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ORIGINAL RESEARCH

Cost-effectiveness analysis of rivaroxaban for treatment and secondary prevention of venous thromboembolism in the Netherlands

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ABSTRACT

Background: Until recently, standard treatment of venous thromboembolism (VTE) concerned a combination of short-term low-molecular-weight heparin (LMWH) and long-term vitamin-K antagonist (VKA). Risk of bleeding and the requirement for regular anticoagulation monitoring are, however, limiting their use. Rivaroxaban is a novel oral anticoagulant associated with a significantly lower risk of major bleeds (hazard ratio = 0.54, 95% confidence interval = 0.37–0.79) compared to LMWH/VKA therapy, and does not require regular anticoagulation monitoring.

Aims: To evaluate the health economic consequences of treating acute VTE patients with rivaroxaban compared to treatment with LMWH/VKA, viewed from the Dutch societal perspective.

Methods: A life-time Markov model was populated with the findings of the EINSTEIN phase III clinical trial to analyze cost-effectiveness of rivaroxaban therapy in treatment and prevention of VTE from a Dutch societal perspective. Primary model outcomes were total and incremental quality-adjusted life years (QALYs), as well as life expectancy and costs.

Results: Over a patient's lifetime, rivaroxaban was shown to be dominant, with health gains of 0.047 QALYs and cost savings of €304 compared to LMWH/VKA therapy. Dominance was robustly present in all sensitivity analyses. Major drivers of the differences between the two treatment arms were related to anticoagulation monitoring (medical costs, travel costs, and loss of productivity) and the occurrence of major bleeds.

Conclusion: Rivaroxaban treatment of patients with venous thromboembolism results in health gains and cost savings compared to LMWH/VKA therapy. This conclusion holds for the Dutch setting, both for the societal perspective, as well as the healthcare perspective.

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Introduction

Venous thromboembolism (VTE) comprises deep vein thrombosis (DVT) and pulmonary embolism (PE). Within Europe, annual VTE incidence is estimated at 100–200 per 100,000 inhabitants[1–3], which would correspond to 17,000–34,000 yearly cases in the Netherlands. Dutch sources report higher estimates of 16,000–20,000 DVT cases, and 15,000–20,000 PE cases per year[4,5]. Incidence is expected to rise due to an aging population[6,7]. Risk of recurrence is estimated at 30% within 10 years[8,9].

A European 2004 estimate of deaths related to VTE amounted to 700 cases per 1 million inhabitants, with only an estimated 7% correctly diagnosed with VTE before death[1,3]. Both PE and DVT significantly impact quality-of-life (QoL)[10,11]. Long-term sequelae concern chronic thromboembolic pulmonary hypertension (CTEPH), which affects 1–4% of PE patients within 2 years after the initial event[12–15], and post-thrombotic syndrome (PTS), which affects approximately one-third of DVT patients[3,16]. Approximately half of the patients (57%[17]) who develop CTEPH will be surgically treated with pulmonary endarterectomy (PEA). Concerning complications, PTS has been identified as one of the main cost drivers of VTE within a European context[18,19].

Given the humanistic implications of VTE, the risk of recurrence, and the risk of severe sequelae, anticoagulants are the cornerstones of VTE treatment—both in curative and preventive settings. Until recently, standard treatment concerned a short-term parenteral anticoagulant (low-molecular-weight heparin, LMWH) and a long-term (usually 3–12 months) vitamin K antagonist (VKA). Recently, the class of novel oral anticoagulants (NOACs) has become available, i.e. apixaban, dabigatran, rivaroxaban, and edoxaban[1,20].

Optimal VKA effectiveness and safety are carefully safeguarded with regular anticoagulation monitoring, due to VKAs' narrow therapeutic INR (international normalized ratio) range. According to both European and Dutch guidance, the therapeutic range equals 2.0–3.0[1,21,22]. Failure to achieve an INR inside this range for most of the time (i.e. time in therapeutic range, TTR) increases the risk of thrombosis (INR too low) or bleeding (INR too high). In the Netherlands, regular

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Supplemental data for this article can be accessed here.

INR monitoring is organized via specialized anticoagulation clinics, which monitor patients either at home or at the clinic. As in most countries monitoring is performed by the general practitioner, this infrastructure and its associated costs are rather unique to the Netherlands. In contrast to VKA therapy, NOAC therapy is not associated with such precarious dose titration and monitoring.

Safety and efficacy of rivaroxaban in patients with acute symptomatic DVT or PE have been tested in the EINSTEIN phase III clinical trial program (EINSTEIN Acute DVT [NCT00440193]; EINSTEIN Acute PE [NCT00439777])[23,24]. Within these trials, patients were assigned to treatment duration groups (3, 6, or 12 months) according to the indication of their treating physician, before being randomized to either rivaroxaban or LMWH/VKA treatment. The pre-specified pooled analysis of both trials demonstrated that the primary efficacy outcome—i.e. fatal or non-fatal PE or DVT—occurred in a numerically lower percentage of rivaroxaban-treated patients compared to VKA-treated patients (2.1% vs 2.3%; $p_{\text{non-inferiority}} < .001$) and that major bleeding occurred in a significantly lower percentage of rivaroxaban-treated patients (1.0% vs 1.7%; $p = .002$)[25].

Recent cost-effectiveness analyses have shown cost savings associated with rivaroxaban in the treatment of VTE in the US[26,27], Portugal[28], and the UK[29]. The aim of the current study is to evaluate the health economic consequences of treating acute VTE patients with rivaroxaban compared to treatment with LMWH/VKA, viewed from the Dutch societal perspective; with the inclusion of loss of productivity and patient travel costs being rather specific to the Dutch guidelines. For this purpose, a life-time projection cost-effectiveness model has been built, based on the findings of the EINSTEIN phase III clinical trial program. The present model provided the basis for the health economic evidence submissions for rivaroxaban in VTE made to the Dutch National Health Care Institute[30,31].

Methods

Cost-effectiveness analyses were conducted from a Dutch societal perspective, including direct medical costs, direct non-medical costs—in the form of patient travel associated with INR monitoring—and indirect non-medical costs—in the form of loss of productivity (cost year 2015). A life-time horizon was used to present a balanced trade-off between costs and effects; as costs are incurred in the period immediately following the index event, whereas benefits can be life-long. Costs and effects were discounted at 4% and 1.5%, respectively[32]. The primary model outcomes are total and incremental quality-adjusted life years (QALYs), as well as life expectancy and costs.

Patient characteristics and treatment regimens

Differences in characteristics and treatment duration between patients entering with an index DVT event and those with an index PE event (with or without concomitant DVT) have been taken into account by making use of an index-DVT module and an index-PE module within the overarching cost-effectiveness model. These modules function independently. The modeled patient characteristics reflect those of the populations recruited into EINSTEIN Acute DVT and EINSTEIN Acute PE[23,24], and correspond well with those in Dutch observational studies[33,34]. On average, patients were 57 years of age at the time of index event. Further patient characteristics are provided in Table 1. Relative contributions to overall VTE results were assumed at 56% for index DVT and 44% for index PE, as reported by the Dutch Federation of Anticoagulation Clinics (FNT report 2014[35]). In combination with the distributions across treatment duration groups (Table 1), this leads to an average indicated treatment duration of 7.6 months (7.2 months in the case of an index DVT and 8.1 months in the case of an index PE event).

Table 1. Baseline characteristics of modeled populations, based on ITT in EINSTEIN phase III clinical study program (combined across treatment arms).

Patient characteristics	Index DVT[24]	Index PE with or without DVT[23]
n	3,449	4,832
with 3-month duration	411 (12%)	249 (5%)
with 6-month duration	2,166 (63%)	2,774 (57%)
with 12-month duration	872 (25%)	1,809 (37%)
Mean age (years)	55.8	57.7
Proportion male	57.4%	52.9%
Idiopathic	62.0%	64.5%

In line with clinical practice, trial participants were prescribed anticoagulation for the duration of either 3, 6, or 12 months and randomly assigned to either LMWH/VKA (enoxaparin and warfarin or acenocoumarol) or rivaroxaban:

- LMWH 1.0 mg/kg of body weight, once- or twice-daily for the first 8 days; concurrently started with once-daily dose-adjusted VKA treatment—approximated in the model with an average dose of 4.5 mg[36,37]—for the intended 3, 6, or 12 months of treatment.
- Rivaroxaban 15 mg, twice-daily for the first 21 days; followed by 20 mg once-daily for the intended 3, 6, or 12 months of treatment.

Model structure

The current cost-effectiveness model has been informed by prior research[38–42], and shares its core with the models recently presented for the Portuguese setting[28] and the British setting[29]. Departing from this common basis, the current model was adapted and expanded to capture the particulars of the Dutch INR monitoring practice, the Dutch patient population, Dutch cost and utilities, loss of productivity, and patient travel.

The Markov model includes health states describing patient management (on/off treatment), recurrence (DVT/PE with or without DVT), safety events (major bleed [intracranial (IC)/extracranial (EC)], clinically relevant non-major [CRNM] EC bleed), long-term complications (PTS, CTEPH, post-IC bleed), and death. Figure 1 concerns a schematic representation of both the index-DVT and the index-PE module. The modules differ only in a few aspects. Additional elements of the index-PE module with respect to index-DVT module are

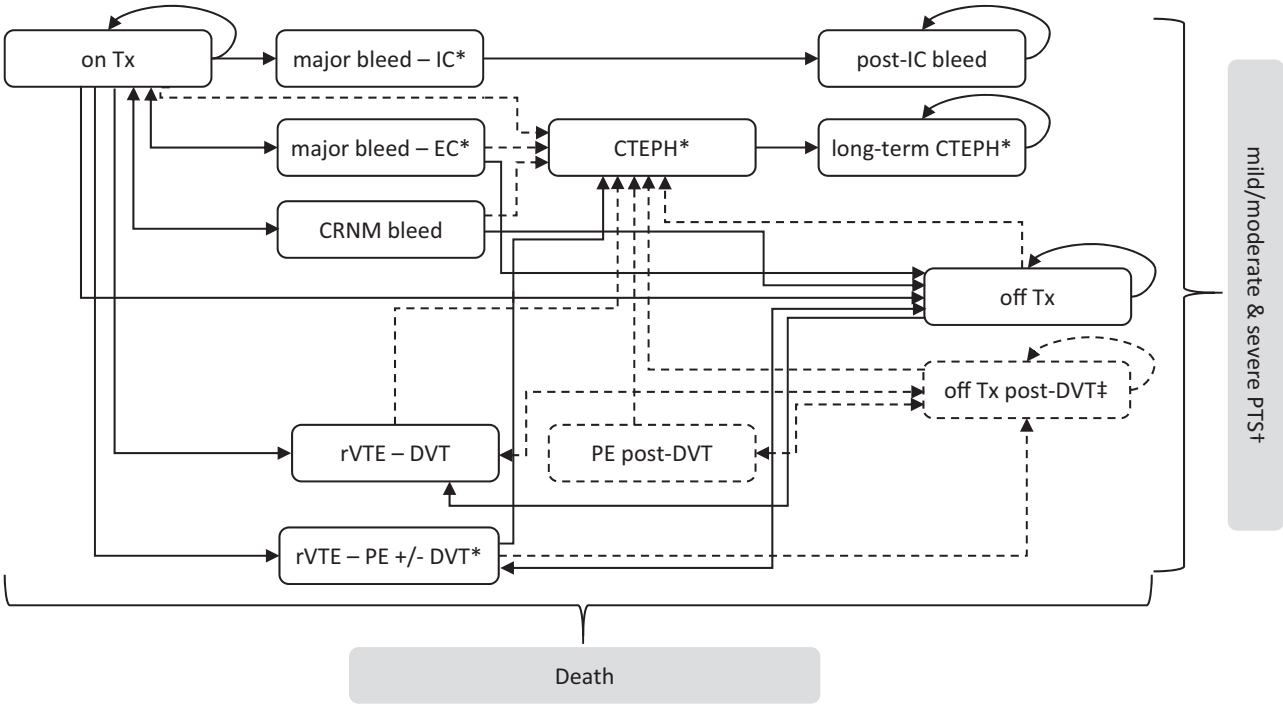

Figure 1. Model structure depicting both the index-PE and index-DVT module. Dashed health states/arrows indicate additional states/pathways in index-PE module with respect to index-DVT module. All patients who have had a PE are at risk of CTEPH, with the exception of those in the acute IC and post-IC bleed states (as these states are considered worse than CTEPH). On Tx, On treatment; Off Tx, Off treatment; rVTE, Recurrent VTE event; DVT, Deep-vein thrombosis (ipsilateral and contralateral); PE, Pulmonary embolism; PTS, Post-thrombotic syndrome; CTEPH, Chronic thromboembolic pulmonary hypertension; IC, Intracranial; EC, Extracranial; CRNM, Clinically relevant non-major. *Health states with increased mortality risk. ‡ Health state in the index-PE module for patients who have experienced a DVT and are, therefore, at risk of PTS. † PTS costs and utilities are applied to proportion of patients in the Off Tx post-DVT state.

depicted with dashed lines (Supplementary Figure S1 shows the index-DVT module in isolation). The index-PE module has two off-treatment states instead of one, a PE post-DVT state is included, and all patients are at risk of CTEPH, instead of only those with a recurrent event in the form of a PE (due to the index PE event). The additional health states allow tracking of patients at risk of PTS. In the index-DVT module, such tracking is unnecessary as all index DVT patients are at risk of PTS. As visible in the model schematic, PTS was not included as a genuine health state. Instead, PTS-associated costs and consequences were applied to relevant proportions of patients in other health states. This was to ensure that patients with PTS were not precluded from risks of alternative events.

Patients enter the model as receiving treatment for their index VTE event. While on treatment, patients are exposed to trial-based treatment-specific risks of VTE recurrence and bleeding events. After the intended treatment duration (3, 6, or 12 months) or earlier discontinuation, patients transfer to a "no treatment" state in which they are exposed to observational-studies based risks of VTE recurrence, CTEPH, and PTS. Quarterly cycles are used to appropriately reflect treatment duration and patient management. Expected costs and outcomes are accumulated over time per treatment cohort. In modeling possible patient trajectories, the following assumptions were made:

- All patients were assumed to discontinue treatment after an IC bleed, with those surviving the acute phase remaining in the post-IC bleed state until death.
- Extracranial bleeds were modeled as only having an acute impact, with 40% of the index DVT patients and 16% of the index PE patients discontinuing treatment after a major EC bleed; and, after a CRNM bleed, 11% and 5%, respectively[23,24].
- A distinction was made between an ipsilateral and a contralateral recurrence of DVT, as the risk of PTS is higher after an ipsilateral recurrence (risk ratio = 2.4[16]).
- It was assumed that a VTE event can only be fatal in the shape of a PE.
  Patients were assumed to only experience an increased mortality risk in the acute PE state, the IC bleed state, the EC bleed state, and due to CTEPH.

Transition probabilities

Efficacy (intention-to-treat population) and safety (safety population) data from the EINSTEIN Acute DVT and the EINSTEIN Acute PE studies have been previously assessed in a pooled analysis[25]. That assessment formed the basis for the current cost-effectiveness analysis. Rivaroxaban treatment effect was modeled through the application of a hazard ratio (HR) to the baseline risks on LMWH/VKA treatment (Table 2). Differences between the treatment duration groups were incorporated via the baseline risks. The relative effect of rivaroxaban was assumed to be equal across duration groups. The on-treatment proportion of a recurrent VTE in the shape of a DVT was based on the per-treatment arm trial observations; i.e. 47.4% (45/95) in the VKA/LMWH arm and 37.2% (32/86) in the rivaroxaban arm (Supplementary Table S1).

Table 2. Baseline risks (LMWH/VKA) and hazard ratios (rivaroxaban) based on the pooled EINSTEIN trial data (DVT/PE). Figures regarding major bleed are based on the first major bleed event (Prins *et al.*[25] considered first bleed event).

Duration group	Period	Baseline risk recurrent VTE (95% CI)	Baseline risk major bleed (95% CI)	Baseline risk CRNM bleed (95% CI)
3 months	0–3 months	1.54% (0.20–2.88%)	2.79% (0.99–4.58%)	6.19% (3.56–8.82%)
6 months	0–3 months	1.94% (1.40–2.49%)	1.10% (0.69–1.51%)	5.85% (4.92–6.78%)
	3–6 months	0.22% (0.03–0.41%)	0.63% (0.29–0.96%)	1.83% (1.25–2.40%)
12 months	0–3 months	2.17% (1.39–2.95%)	1.20% (0.62–1.79%)	5.78% (4.53–7.03%)
	3–6 months	0.48% (0.10–0.86%)	0.26% (0.00–0.55%)	2.76% (1.82–3.71%)
	6–12 months	0.16% (0.00–0.39%)	0.38% (0.01–0.75%)	3.23% (2.16–4.30%)
		quart. prob.: 0.08%	quart. prob.: 0.19%	quart. prob.: 1.63%
Rivaroxaban hazard ratio	0–12 months	0.89 (0.66–1.19)	0.54 (0.37–0.79)	1.02 (0.89–1.18)

All other VTE events (PE, PE + DVT, death due to PE, and death where PE cannot be ruled out) were treated as PE-related in the model. The coincidence of PE + DVT occurred in 3.4% (2/59 PE recurrences in the EINSTEIN Acute PE study; pooled across treatment arms). The on-treatment probability of a major bleed event was based on the incidence of first major bleed events, and the probability of that event being an IC bleed was based on the per-treatment arm trial observations; i.e. 19.4% (14/72) in the VKA/LMWH arm and 12.5% (5/40) in the rivaroxaban arm (Supplementary Table S1).

The following transition probabilities were sourced from observational studies and applied identically to both treatment arms (Supplementary Table S2). First, the share of DVTs recurring ipsilaterally (both on and off treatment) was assumed equal to 58.8% (47/80)[16]. Second, long-term off-treatment risk of VTE recurrence was assumed to be equal for both treatment arms; namely, 1.26% per quarter (10-year cumulative probability of recurrence at 39.9% converted to a quarterly probability)[43]. Third, the manifestation form of an off-treatment VTE recurrence was based on the same study; i.e. recurrence in the shape of a DVT was assumed higher in patients with an index DVT (75.6% [189/250]) than in patient with an index PE (43.4% [53/122])[43]. Fourth, the risk to develop mild/moderate or severe PTS as a long-term complication was modeled, irrespective of treatment received, based on a long-term follow-up study including over 500 DVT patients[16]. Using the cumulative incidence of 18.0% (with 2.7% being severe) in the first year post-DVT and of 29.6% (with 8.1% being severe) after 5 years, the quarterly risks of mild/moderate and severe PTS were, respectively, calculated as 4.1% and 0.7% during the first year and as 0.5% and 0.4% during years 2–5. Fifth, based on the 2-year risk of developing CTEPH after a PE (1.25%), as measured in a long-term follow-up study of over 800 patients, the quarterly risk was calculated as 0.16% (applied for a period of 2 years)[13]. Lastly, for the relevant proportion (i.e. 56.8% [386/679][17]) of patients developing CTEPH, the additional costs of pulmonary thrombo-endarterectomy were accounted for.

Mortality risks were based on literature, except for PE fatality at 24.5% (13/53) in the VKA/LMWH arm, at 25.4% (15/59) in the rivaroxaban arm, and at 25.0% (28/112) off treatment (Supplementary Table S1)[25]. For major EC and IC bleed, fatalities were applied at 3.9% (27/689) and 43.6% (82/188), respectively (Supplementary Table S2)[44]. All CTEPH patients were exposed to a quarterly mortality risk of 2.48% (derived from a 26% [122/469] 3-year mortality risk)[45]. Age and sex-specific background mortality rates were based on Dutch lifetables[46] censored for ICD-10 codes I26-I27 and I60-I62 to prevent double-counting.

Utilities

Whenever possible, the utility estimates adapted reflect the specific Dutch setting (Table 3). The applied model norm reflects the Dutch population at 50–59 years of age[47]. The significant difference in treatment satisfaction between the two treatment arms, as reported by patients in the EINSTEIN program[48,49], was captured by means of a treatment disutility for LMWH/VKA. Two appropriate sources were identified, one in the context of atrial fibrillation (British[50]), the other in the context of VTE (Dutch[10]). The former source specifically clarified which treatment-associated drawbacks were captured, so that they could be ruled out for rivaroxaban (e.g. frequent monitoring tests and dietary restrictions), arriving at a utility multiplier of 0.948 (applied in the model). The latter source provided a less elaborate description of the captured drawbacks, yet supported the former estimate with a utility decrement of 0.04. Conservatively, a penalty for LMWH injections was not included in the applied disutility for LMWH/VKA treatment. DVT, PE, and major EC bleed disutilities were sourced from a Dutch study[10]. The utility decrement for a minor bleed was based on a British study and represents hemorrhoids (ICD-9: 455)[51]. Stroke utilities as measured in a Dutch setting were used to represent IC bleed utilities[52]. The authors reported an acute utility—i.e. at discharge—as well as a post-stroke utility—i.e. 6 months post-discharge, for four severity levels. As the current model contains only one severity level, model utilities represent the frequency-weighted mean utilities of the published severity levels; i.e. 0.451 in the acute IC bleed health state and 0.666 in the post-IC bleed state. CTEPH utility was sourced from the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) utility index, i.e. a disease-specific index[53]. The extracted utility value at 0.56 was assumed comparable as when measured with the EQ-5D[54,55], and, therefore, used without any adjustment. Severe PTS utility was sourced from a Dutch study[10], while mild/moderate PTS utility was sourced from a US study[56].

Resource use and costs

Treatment-related costs are presented in Table 4. Rivaroxaban, VKA, and LMWH unit costs were based on

Table 3. Health state utility weights, as applied in the cost-effectiveness analysis.

Health state	Utility	Source
Population norm	0.899	Lamers *et al.*[47] (2006)
Disutility VKA treatment	0.948 (multiplier while on treatment)	Robinson *et al.*[50] (2001)
Deep-vein thrombosis	0.884[a] (multiplier for duration of 1 month)	Locadia *et al.*[10] (2004)
Pulmonary embolism	0.663[b] (multiplier for duration of 1 month)	Locadia *et al.*[10] (2004)
Bleed		
Extracranial:		
major	0.684[c] (multiplier for duration of 1 month)	Locadia *et al.*[10] (2004)
minor	0.0049 (utility decrement for cycle duration)	Sullivan *et al.*[51] (2011)
Intracranial:		
intracranial	0.451	Baeten *et al.*[52] (2010)
post-intracranial	0.666	Baeten *et al.*[52] (2010)
Chronic thromboembolic pulmonary hypertension		
acute CTEPH	0.560	Meads *et al.*[53] (2008)
long-term CTEPH	0.560	Meads *et al.*[53] (2008)
Post-thrombotic syndrome		
mild/moderate PTS	0.98 (multiplier for cycle duration)	Lenert *et al.*[56] (1997)
severe PTS	0.863[d] (multiplier for cycle duration)	Locadia *et al.*[10] (2004)

[a]DVT utility/norm = 0.84/0.95 = 0.884;
[b]PE utility/norm = 0.63/0.95 = 0.663;
[c]gastrointestinal bleed utility/norm = 0.65/0.95 = 0.684;
[d]severe PTS utility/norm = 0.82/0.95 = 0.863[10].

pharmacist purchasing prices (December 2015), covering a 90-day prescription period, with dosing as per SPC (Summary of Product Characteristics). VKA drug acquisition costs represent a weighted average of phenprocoumon (20%) and acenocoumarol (80%)[57]. LMWH costs were based on 8 days of once-daily dosing (conservative compared to bi-daily), a mean body weight of 80 kg (55% male × 85.5 kg +45% female × 71.0 kg, Statistics Netherlands; *Centraal Bureau voor de Statistiek*), and a weighted average of enoxaparin (9%), nadroparin (63%), and dalteparin (28%)[57]. Outpatient home care compression therapy costs for DVT patients were based on the Dutch AMUSE study[58]. Although outpatients treated with rivaroxaban do not receive LMWH injections and do not need instructions on self-injection, they do need to receive compression bandaging. Therefore, home care compression therapy costs were conservatively assumed equal for both treatment arms. For INR monitoring, the reference tariff of €15.37, as published by the Dutch Healthcare Authority, was used (DRG codes 79995 and 70706)[59]. We conservatively assumed no difference between monitoring in a clinical setting and at home. The number of monitoring visits was based on the Dutch participants in the EINSTEIN clinical study program ($n = 450$), who were managed according to local guidelines. The average number of 12.2 (4.2 during initial LMWH/VKA therapy and 8 during subsequent VKA monotherapy) monitoring visits in the first 3 months, followed by 3.0 visits in subsequent quarterly cycles, is supported by a recent Dutch real-world resource utilization study focusing on INR monitoring in DVT patients[60]. Namely, the authors reported an average number of monitoring visits in the first 6 months of 12.3, in which only the period on VKA monotherapy was taken into account. Patient monitoring by the general practitioner was assumed the same for both treatment arms[61].

Treatment-related patient travel costs (Table 4) were taken into account for patients being monitored at the anticoagulation clinic (57.5%), as opposed to at home (42.5%)[62]. Travel distance to a clinic was approximated as 4.1 km (midpoint between GP distance [1.1 km] and hospital distance [7.0 km])[61]. It was assumed that one third of patients travel by personal car, one third by public transport, and one third by taxi[61]. Travel costs for GP visits were not included, as the average travel distance to a GP practice is small in the Netherlands.

Quarterly event-associated costs are presented in Table 5. In the EINSTEIN clinical study program, 91.2% of the Dutch index DVT patients were treated in an outpatient setting. In accordance with Dutch guidance, PE patients were assumed to be treated as inpatients[7]. Outpatient DVT costs were constituted out of several items, whereas inpatient (DVT or PE) costs were based on a single DRG code. The weighted average (inpatient/outpatient) DVT event costs equal €623.22. This amount, as well as the inpatient PE costs, are in line with an earlier Dutch publication[58]. A Dutch study on gastrointestinal ulcer complications was used to inform costs associated with major EC bleeds[63]. Costs associated with minor EC bleeds were modeled using an emergency admission as proxy[61]. Intracranial bleed costs were based on the same source as the IC bleed utilities[52]. For CTEPH diagnosis, rehabilitation, and surgery, NZa DRG codes were used. Due to lack of Dutch data, PTS costs were based on a US source[64].

Loss of productivity was relevant for the first 10 years of the model simulation (57 until 67 years of age) and accounted for via the friction method (friction period of 61 working days)[61]. Calculation of the average daily wage was based on the productivity cost per day per working person; i.e. €305.16 for men and €254.44 for women[61]. Age-specific gross participation (64.3% among men and 38.2% among women according to Statistics Netherlands; *Centraal Bureau voor de Statistiek*) and part-time employment (89% of men and 35% of women have a large part-time job or fulltime job[65]) were taken into account. The resulting sex-weighted (55% male) average daily wage equaled €110.70. Dutch data on the duration of absence is limited. Therefore, besides assumptions and a single Dutch source[66], Swedish data were

Table 4. Quarterly treatment-related costs (2015).

Cost item	Rivaroxaban			Reference	LMWH/VKA			Reference
	Unit cost	Units	Costs		Unit cost	Units	Costs	
Anticoagulant	€2.16	111	€239.76	Pharmacist purchasing price, December 2015	€0.08	90	€7.12	Pharmacist purchasing price, December 2015, phenprocoumon, acenocoumarol[57]
		90	€194.40					
LMWH	—	—	—	—	€9.44	8	€75.54	Pharmacist purchasing price, December 2015, enoxaparin, nadroparin, dalteparin[57]
Home care compression therapy[a]	€576.33	1	€576.33	Dutch AMUSE study[58]	€576.33	1	€576.33	Dutch AMUSE study[58]
INR monitoring (medical costs)[b]	—	—	—	—	€15.37	12.2	€187.45	Reference tariff[59], Dutch participants in EINSTEIN clinical study program ($n = 450$)
						3.0	€45.35	
GP visit	€30.59	3	€91.77	Dutch costing manual[61]	€30.59	3	€91.77	Dutch costing manual[61]
		1	€30.59			1	€30.59	
Patient travel costs associated with INR monitoring visits[c]	—	—	—	Dutch costing manual[61]	€10.36	12.2	€126.32	Dutch costing manual[61]
						3.0	€30.56	

In case of two rows per cost item: 1st row represents 1st cycle; 2nd row represents subsequent cycles.
[a]Only applies to DVT outpatients.
[b]For inpatients, INR monitoring during LMWH therapy (4.2 out of 12.2) is included in the overall event cost and not counted separately.
[c]Applicable to 57.5% of patients[64].

used as proxies[67,68] (Table 6). All estimates of duration of absence were conservative; i.e. rather under-estimating than over-estimating. For instance, most patients would be longer absent from work than just the duration of hospitalization.

Sensitivity analyses

One-way sensitivity analyses were conducted by setting model parameters at the outer limits of their 95% confidence intervals. All the above-described trial-based assumptions, observation-based assumptions, utilities, resource use, direct medical costs, direct non-medical costs, and indirect non-medical costs were varied one by one. Furthermore, a probabilistic sensitivity analysis (PSA) was performed to simultaneously incorporate uncertainty around all model parameters except for drug acquisition costs (1,000 simulations). For parameters with unknown uncertainty, the standard error was assumed equal to 30% of the mean. Beta distributions were used for utilities and probabilities, whereas gamma distributions were used for costs. Random draws of relative risks were obtained via a log transformation and subsequent exponentiation. Finally, three scenario analyses were conducted. One considering a time horizon of 5 years, another without assuming any VKA treatment disutility, and yet another with equal discounting applied to costs (4%) and effects (4%).

Results

Total and incremental life-time effects and costs per patient are shown in Table 7 for the modeled VTE population. With rivaroxaban treatment, an average of 0.017 discounted life years and 0.047 discounted QALYs are gained over LMWH/VKA treatment. A gain in QALYs can be primarily attributed to a reduced occurrence of bleeding events and lower mortality with rivaroxaban, and the disutility associated with VKA treatment. Per 1,000 VTE patients, 8.2 major bleeds are avoided with rivaroxaban compared to LMWH/VKA treatment. Both from the societal perspective as well as the healthcare perspective, rivaroxaban treatment is cost-saving compared to LMWH/VKA treatment, with indirect savings amounting to €171 per patient (87% caused by INR monitoring visits). Incremental drug costs (€403) are more than compensated by savings on INR monitoring visits (€280; 72% direct medical costs and 28% direct non-medical costs) and bleed events (€259). The incremental cost-effectiveness ratio (savings of €304 and 0.047 QALYs gained per patient) is, therefore, dominant. Although incrementally hardly having an impact, PTS and CTEPH contribute significantly (∼€1.6k) to the total costs. The scenario analysis with equal discounting leads to the same conclusion (savings of €304 and 0.042 QALYs gained per patient; Table 7). If results were to be assessed at a shorter time-horizon, namely after the first 5 years (Supplementary Table S3), the cost-effectiveness analysis (savings of €203 and 0.031 QALYs gained per patient) still indicates dominance. This scenario analysis shows that 67% of cost savings and 66% of QALY gains are accrued in the first 5 years.

Table 5. Quarterly event-associated costs (2015).

Event	Cost	Reference
Deep-vein thrombosis—inpatient	€3,534.38	DRG code 141418
Deep-vein thrombosis—outpatient	€385.36	Ultrasound lower extremities; DRG code 77433 (D-dimer); Emergency admission[61]
Pulmonary embolism—inpatient	€4,488.29	DRG code 141419
Bleed		
Extracranial:		
major	€10,167.21	Gastrointestinal[62]
minor	€260.68	Emergency admission[61]
Intracranial:		
acute[a]	€24,815	Stroke[52]
post-intracranial	€1,819	Post-stroke[52]
Chronic thromboembolic pulmonary hypertension		
acute CTEPH	€212.47	DRG code 140709 (diagnosis)
ongoing care CTEPH[b]	€254.52	DRG code 140458 (rehabilitation)
CTEPH surgery	€7,207.86	DRG code 140307 (treatment)
Post-thrombotic syndrome		
mild/moderate PTS—1st year	€170.28	Mild-to-moderate PTS[63]
mild/moderate PTS—subsequent years	€69.21	Mild-to-moderate PTS[63]
severe PTS—1st year	€774.66	Severe[63]
severe PTS—subsequent years	€340.35	Severe[63]

[a]Additional costs accrued during the first four quarters, compared to subsequent quarters, were accumulated in quarter 1; while correcting for mortality.
[b]Also applicable to first quarter.

Table 6. Event and treatment-related number of days absent from work.

Event	Days absent from work	Source
VTE event		
deep-vein thrombosis—inpatient	3.0 (4.2 × 5/7)	ICD10 I80 hospitalization 2013[67]
deep-vein thrombosis—outpatient	1	Assumption
Pulmonary embolism—inpatient	5.7 (8 × 5/7)	Assumed equal to acute LMWH treatment period
Monitoring		
outpatient hospital visit	0.25 (2 h)	Hospital visit[68]
GP/physician visit	0.13 (1 h)	Hospital visit[68] × 0.5
AC clinic visit (INR)	0.13 (1 h)	Hospital visit[68] × 0.5
home visit (INR)	0.06 (0.5 h)	Assumption
Bleed		
Extracranial:		
major	2.7 (3.8 × 5/7)	ICD10 K92 hospitalization 2013[67]
minor	1	Assumption
Intracranial	61	Stroke absence 1993 (221–249 days)[66]
Chronic thromboembolic pulmonary hypertension		
acute CTEPH	4.3 (6.0 × 5/7)	ICD10 I27 hospitalization 2013[67]
ongoing impact CTEPH	1/quarter	Assumption
Post-thrombotic syndrome		
mild/moderate PTS—1st year	0	Assumption
mild/moderate PTS—subsequent years	0	Assumption
severe PTS—1st year	3.8 (5.3 × 5/7)	ICD10 I87 hospitalization 2013[67]
severe PTS—subsequent years	1/quarter	Assumption
Death	61	Definition

Figure 2 presents a tornado diagram illustrating the top 15 parameters with most influence on incremental QALYs, when varied between the outer limits of their 95% confidence intervals. The parameter "Death given treated PE (RIV)" caused the largest variation; from 0.0254–0.0687. All variations resulted in positive incremental QALYs. Utility values sourced from non-Dutch references—i.e. for minor bleed, mild PTS, and CTEPH—are not part of this top 15. If the disutility associated with VKA treatment were to be completely discarded, incremental QALYs per patient would be reduced to 0.022 (Table 7).

Figure 3 presents a tornado diagram with the top 15 parameters with most influence on incremental costs. The largest variation is from –€444 to –€200 (Medical cost component of INR monitoring visit). All variations resulted in cost savings. Incremental costs are sensitive to indirect cost

Table 7. Lifetime time-horizon results (base case: costs discounted at 4% and effects at 1.5%).

	Rivaroxaban	LMWH/VKA	Incremental
Effects			
Life years	19.73	19.72	0.017
life years (4% discounted)	14.94	14.92	0.013
QALYs	17.53	17.48	0.047
QALYs (4% discounted)	13.27	13.23	0.042
QALYs (scenario without VKA disutility)	17.53	17.51	0.022
Costs			
Total	€8,509	€8,813	–€304
Direct	€7,256	€7,390	–€133
drug	€495	€92	€403
INR monitoring visits[b]	€429	€709	–€280
VTE-related[a]	€4,468	€4,465	€3.73
bleed-related	€230	€489	–€259
PTS/CTEPH	€1,634	€1,636	–€1.57
Indirect costs	€1,253	€1,424	–€171

[a]Visit (medical costs; contributing 72% to incremental INR monitoring costs [–€202]) and patient travel costs to visits (non-medical; contributing 28% to incremental INR monitoring costs [–€78]).
[b]Including index event costs.

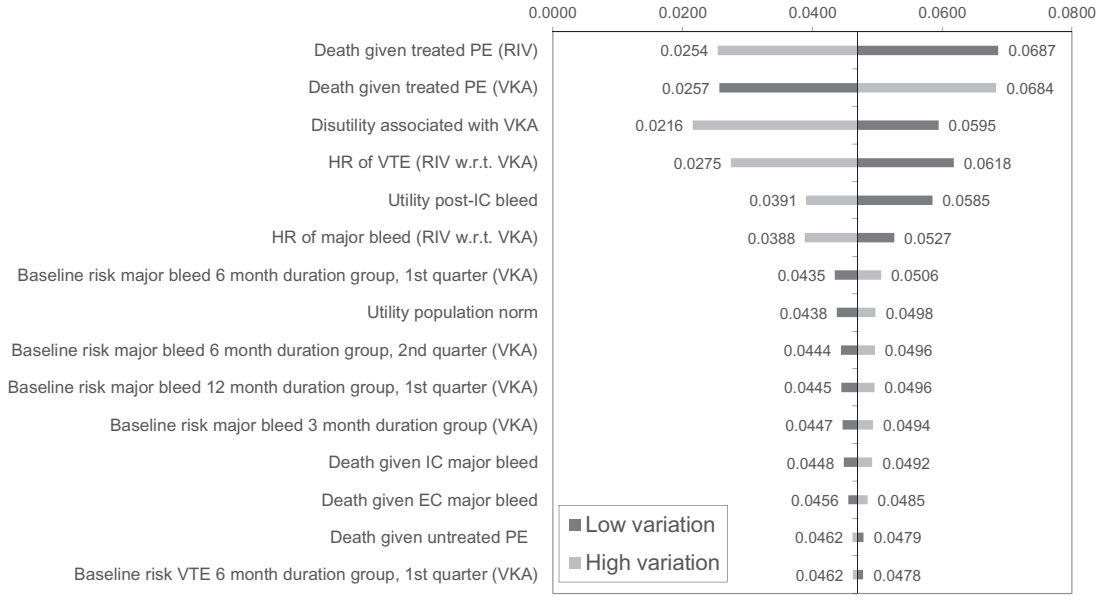

Figure 2. Tornado diagram for total discounted (1.5%) incremental QALYs per patient (top 15 parameters).

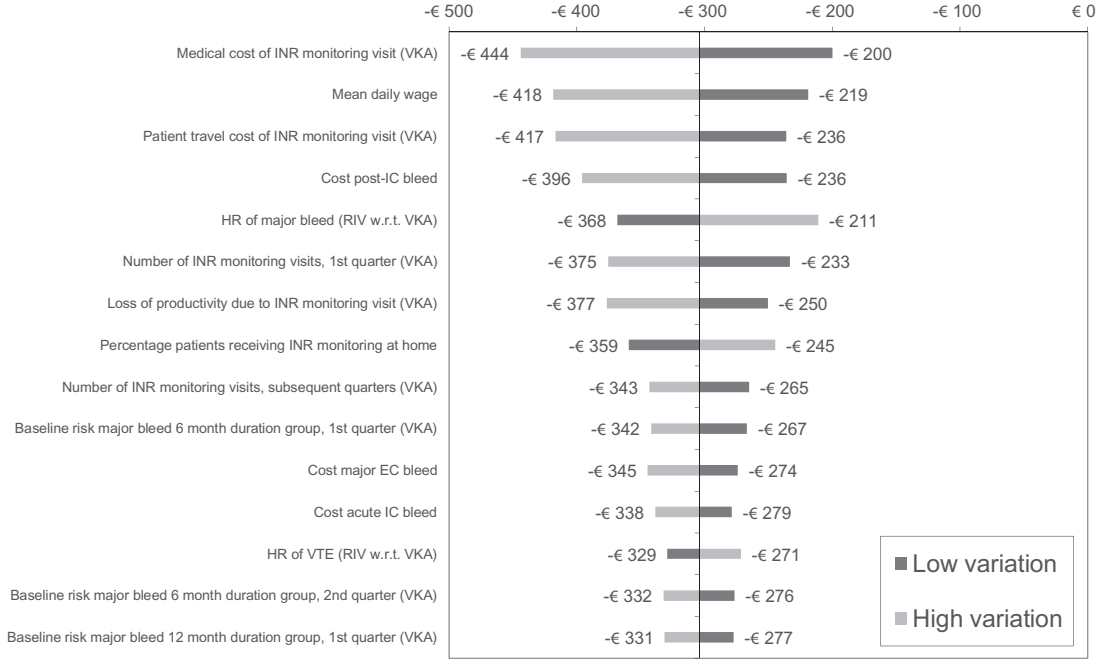

Figure 3. Tornado diagram for total discounted (4%) incremental costs per patient (top 15 parameters).

parameters, such as the mean daily wage and the number of work days lost due to visits to the anticoagulation clinic. Also, the direct costs associated with INR monitoring play a large role. Furthermore, several parameters related to major bleed occurrence or costs are part of this top 15. In the probabilistic sensitivity analysis (Figure 4), 99.8% of simulations were located in the southeast quadrant (health gains and cost savings) and 0.2% in the northeast quadrant (health gains and incremental spendings).

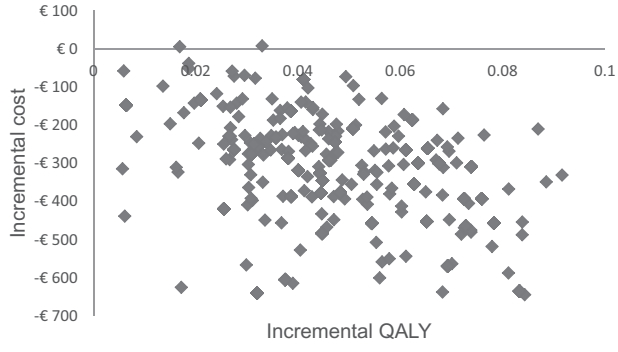

Figure 4. Scatter plot of probabilistic sensitivity analysis; incremental costs per patient vs incremental QALYs per patient.

Discussion

We have estimated the cost-effectiveness of rivaroxaban compared to LMWH/VKA in treatment and secondary

prevention of VTE, viewed from the Dutch societal perspective. Over a patient's lifetime, rivaroxaban was shown to be dominant, with health gains of 0.047 QALYs and cost savings of €304 compared to LMWH/VKA therapy. Dominance was robustly present in all sensitivity analyses, including a scenario in which the disutility associated with VKA treatment was discarded. Major drivers of the differences between the two treatment arms are related to INR monitoring (medical costs, travel costs, and loss of productivity) and the beneficial safety profile of rivaroxaban concerning major bleeds (HR = 0.54).

Apart from the important role of loss of productivity and patient travel—which is a new insight—these results are in accordance with several recent studies on the cost-effectiveness of rivaroxaban in acute VTE in other countries. First, a Portuguese study reported per patient cost savings (€322) for index DVT patients (cost-minimization analysis) as well as for index PE patients (€293, combined with QALY gains of 0.005 in a cost-effectiveness analysis), using a 5-year time horizon[28]. The perspective of that study was societal, although indirect costs and patient travel costs were not included. Costs savings after 5 years were found to be higher in the Portuguese study than in the underlying study (€203), partly due to higher INR (medical) monitoring costs in Portugal compared to the Netherlands. Second, a cost-effectiveness analysis from the US payer perspective demonstrated rivaroxaban to be dominant over LMWH/VKA, with health gains of 0.0058 QALYs, and cost savings of $2,448 per patient over a 5-year time horizon[27]. On one hand, estimated health gains accrued over 5 years were lower than in the current study (0.0058 vs 0.031), whereas, on the other hand, estimated cost savings were larger in the US study than in the current one ($2,448 over 5 years vs €203 in the first 5 years). An important factor in the latter difference is that the US study took a reduced length of hospital stay into account when patients were treated with rivaroxaban (3 days for DVT patients vs 1 day for PE patients, including the index event). Such a potential reduction in length of hospital stay with rivaroxaban treatment was not modeled in the current analysis. Third, another US cost-effectiveness analysis—this time with a societal perspective (although no indirect costs nor patient travel costs were included)—used a more compact Markov model and EINSTEIN-PE efficacy and safety data only. The authors arrived at per patient health gains of 0.15 QALYs and cost savings of $2,994 over a 10-year time horizon[26]. The main drivers for these cost savings were the reductions in EC and IC bleeds with rivaroxaban. Lastly, a British study reported dominance for rivaroxaban over a life-time horizon for both indications (index DVT and index PE) in all three treatment duration groups (3, 6, and 12 months) from a UK payer perspective[29]. If we apply the same weighting to the different groups as applied in the current study, this would result in £173 cost savings and 0.023 QALY gains for the overall VTE population. The higher direct cost savings compared with the current study (€133) can be explained by the British study taking into account a reduced length of stay for patients treated with rivaroxaban (3 days for DVT patients vs 1 day for PE patients, including the index event). The lower QALY gains compared with the current study (0.047) can largely be explained by a different assumption regarding VKA disutility (a multiplier of 0.988[41] instead of 0.948[50]). Overall, as the utility value assigned to the post-IC bleed state plays an important role, we verified that our assumption (i.e. 0.67) lies within the reported range (i.e. 0.60–0.71)[26–29]. The above-described cost-effectiveness analyses show a consistent pattern of rivaroxaban being a cost-saving alternative for LMWH/VKA therapy. This is in line with the wider literature on NOACs as a class, including positive cost-effectiveness assessments by HTA bodies on apixaban[69,70], dabigatran[71–73], and rivaroxaban[74,75]; as well as a recent Dutch cost-effectiveness study from the societal perspective concerning dabigatran in acute DVT patients[60], where the authors demonstrated per patient cost savings (€18.90) over the treatment period of 6 months, at an incremental QALY gain of 0.041. Cost-effectiveness studies directly comparing NOACs with one another are not addressed in the above literature overview. The rationale being that we cannot condense in this discussion section an assessment of trial heterogeneity—and how, if at all, this was accounted for in the indirect treatment comparisons informing the economic models—economic model design, and country-specific model settings.

The results must be interpreted within the framework and limitations of the current analysis. The underlying model was built based on the findings of the EINSTEIN phase III clinical trial program (conducted in 38 countries, including the Netherlands). In the execution of the current cost-effectiveness analysis, utmost care was taken to reflect the specific Dutch VTE treatment setting and Dutch cost-effectiveness analysis guidelines as much as possible. Whereas in the Netherlands the most-commonly used LMWHs are nadroparin and dalteparin, enoxaparin was used in the EINSTEIN clinical study program. The clinical effects of these three LMWHs have, however, been previously assessed to be similar[76,77]. Also, the most-commonly used VKAs in the Netherlands are acenocoumarol and phenprocoumon, as warfarin is not registered in the Netherlands. Although these VKAs differ in their half-lives, there is no clinically relevant difference as their dosing frequency should be titrated based on INR[78,79]. Therefore, efficacy and safety as measured in the LMWH/VKA study arm of the EINSTEIN clinical study program are considered representative for the Dutch setting. The duration of LMWH treatment was assumed equal to 8 days. This is a conservative assumption, as the average real-world (Netherlands) duration may be longer[80]. The INR monitoring frequency was based on only the Dutch participants in the EINSTEIN program, as inter-country differences in monitoring approach exist. The applied INR monitoring tariff (€15.37) concerns a maximum tariff, with tariffs in practice being negotiable. However, as the same tariff was applied to the home setting—with a maximum tariff of €28.79 (DRG codes 79995, 79992, and 70706)[59]—we believe this to be a fair assumption. With an average age of 57 years at time of index VTE event, loss of productivity emerged as one of the model drivers. Because the availability of Dutch absence from work data is limited, conservative assumptions have been used. Namely, the estimates for PE, DVT, acute CTEPH, major EC bleed, and PTS only account for hospitalization time (based on Swedish data); with the total sick leave most probably taking longer.

Moreover, it was conservatively assumed that persons working fewer hours than a large part-time job (< 28 hours per week) would schedule their monitoring visits outside their working hours.

Conclusion

Our findings show that rivaroxaban treatment of patients with venous thromboembolism results in health gains and cost savings compared to LMWH/VKA therapy. This conclusion holds for the Dutch setting, both for the societal perspective as well as the healthcare perspective. Dominance was robustly present in all sensitivity analyses.

Transparency

Declaration of funding

This research was financially supported by Bayer, Mijdrecht, the Netherlands. The authors declare that study results were not influenced by Bayer.

Declaration of financial/other relationships

MH and MJT are employed by Pharmerit International, a consultancy agency in health economics and outcomes research. Due to the nature of their work, they have received research funding from many pharmaceutical companies in the healthcare industry, including Bayer B.V. HEH is an employee of Bayer. EBWG is an employee and stockholder of Bayer. During the past 2 years, MJP has received grants from Sigma Tau, GSK, Boehringer Ingelheim, Pfizer, MundiPharma, GMASOL, Ingress Health, Bayer, BMS, AbbVie, MSD, Sanofi, and AstraZeneca, as well as honoraria to advise Vertex (member Sci Adv Comm), Pfizer (member Sci Adv Comm), Quintiles, Mapi, Astellas, Novartis (member Agora initiative), OptumInsight, Swedish Orphan, Innoval, Jansen, Sanofi, Intercept, Pharmerit, GSK, and MSD. MJP is also a stockholder of Ingress Health. JME peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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