, this assumption was conservatively not captured in the base-case analyses. For the PE indication, additional scenario analyses were performed in which equal efficacy and equal safety (cost-minimisation analyses) was assumed, either with or without cost-savings associated with reduced length of hospitalisation with rivaroxaban. In both scenarios, the results showed that rivaroxaban was associated with cost-savings. Lastly, an analysis was conducted for the combined DVT and PE indications in order to assess the cost-effectiveness of rivaroxaban for the whole VTE population. The results indicated that rivaroxaban was both more effective and cost saving when compared to standard of care treatment.

CONCLUSION

Rivaroxaban provides a simple, single-drug approach for the acute and continued treatment of VTE with an improved overall net clinical benefit profile. Rivaroxaban for the management of VTE was found to offer the potential of substantial cost offsets due to the absence of need for VKA monitoring and so is likely to be associated with cost savings. Sensitivity analyses and scenario analyses further supported that rivaroxaban is a cost-effective alternative to the standard of care in Portugal.

CONFLICTS OF INTEREST

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REFERENCES

1. Reis A, Rocha N, Santos M, Gonçalves F, Soares A, Marques I, et al. Normas para a prevenção, diagnóstico e tratamento do tromboembolismo venoso no doente médico. Rev Port Med Interna. 2010;17:37-58
2. Cohen AT, Agnelli G, Anderson FA, Arcelus JI, Bergqvist D, Brecht JG, et al. VTE Impact Assessment Group in Europe (VITAE). Venous thromboembolism (VTE) in Europe. The number of VTE events and associated morbidity and mortality. Thromb Haemost. 2007;98:756-64.
3. Pengo V, Lensing AW, Prins MH, Marchiori A, Davidson BL, Tiozzo F, et al. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. N Engl J Med. 2004:27:2257-64.
4. Lang IM, Klepetko W. Update on chronic thromboembolic pulmonary hypertension, a frequently undiagnosed condition. Rev Esp Cardiol. 2009;62:120-5.
5. Becattini C, Agnelli G, Pesavento R, Silingardi M, Poggio R, Talliani MR, et al. Incidence of chronic thromboembolic pulmonary hypertension after a first episode of pulmonary embolism. Chest. 2006;130:172-5.
6. Cohen AT, Dobromosrski M. The use of rivaroxaban for short- and long-term treatment of venous thromboembolism. Thromb Haemost. 2012;107:1035-43.
7. Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th edition. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141: e419S-94.
8. Snow V, Qaseem A, Barry P, Hornbake ER, Rodnick JE, Tobolic T, et al. Management of venous thromboembolism: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. Ann Intern Med, 2007;146:204-10.
9. Nicolaides A, Hull RD, Fareed J. Prevention and treatment of venous thromboembolism: international consensus statement (guidelines according to scientific evidence). Clin Appl Thromb Hemost. 2013;19:116-8.
10. Excellence, National Institute for Health and Clinical. Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing. NICE Clinical Guideline 144.2012; [consultado 2011 Mai 27]. Disponível em: http://www.nice.org.uk/nicemedia/live/13767/59720/59720.pdf.
11. Galie N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, et al. Orientações para o diagnóstico e tratamento da hipertensão pulmonar. Rev Port Cardiol, 2012;31:11-75.
12. Buller HR, Sohne M, Middeldorp S. Treatment of venous thromboembolism. J Thromb Haemost. 2005;3:1554-60.
13. Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ, et al. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. 8th ed. Chest. 2008;133:454S-545.
14. Bounameaux H, Perrier AA. Duration of anticoagulation therapy for venous thromboembolism. Hematology Am Soc Hematol Educ Program. 2008;252-8.
15. Warkentin TE, Greinacher A, Koster A, Lincoff AM, Physicians, American College of Chest. Treatment and prevention of heparin-induced thrombocytopenia: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. 8th ed. Chest. 2008;133:340S-80.
16. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G et al. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. 8th ed. Chest. 2008;133:160S-98.
17. Investigators, The EINSTEIN. Oral rivaroxaban for symptomatic venous thromboembolism. N Eng J Med. 2010;363:2499-510.
18. Investigators, The EINSTEIN-PE. Oral rivaroxaban for symptomatic pulmonary embolism. N Engl J Med. 2012;366:1287-97.
19. Quarterly of the European Observatory on Health Systems and Policies. EuroHealth 18.1. Health systems and the financial crisis. [consultado 2013 Nov 26]. Disponível em: http://www.euro.who.int/__data/assets/pdf_file/0005/162959/Eurohealth_Vol-18_No-1_web.pdf.
20. Aujesky D, Smith KJ, Cornuz J, Roberts MS. Cost-effectiveness of low-molecular-weight heparin for treatment of pulmonary embolism. Chest. 2005;128:1601–10.
21. Aujesky D, Smith KJ, Roberts MS. Oral anticoagulation strategies after a

first idiopathic venous thromboembolic event. Am J Med. 2005;118:625–35.
22. Gomez-Outes A, Berto P, Prandoni P. Cost-effectiveness of bemiparin in the prevention and treatment of venous thromboembolism. Expert Rev Pharmacoecon Outcomes Res. 2006;6:249–59.
23. Marchetti M, Pistorio A, Barone M, Serafini S, Barosi G, et al. Low-molecular-weight heparin versus warfarin for secondary prophylaxis of venous thromboembolism: a cost-effectiveness analysis. Am J Med. 2001;111:130–9.
24. Caro JJ, Getsios D, Caro I, O'Brien JA. Cost effectiveness of tinzaparin sodium versus unfractionated heparin in the treatment of proximal deep vein thrombosis. Pharmacoeconomics. 2002;20:593-602.
25. Silva EA, Pinto C, Sampaio C, Pereira JA, Drummond N, Trindade R. Orientações Metodológicas para Estudos de Avaliação Económica de Medicamentos. Lisboa: Ministério da Saúde/INFARMED; 1998.
26. European Medicines Agency (EMA)/Committee for Medicinal Products for Human Use (CHMP). Xarelto Assessment Report. Procedure No.: EMEA/H/C/000944/X/0010. 2011. EMA/CHMP/301607/2011.
27. Prandoni P, Noventa F, Ghirarduzzi A, Pengo V, Bernardi E, Pesavento R, et al. The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients. Haematologica. 2007;92:199-205.
28. Prandoni P, Villalta S, Bagatella P, Rossi L, Marchiori A, Piccioli A, et al. The clinical course of deep-vein thrombosis. Prospective long-term follow-up of 528 symptomatic patients. Haematologica. 1997;82:423-8.
29. Miniati M, Monti S, Bottai M, Scoscia E, Bauleo C, Tonelli L, et al. Survival and restoration of pulmonary perfusion in a long-term follow-up of patients after acute pulmonary embolism. Medicine. 2006;85:253-62.
30. Instituto Nacional de Estatística. Tábua completa de mortalidade para Portugal 2008-2010; [consultado 2011 Mai 27]. Disponível em: http://www.ine.pt/xportal/xmain?xpid=INE&xpgid=ine_destaques&DESTAQUESdest_boui=107454674&DESTAQUESmodo=2&xlang=pt.
31. Linkins L, Oædonnell M, Julian JA, Kearon C. Intracranial and fatal bleeding according to indication for long term oral anticoagulant therapy. J Thromb Haemost. 2010;8:2201-7.
32. Condliffe R, Kiely DG, Gibbs JSR, Corris PA, Peacock AJ, Jenkins DP, et al. Improved outcomes in medically and surgically treated chronic thromboembolic pulmonary hypertension. Am J Respir Crit Care Med. 2008;177:1122-27.
33. Drummond MJ, O'Brien B, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. 2nd ed. Oxford: Oxford Medical Publications; 1997.
34. Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey. BMJ. 1998;316:736–41.
35. Locadia M, Bossuyt PM, Stalmeier PF, Sprangers MA, van Dongen CJ, Middeldorp S, et al. Treatment of venous thromboembolism with vitamin K antagonists: patients' health state valuations and treatment preferences. Thromb Haemost. 2004;92:1336–41.
36. Lenert LA, Soetikno RM. Automated computer interviews to elicit utilities: potential applications in the treatment of deep venous thrombosis. J Am Med Inform Assoc. 1997;4:49-56.
37. Rivero-Arias O, Ouellet M, Gray A, Wolstenholme J, Rothwell PM, Luengo-Fernandez R. Mapping the modified Rankin scale (mRS) measurement into the generic EuroQol (EQ-5D) health outcome. Med Decis Making. 2010;30:341-54.
38. Meads DM, McKenna SP, Doughty N, Das C, Gin-Sing W, Langley J, et al. The responsiveness and validity of the CAMPHOR Utility Index. Eur Respir J. 2008;32:1513-9.
39. Ministério da Saúde. Portaria n.º 132/2009, de 30 de Janeiro. Diário da República. 2009. I Série, N.º 21.
40. Portaria n.º 220/2011, de 11 de Junho. Diário da República, 2011. I Série, N.º 106.
41. Administração Central dos Serviços de Saúde. Contabilidade Analítica dos Hospitais do SNS. 2006; [Consultado 2013 Nov 26]. Disponível em: http://www.acss.min-saude.pt/Portals/0/DownloadsPublicacoes/SNS/Info_gestao/Contab_Analitica_2006_Hospitais_SNS.pdf.
42. Macedo A, Carrasco J, Andrade S, Moital S. Estudo de avaliação do custo incremental da auto-monitorização do INR *versus* controlo laboratorial ou monitorização no centro de saúde, em Portugal. Acta Med Port. 2010;23:203-12.
43. Kim SY, Goldie SJ, Salomon JA. Exploring model uncertainty in economic evaluation of health interventions: the example of rotavirus vaccination in Vietnam. Med Decis Making. 2010;30:E1–28.
44. Van Bellen B, Prins M, Bamber L, Wang M, Lensing A. Reduction in initial length of stay with rivaroxaban single-drug regimen versus LMWH-VKA standard of care: findings from the EINSTEIN trial program. Atlanta, GA, USA. Am Soc Hematol 54th Annual Meeting and Exposition. December 8-11, 2012.
45. White RH. The epidemiology of venous thromboembolism. Circulation. 2003;107:I4-8.
46. Heit J, Cohen A, Anderson FJ. Estimated annual number of incident and recurrent, non-fatal and fatal venous thromboembolism (VTE) events in the US. Blood. 2005;106:267A.

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