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Cost-effectiveness analysis and budget impact of rivaroxaban in cancer patients at risk of recurrent venous thromboembolism

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3 1 Cost-effectiveness analysis and budget impact of rivaroxaban in cancer patients at risk of recurrent
4 2 venous thromboembolism
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7 4 Short title: Economic evaluation of rivaroxaban in cancer patients
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Abstract

Objectives: We aim to calculate the cost-effectiveness and budget impact of rivaroxaban compared to low molecular weight heparin (LMWH) in cancer patients at risk of recurrent venous thromboembolism (VTE).

Setting: The analyses were performed for the Dutch healthcare setting. We built a Markov model to calculate the cost-effectiveness from a societal perspective over a five-year time horizon.

Participants: A hypothetical cohort of 1,000 cancer patients with VTE entered the model with baseline characteristics based on the SELECT-D trial.

Intervention: Six months treatment with rivaroxaban (15 mg twice daily for first three weeks followed by 20 mg once daily) was compared to six months treatment with LMWH dalteparin (200 IU/kg daily during month one followed by 150 IU/kg daily).

Primary and secondary outcome measures: The primary outcome of the cost-effectiveness analysis was the incremental cost-effectiveness ratio (ICER). The robustness of the model was evaluated in probabilistic and univariate sensitivity analyses. A budget impact analysis was performed to calculate the total annual financial consequences.

Results: In the base case and all scenarios, rivaroxaban appeared to be cost-saving while also increasing the patient's health, resulting in dominant ICERs. In the probabilistic sensitivity analysis, 64.1% and 97.3% of the simulations were cost-saving and more effective for a five year and six month time horizon, respectively. Rivaroxaban can save up to €9,834,144 in approximately 8,000 cancer patients with VTE per year compared to LMWH.

Conclusions: Treatment with rivaroxaban is dominant over LMWH in cancer patients at risk for recurrent VTE in the Netherlands. The use of rivaroxaban instead of LMWH can save almost ten million euros per year, primarily driven by the difference in drug costs. Since treatment with rivaroxaban is cost-saving and less invasive, we feel that many cancer patients can benefit from direct oral anticoagulant treatment.

Strengths and limitations of this study

- This analysis includes both cost-effectiveness and budget impact analyses; this way we present the economic impact of the treatment of cancer patients with rivaroxaban on a patient level as well as on a population level.
- To reflect clinical practice, tunnel states were used to model the occurrence of time-dependent events, such as recurrent VTE and bleeding.
- Various additional scenarios were evaluated to show the effect of different assumptions and clinical situations.
- Based on the design of the SELECT-D trial, we assumed a six month treatment duration for all patients, while in clinical practice the treatment duration may vary between patients.
- Although trials have recently shown that apixaban and rivaroxaban are also effective as a primary prophylaxis of VTE in cancer patients compared to a placebo, this study focuses just on the secondary prevention of VTE in cancer patients.

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75 Introduction

76 Venous thromboembolism (VTE), comprising both pulmonary embolism (PE) and deep vein
77 thrombosis (DVT), is a major challenge in patients with cancer [1]. In addition to the characteristics of
78 the cancer itself, cancer therapy (chemotherapy and cancer surgery) has effects on the patient's
79 coagulation system and therefore increases the risk of VTE and bleeding [2–4]. VTE in cancer patients
80 can cause unnecessary hospitalizations, interruption or postponement of cancer treatment, and
81 increased mortality, leading to decreased quality of life and increased costs.

82 VTE is treated with anticoagulation therapy, and this is continued as prophylaxis over a longer
83 period because of the high risk of recurrence during the first months after the initial VTE [5]. Vitamin
84 K antagonists (VKAs) or direct oral anticoagulants (DOACs) are indicated for the treatment and
85 prevention of VTE in the general population [6]. However, guidelines recommend therapeutic
86 treatment with a daily subcutaneous injection of low molecular weight heparin (LMWH, e.g.,
87 dalteparin) in cancer patients [4,7–9].

88 The guidelines recommend against the use of VKAs in cancer patients because of potential
89 drug interactions, liver dysfunction, and malnutrition, all of which lead to fluctuations of the
90 international normalized ratio (INR) and could result in negative patient outcomes [4]. Moreover, trials
91 in cancer patients with VTE have shown that LMWH is more effective in the prevention of recurrent
92 VTE compared to VKA, without increasing bleeding risk [10–12].

93 DOACs have a more beneficial efficacy/safety ratio, do not require routine measurements of
94 the INR, and show fewer food-drug and drug-drug interactions compared to VKAs [4,13]. Therefore, it
95 is suggested that, unlike VKAs, DOACs can play an important role in the VTE treatment paradigm for
96 cancer patients. However, the use of DOACs is not yet recommended by oncology guidelines because
97 of the limited available data in cancer patients with VTE [4,9].

98 The SELECT-D is a multicenter, randomized, clinical pilot trial in the UK; it is a head-to-head
99 comparison of rivaroxaban and the LMWH dalteparin in 406 patients with active cancer who had
100 experienced a symptomatic PE, incidental PE, or symptomatic DVT [14]. Patients with upper
101 gastrointestinal (GI) cancer were excluded because of a high bleeding risk. They found that rivaroxaban
102 reduces the recurrence of VTE (six month cumulative VTE recurrence rate: 4% versus 11%) at the cost
103 of an increased risk of bleeding (six month cumulative major bleeding [MB] rate: 6% versus 4%; six
104 month cumulative clinically relevant non-major bleeding [CRNMB] rate: 13% versus 4%) compared to
105 dalteparin. These results were comparable to those of a large retrospective study by Streiff et al. [15].

106 Based on the results of these studies and the fact that DOACs can be orally administered (unlike
107 the subcutaneously injected LMWHs), an increase in the use of DOACs for VTE in cancer patients might
108 be expected. Since the introduction of DOACs there has been an ongoing discussion about the
109 economic impact of these drugs. By designing an economic model based on the SELECT-D trial, we aim
110 to evaluate the cost-effectiveness and budget impact of rivaroxaban compared to LMWH in cancer
111 patients at risk of recurrent venous thromboembolism in the Netherlands.

114 Methods

115 The economic model comparing rivaroxaban to LMWH was designed based on the SELECT-D trial [14],
116 since this study presented the most comprehensive results reflecting recurrent VTE and bleeding
117 complications per event type (symptomatic PE, incidental PE, and DVT) or severity (MB and CRNMB).
118 The primary outcome of the cost-effectiveness analysis is the incremental cost-effectiveness ratio

(ICER); this is calculated by dividing the incremental costs by the incremental health effects, expressed in quality adjusted life-years (QALYs). In accordance with Dutch costing guidelines for economic evaluations in healthcare, the ICER was calculated from a societal perspective, which incorporates direct as well as indirect costs both inside and outside the healthcare sector [16]. We performed sensitivity and scenario analyses to test the robustness of the model. Additionally, we conducted a budget impact analysis to reflect the annual financial consequences of the use of rivaroxaban in the Netherlands.

Model outline

We developed a decision-tree-based Markov model to calculate the ICER. Figure 1 shows a schematic representation of the model, with the disease course being represented by separate health states. A hypothetical cohort of 1,000 cancer patients with VTE entered the model with incidental PE, symptomatic PE, or DVT, represented by the 'index VTE' health state. Incidental PEs are non-symptomatic PEs that are incidentally found during tumour imaging. According to guidelines, patients with incidental PE should be treated identically to those with symptomatic PE [8,9]. Patient characteristics were based on the SELECT-D trial (Table 1) [14]. The SELECT-D population is representative for the Dutch population, based on age, tumour type, and gender distribution [17]. Patients move through various health states in the model during the follow-up time of five years; five years was used because overall survival was assumed to be low after five years since the majority (58%) of the SELECT-D trial population had metastatic cancer [14]. We included the following health states in our model (see legend of Figure 1 for abbreviations): 'recurrent incidental PE', 'recurrent symptomatic PE', 'fatal recurrent VTE', 'recurrent DVT', 'ICH', 'non-ICH MB', 'fatal MB', 'CRNMB', 'death by any cause', and 'no event'. Patients were assumed to remain in these states for one cycle, after which they moved back to the 'index VTE' state or the chronic, debilitating 'post-ICH' state, in which they remained until death without being at risk for any further complications. Tunnel states (one month post-VTE, two months post-VTE, ..., 60 months post VTE) were used to implement time-dependency, with future transitions, costs, and health-related quality of life dependent on how long the patient has gone without a recurrent VTE event [18]. The chronic complications post-thrombotic syndrome (PTS) and chronic thromboembolic pulmonary hypertension (CTEPH) were modelled in the background. Only severe PTS was modelled, since the costs of minor PTS are considered negligible. For these chronic complications we also used tunnel states since the risks of PTS and CTEPH were also time-dependent.

Figure 1. Model outline. All patients enter the model in the 'Index VTE' state and move to other states upon the occurrence of one of the following events: recurrent incidental PE, recurrent symptomatic PE, fatal recurrent VTE, recurrent DVT, ICH, non-ICH MB, fatal MB, CRNMB, or death by any cause. The triangles represent the health state a patient will enter after an event. The blue squares are permanent states, in which a patient will remain until death while not being at risk for other events. The red squares represent a transient state: the patient will re-enter the model in the 'Index VTE' state.
Abbreviations: CRNMB, clinically relevant non-major bleeding; DVT, deep vein thrombosis; ICH, intracranial haemorrhage; MB, major bleeding; PE, pulmonary embolism; VTE, venous thromboembolism

Table 1. Patient characteristics of the hypothetical cohort of 1,000 cancer patients at risk of recurrent VTE.

Unit	Value	Reference
Age (years)	67	[14]
Proportion male	53%	[14]
BMI (kg/m ²)	25.6	[14]
Type of cancer		
<i>Early or locally advanced cancer</i>	39%	[14]
<i>Metastatic cancer</i>	58%	[14]
<i>Haematologic malignancy</i>	2%	[14]
Distribution of PE and DVT		
<i>% index VTE that is symptomatic PE</i>	20%	[14]
<i>% index VTE that is incidental PE</i>	53%	[14]
<i>% index VTE that is DVT</i>	27%	[14]

Abbreviations: BMI, body mass index; DVT, deep vein thrombosis; LMWH, low-molecular weight heparin; PE, pulmonary embolism; VTE, venous thromboembolism

Transition probabilities

Transition probabilities were used to calculate the number of patients in each state per cycle. The cycle length was one month. Table S1 summarizes all event rates presented in six-month risks (transition probabilities). Event rates of recurrent VTE, MB, and CRNMB in the first six months of treatment were based on the SELECT-D trial [14]. If the patient did not experience a recurrent event during this period, anticoagulation treatment was discontinued. Recurrent VTE rates after treatment discontinuation were based on a retrospective study in active-cancer patients experiencing a VTE [5]. Upon the occurrence of a non-fatal recurrent VTE, patients were assigned to another six months treatment, with corresponding event rates. Bleeding risks after treatment discontinuation were based on the outcomes of the cancer population of the HOKUSAI VTE Cancer trial (which followed patients after edoxaban discontinuation for an additional six months) because this data is not reported for the SELECT-D trial [19]. The HOKUSAI VTE Cancer trial was also used to determine the distribution of ICH, non-ICH, and fatal bleeding. The distributions of the types of VTE and MB were calculated based on the total number of events and assumed to be treatment-independent, since the total number of events was low. The distributions of the types of VTE event were based on the number of recurrent VTE events in the lower extremities and pulmonary embolisms— other locations of VTE events (brachial, subclavian, jugular, renal plus inferior vena cava, or the extrahepatic vein) were excluded [14]. Mortality rates (death by any cause) were based on Dutch cancer mortality data from the Netherlands Cancer Registry [20]. In the sensitivity analysis, all transition probabilities were varied over beta distributions. For percentages of the type of recurrent VTE and MB, a Dirichlet distribution was used in the sensitivity analysis [18].

Costs

All cost parameters are presented in Table S2. Event-related healthcare costs were based on a previous Dutch cost-effectiveness study for rivaroxaban in the general VTE population [21]. Costs of fatal recurrent VTE were assumed to be similar to those of non-fatal symptomatic PE. We assumed no event-related healthcare costs for patients with incidental PE. Costs for ICH and CTEPH consisted of acute care costs during the first month after diagnosis, followed by long-term care costs until the patient moved to the 'death' state. Costs of a fatal MB were assumed to be equal to those of non-fatal non-ICH MB.

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3 199 Drug costs were retrieved from the national medication costs database [22]. For rivaroxaban these
4 200 costs were based on 15 mg twice daily for three weeks followed by 20 mg once daily. Drug costs of
5 201 LMWH dalteparin were based on 200 IU/kg daily during month one followed by 150 IU/kg daily in
6 202 months two to six [14,23]. Based on an average body mass index of 25.6 from the SELECT-D trial and
7 203 an average height of 1.72 m for the Dutch population, we calculated that the average weight was
8 204 between 69 and 82 kg, which corresponds with a dose of 15,000 IU daily during month one followed
9 205 by 12,500 IU daily in months two to six [14,24]. Rivaroxaban users were assumed to require an annual
10 206 check-up of their renal function [13]. We assumed no administration costs for LWMH because most
11 207 patients can perform the injection themselves or through their proxies.
12 208 Informal care costs were only applied to patients with early or locally advanced cancer (39%), since
13 209 patients with metastatic cancer or haematologic malignancies often already have home care or
14 210 informal care. Based on a previously published report on informal care in the Netherlands, we made a
15 211 distinction between intensive (26 hours per week) and non-intensive (8 hours per week) informal care
16 212 [25]. This was multiplied by the average duration and tariff for informal care, obtained from the Dutch
17 213 cost manual [16]. To prevent double counting, we did not include informal care costs for the chronic
18 214 complications. Travel costs were taken into account for renal monitoring visits and upon the
19 215 occurrence of a DVT or CRNMB. Considering the burden of cancer and the average age of 67 years
20 216 (which is the Dutch retirement age), productivity losses were assumed to be negligible. Costs related
21 217 to forgone leisure activity were not taken into account since there is no data available on the impact
22 218 of a VTE or bleeding on leisure losses in cancer patients.
23 219 Costs were discounted at an annual rate of 4% [16]. In the sensitivity analysis, the costs were varied
24 220 with gamma distributions corresponding to the 95% confidence interval (CI), as indicated in Table S2
25 221 [18].
26 222
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224 Utilities

225 Utility scores were derived from a sub-analysis from the CATCH study assessing the EQ-5D scores
226 associated with VTE and recurrent VTE in cancer patients (Table S3) [26]. The CATCH study assessed
227 the effectiveness of six months of treatment with tinzaparin versus warfarin for the treatment of acute
228 venous thromboembolism in patients with active cancer; It was chosen because it aligns well with our
229 population and events of interest. Utility decrements for CTEPH were based on a study assessing EQ-
230 5D VAS scores in CTEPH patients more than 7 years after initial diagnosis [27]. Utility decrements for
231 ICH and long-term PTS (> six months after diagnosis) were obtained from a previous cost-effectiveness
232 study [28]. Utilities were discounted at 1.5% according to Dutch guidelines [16]. In the sensitivity
233 analyses, utility scores were varied over their 95% CI with a beta distribution [18].
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236 Sensitivity analysis

237 Sensitivity analyses were conducted to check the robustness of the model. In the probabilistic
238 sensitivity analysis, all input parameters were varied simultaneously over their 95% CI. If the 95% CI
239 was unavailable and calculating the 95% CI based on the number of events was not possible, the 95%
240 CI was calculated based on a 25% standard error. The ICER was calculated with 2,000 iterations and
241 plotted in a cost-effectiveness plane. A univariate sensitivity analysis was conducted to show the

242 influence of an individual parameter on the ICER. The fifteen most influencing parameters were
243 presented in a tornado diagram.

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246 Scenario analysis

247 We conducted several scenario analyses to show the effect on the outcomes of different (clinical)
248 situations. In the Netherlands, guidelines advise to calculate the ICER from a societal perspective, while
249 in countries such as the UK or Belgium, the healthcare payer's perspective is preferred. To make results
250 comparable to other countries we also calculated the base case ICER from a healthcare payer's
251 perspective, by excluding the indirect costs (scenario 1). The costs of LMWH vary with the patient's
252 weight. For the base case analysis we assumed an average weight between 69 and 82 kg. In scenarios
253 2 and 3 we calculated the base case ICER with the costs of dalteparin based on weight categories of
254 57–68 kg (12,500 IE daily during month one followed by 10,000 IE daily in month two to six) and 83–
255 98 kg (18,000 IE daily during month one followed by 15,000 IE daily in month two to six), respectively.
256 The follow-up period of the SELECT-D trial was six months; therefore, outcomes beyond six months
257 had to be based on other publications. In the scenario 4 analysis we calculated the ICER with a time
258 horizon of six months. Scenario 5 was similar to scenario 4, except for the treatment period which was
259 based on a study of Streiff et al., who—comparable to SELECT-D—compared rivaroxaban to LMWH for
260 the prevention of recurrent VTE in cancer patients [15]. They found an average treatment duration of
261 one month and three months for LMWH and rivaroxaban, respectively. In scenario 6 we assessed the
262 effect of using drug-specific distributions of the types of VTE and MB based on the results of the
263 SELECT-D and HOKUSAI VTE Cancer trials [14,19].

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266 Budget impact

267 A budget impact analysis was conducted to estimate the total financial consequences of the
268 implementation of rivaroxaban for the treatment and prevention of VTE in cancer patients within the
269 Dutch healthcare setting. The budget impact was calculated from a societal perspective over a one-
270 year time horizon. Results from the first year of the cost-effectiveness analysis were multiplied by the
271 annual number of cancer patients with VTE in the Netherlands. This incidence and the total number of
272 Dutch cancer patients were used to calculate the yearly number of cancer patients with VTE. The
273 Netherlands Cancer Registry estimated a total of 579,781 cancer patients in 2017 [29]. The incidence
274 of VTE in cancer patients was 13.9 per 1,000 person-years, based on a cohort study of linked UK
275 databases [30]. The outcome of the budget impact analysis was presented as the total budget impact
276 per year, including a subdivision of the costs per type (event-related costs, treatment costs and indirect
277 costs) and corresponding 95% CIs derived from PSA.

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280 Results

281 Cost-effectiveness analysis

282 Table 2 represents the deterministic results of the base case and scenario analyses. In each scenario,
283 rivaroxaban appeared to be cost-saving compared to LMWH where the patient's health was
284 comparable (incremental QALYs of 0.012 in the base case analysis). In the base case analysis,
285 rivaroxaban saved €1,310 per patient compared to LMWH. There was increased cost savings compared

286 to the societal perspective when calculated from a healthcare payer’s perspective (scenario 1). In
 287 scenario 2 and 3 we assessed the effect of variations in the patient’s weight (and thus LMWH dosing)
 288 on the ICER. Compared to the base case analysis, there was decreased cost savings with a lower LMWH
 289 dose and increased cost savings with a higher LMWH dose, both still resulting in dominant ICERs. The
 290 scenario calculating the cost-effectiveness over six months resulted in cost savings of €1,147 per
 291 patient (scenario 4). When comparing three months of rivaroxaban treatment to one month of LMWH
 292 treatment, we found incremental QALYs of 0.017 and cost savings of €327 per patient (scenario 5). We
 293 assessed the effect of using drug-specific distributions of the types of VTE and MB, resulting in cost
 294 savings of €1,652 and incremental QALYs of 0.038 (scenario 6).
 295 The number of events and the corresponding average costs per patient are presented in Table 3.
 296 Rivaroxaban is associated with a lower number of recurrent VTE events, preventing on average €131
 297 and €108 in costs per patient over five years and over six months, respectively. On the other hand,
 298 rivaroxaban causes more bleeding events, especially in the treatment period. ICH, non-ICH MB, and
 299 CTEPH have the highest event-related costs. Treatment costs are higher for LMWH compared to
 300 rivaroxaban, with incremental costs of €1,559 and €1,306 in the five-year and the six-month time
 301 horizon, respectively. The indirect costs for rivaroxaban were higher compared to LMWH resulting in
 302 a difference of €23 and €2 for the five-year and the six-month time horizon, respectively.

303
304
305 **Table 2. Deterministic results per patient of the base case and scenario analyses in a cohort of 1,000 cancer patients.**

	Costs	QALYs	Δ Costs	Δ QALYs	ICER
Base case analysis - 5 year time horizon from societal perspective					
Rivaroxaban	€3,127	2.460	-€1,310	0.012	Dominant
LMWH	€4,437	2.448			
Scenario 1 – base case analysis from healthcare payer’s perspective					
Rivaroxaban	€2,942	2.460	-€1,334	0.012	Dominant
LMWH	€4,276	2.448			
Scenario 2 – base case analysis with LMWH dose of 12,500 IU					
Rivaroxaban	€3,127	2.460	-€913	0.012	Dominant
LMWH	€4,040	2.448			
Scenario 3 – base case analysis with LMWH dose of 18,000 IU					
Rivaroxaban	€3,127	2.460	-€1,732	0.012	Dominant
LMWH	€4,858	2.448			
Scenario 4 – 6 month time horizon from societal perspective					
Rivaroxaban	€1,358	0.304	-€1,147	0.004	Dominant
LMWH	€2,505	0.300			
Scenario 5 – scenario 4 with treatment duration based on Streiff et al.					
Rivaroxaban	€1,285	0.289	-€327	0.017	Dominant
LMWH	€1,611	0.272			
Scenario 6 – base case analysis using drug-specific distributions for the types of VTE and MB					
Rivaroxaban	€3,047	2.463	-€1,652	0.038	Dominant
LMWH	€4,699	2.426			

306 Abbreviations: ICER, incremental cost-effectiveness ratio; IU, international units; LMWH, low molecular weight heparin;
 307 QALY, quality adjusted life-years
 308
 309
 310

Table 3. Number of events and costs per event per patient in a cohort of 1,000 cancer patients.

Base case (5 year time horizon)			
	Rivaroxaban	LMWH	Incremental

	Number of events	Costs per patient	Number of events	Costs per patient	Number of events	Costs per patient
Event costs						
Recurrent VTE	191	€311.85	275	€442.92	-84	-€131
Non-fatal symptomatic recurrent PE	33	€168.36	48	€239.13	-15	-€71
Non-fatal incidental recurrent PE	58	-	84	-	-26	
Non-fatal recurrent DVT	83	€59.31	120	€84.23	-37	-€25
Fatal recurrent VTE	17	€84.18	24	€119.56	-7	-€35
ICH	11	€550.70	9	€438.40	2	€112
Non-ICH MB	98	€1,106.87	79	€902.47	19	€204
Fatal MB	5	€51.48	4	€41.98	1	€10
CRNMB	197	€56.28	92	€26.93	105	€29
PTS	61	€92.72	61	€92.37	0	€0
CTEPH	20	€223.79	20	€222.83	0	€1
Treatment costs		€548.83		€2,108.33		-€1,559
Indirect costs		€184.22		€160.77		€23
Scenario 4 (6 month time horizon)						
	Rivaroxaban		LMWH		Incremental	
	Number of events	Costs per patient	Number of events	Costs per patient	Number of events	Costs per patient
Event costs						
Recurrent VTE	38	€58.95	109	€166.96	-70	-€108
Non-fatal symptomatic recurrent PE	7	€31.82	19	€90.14	-12	-€58
Non-fatal incidental recurrent PE	12	-	33	-	-21	-
Non-fatal recurrent DVT	17	€11.21	47	€31.75	-31	-€21
Fatal recurrent VTE	3	€15.91	9	€45.07	-6	-€29
ICH	6	€142.82	4	€94.25	2	€49
Non-ICH MB	50	€539.38	33	€355.95	17	€183
Fatal MB	2	€25.09	2	€16.56	1	€9
CRNMB	130	€35.99	38	€10.62	91	€25
PTS	14	€20.59	14	€20.56	0	€0
CTEPH	3	€21.96	3	€21.93	0	€0
Treatment costs		€479.40		€1,785.45		-€1,306
Indirect costs		€33.79		€32.22		€2

Abbreviations: CRNMB, clinically relevant non-major bleeding; CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; ICH, intracranial haemorrhage; LMWH, low molecular weight heparin; MB, major bleeding; PE, pulmonary embolism; PTS, post thrombotic syndrome; VTE, venous thromboembolism

In the probabilistic sensitivity analysis we assessed the robustness of the model over a five-year time horizon (base case) and a six-month time horizon (scenario 4). The results are presented in cost-effectiveness planes in Figure 2 and Figure 3. Of the 2,000 iterations of the base case ICER, 77.0% were located in the south-eastern quadrant and 22.8% are considered cost-saving but less effective compared to LMWH. In scenario 4, 98.7% of the calculations were located in the south-eastern quadrant and in 1.2% rivaroxaban is considered cost-saving but less effective compared to LMWH.

The influence of the individual input parameters on the base case incremental costs and QALYs are analysed in the univariate sensitivity analysis. The tornado diagrams (Figure 4 and Figure 5) present the 15 input parameters with the highest impact. The risk of MB for both rivaroxaban and LMWH, treatment duration of LMWH, and recurrent VTE risks during the first six months after a VTE had the highest influence on the incremental costs. Similarly, the risk of MB and recurrent VTE in the first six months for rivaroxaban and LMWH showed the highest influence on the incremental QALYs.

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Figure 2. Probabilistic sensitivity analysis of the base case with five year time horizon (base case analysis). *Abbreviation: QALY, quality adjusted life-year*

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Figure 3. Probabilistic sensitivity analysis with six month time horizon (scenario 4). *Abbreviation: QALY, quality adjusted life-year*

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Figure 4. Tornado diagram from the univariate sensitivity analysis for the base case analysis showing the impact of parameters on the incremental costs. *Abbreviations: ICH, intracranial haemorrhage; LMWH, low molecular weight heparin; MB, major bleeding; PE, pulmonary embolism; VTE, venous thromboembolism*

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Figure 5. Tornado diagram from the univariate sensitivity analysis for the base case analysis showing the impact of parameters on the incremental QALYs. *Abbreviations: CRNMB, clinically relevant non-major bleeding; ICH, intracranial haemorrhage; LMWH, low molecular weight heparin; MB, major bleeding; VTE, venous thromboembolism*

Budget impact

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The results of the budget impact analysis are presented in Table 4. The replacement of LMWH with rivaroxaban can lead to annual cost savings of a maximum of €9,991,357 (€4,419,972–€15,407,533) over approximately 8,000 cancer patients with VTE. A reduction in treatment costs can lead to savings of up to €11.2 million. Event-related costs and indirect costs slightly increase by €1,234,467 (€-2,364,452–€5,177,816) and €27,749 (€-137,276–€189,561), respectively, when LMWHs are replaced by rivaroxaban.

Table 4. Budget impact over one year time in the Netherlands.

Event-related costs	€1,234,467 (€-2,364,452–€5,177,816)
Treatment costs	€-11,253,573 (€-15,363,435–€-7,309,562)
Indirect costs	€27,749 (€-137,276–€189,561)
Budget impact	€-9,991,357 (€-15,407,533–€-4,419,972)

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Discussion

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Thrombosis treatment is a challenge in cancer patients. According to the guidelines, LMWHs are the preferred treatment; however, DOACs have recently also been shown to be effective and safe in cancer patients with VTE. We have assessed the cost-effectiveness and budget impact of rivaroxaban in cancer patients based on the SELECT-D trial [14]. We conclude that, in the Netherlands, rivaroxaban is a cost-saving treatment option with a health benefit of 0.012 QALYs per patient over five years compared to LMWH. In a sensitivity analysis our model appeared to be robust.

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3 372 In both the cost-effectiveness analysis and budget impact analysis we found that the event-
4 373 related costs and indirect costs increase with the use of rivaroxaban compared to LMWH. In total, 42
5 374 events were prevented over five years; however, MB events were more frequent with rivaroxaban
6 375 compared to LMWH (11 ICH and 98 non-ICH versus 9 ICH and 79 non-ICH, respectively). MB events are
7 376 very burdensome and frequently severely disabling, causing high acute care and long-term direct and
8 377 indirect costs which makes these events very expensive. This might explain why the indirect costs were
9 378 higher for rivaroxaban than for LMWH. Moreover, there was no data available on leisure activity losses
10 379 caused by the occurrence of a VTE event in patients who are already burdened with cancer. Therefore,
11 380 the indirect costs might have been underestimated, possibly leading to lower cost savings results. The
12 381 indirect costs account for €160 to €185 per patient over five years—approximately 3-5% of the total
13 382 cost—however, they do not have a major influence on the differences between the two drugs (€23
14 383 and €2 for the five-year and 6-month time horizon, respectively). This suggests that, although the
15 384 indirect costs might have been underestimated, rivaroxaban is still likely to be cost-saving compared
16 385 to LMWH.

17 386 The main driver of the cost savings is the difference in treatment costs. In the cost-
18 387 effectiveness analysis, we estimated that more than €1,500 per patient over a five-year period can be
19 388 saved on treatment costs, compared to LMWH. We conservatively assumed no additional costs for
20 389 training or assistance for administration of the LMWH injection. Moreover, in the scenario analysis we
21 390 varied the price of dalteparin based on weight. Although the lowest dose (12,500 IU daily during month
22 391 one followed by 10,000 IU in months two to six based on weight class 57–68 kg) had a lower price,
23 392 €8.06 versus €9.93, the ICER remained cost-saving. Based on this same weight class, only LMWH
24 393 nadroparin has a lower price compared to dalteparin. However, since the lower dose of dalteparin is
25 394 still highly cost-saving, it is expected that compared to LMWHs other than dalteparin, rivaroxaban will
26 395 also be a cost-saving alternative [22].

27 396 In the budget impact analysis, we calculated that rivaroxaban replacing LMWH leads to cost
28 397 savings of a maximum of €9,991,357 within one year over a total of 8,000 cancer patients. This is the
29 398 absolute maximum, since it is not possible to treat each patient with rivaroxaban from a clinical
30 399 perspective. In practice, the market share of rivaroxaban will be lower—despite the fact that there are
31 400 three other DOACs that could be prescribed—because there are some clinical considerations that
32 401 should be taken into account. Firstly, although DOACs have far fewer drug interactions than VKAs, it
33 402 should be noted that rivaroxaban is metabolized by CYP3A4 enzymes [1]. Cancer patients, especially
34 403 those with haematological cancer, are at high risk for opportunistic and fungal infections, for which
35 404 they are often treated with CYP3A4 inhibitors or inducers [31]. For this reason, prescription of
36 405 rivaroxaban for the prevention of recurrent VTE in cancer patients must be done carefully [1]. This
37 406 interaction does not play a role in LWMH treatment.

38 407 Secondly, the balance between the risk of thrombosis and the risk of bleeding should always
39 408 be a consideration in the prescription of anticoagulants. For example, DOACs are not advised in
40 409 patients with GI tumours, due to a higher risk of GI bleeding; for this reason they were not included in
41 410 the SELECT-D trial [14]. Some prediction scores for primary prevention have been developed to predict
42 411 thrombosis risk in cancer patients, since thrombosis prophylaxis is most effective in patients with an
43 412 increased VTE risk. Unfortunately, for cancer these scores have still not been shown to reliably identify
44 413 patients with the highest risk [32]. Predictive scores for bleeding, such as the HAS-BLED score used for
45 414 atrial fibrillation patients, are also needed.

46 415 A third consideration is the oral administration of rivaroxaban. Although it is less burdensome
47 416 than the LMWH injections, oral administration can be problematic in patients with anorexia and

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3 417 vomiting, which is often seen as a side effect in cancer therapy [14]. Moreover, low food intake might
4 418 influence the metabolism of rivaroxaban resulting in lower bioavailability [33]. Lastly, adherence is
5 419 always a point of discussion, but since adherence to current guidelines is often low [32], we feel that
6 420 adherence might even increase due to the more patient-friendly administration.

7 421 As with all cost-effectiveness models some assumptions need to be made due to lack of data.
8 422 We assumed that patients were treated with anticoagulation over six months, which is in line with the
9 423 guidelines of the Dutch Internist Society (NIV) [7]. Previous studies have shown that adherence to these
10 424 guidelines is poor [32]. As seen in the study by Streiff et al, in practice, treatment with LMWH is often
11 425 not six months, presumably due to the fact that LMWH injections are burdensome, there are concerns
12 426 about the bleeding risk, and the complexity of the treatment of cancer patients [32]. However, this
13 427 recommended treatment period was also not achieved in many patients treated with rivaroxaban,
14 428 which resulted in an average duration of three months. We conducted a scenario analysis (scenario 5)
15 429 to assess this difference in treatment duration. Incremental QALYs increased while still being cost-
16 430 saving. On the other hand, there are some clinical situations in which the treatment period might be
17 431 longer than six months: for example, in patients with a recurrent VTE event, patients with an active
18 432 malignancy, or patients receiving treatment for their malignancy for over more than six months.
19 433 Moreover, in the Netherlands anticoagulation is often continued after six months of initial treatment
20 434 in case the cancer is still active. Unfortunately, we were unable to assess the effect of continued
21 435 anticoagulation treatment due to lack of data. However, since rivaroxaban is associated with cost-
22 436 saving results during the first six months, it is to be expected that during a longer treatment period the
23 437 savings and health gains will increase even more compared to LMWH.

24 438 In the univariate sensitivity analysis we have shown that the risk of MB and VTE for both
25 439 rivaroxaban and LMWH have a high influence on the incremental costs and QALYs. In the SELECT-D
26 440 trial [14], the incidence of symptomatic and fatal PE events was relatively higher in patients treated
27 441 with rivaroxaban. However, due to low numbers of VTE observed in the SELECT-D trial [14], we
28 442 calculated the distribution of the type of VTE based on the total number of events and assumed it to
29 443 be equal for both drugs. This may have led to an overestimation of the effect of rivaroxaban compared
30 444 to LMWH, since symptomatic and fatal PE events have a higher impact on the costs and the patient's
31 445 health compared to DVT and incidental PE. On the other hand, we used this same approach to calculate
32 446 the distributions of the types of MB from the HOKUSAI VTE Cancer trial [19], in which the patients
33 447 treated with LMWH had relatively more severe MB events compared to the NOAC (ICH: 17.6% versus
34 448 6.1%, respectively). This results in an overestimation of the safety of LMWH. We assessed the effect of
35 449 using drug-specific distributions of the type of VTE and MB in scenario six, showing an increase in
36 450 incremental cost savings and QALYs compared to the base case analysis. Therefore, we conclude that
37 451 our approach of using equal distributions of the types of VTE and MB for rivaroxaban and LMWH is
38 452 conservative.

39 453 This study focuses on the secondary prevention of VTE, based on the results of the SELECT-D
40 454 and, partially, the HOKUSAI VTE Cancer trials. However, the AVERT and CASSINI trials have recently
41 455 shown that apixaban and rivaroxaban are also effective as a primary prophylaxis of VTE in cancer
42 456 patients compared to a placebo [34–36]. Based on these two studies, clinicians may consider DOAC
43 457 prophylaxis in some of their cancer patients [36]. Therefore, future research is needed to assess if
44 458 DOACs are also cost-effective for the primary prevention of VTE.

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461 Conclusion

462 Treatment with rivaroxaban is dominant (cost-saving while slightly increasing the patient's
463 health) over LMWH in cancer patients at risk for recurrent VTE in the Netherlands. The use of
464 rivaroxaban instead of LMWH can save almost ten million euros per year, which is primarily driven by
465 the difference in drug costs. Since treatment with rivaroxaban is cost-saving and less invasive, we feel
466 that many cancer patients can benefit from DOAC treatment. However, with DOAC treatment
467 interactions, oral administration and adherence should be kept in mind.

470 References

- 471 1. Gerotziapas GT, Mahé I, Elalamy I. Therapeutics and Clinical Risk Management Dovepress New
472 orally active anticoagulant agents for the prevention and treatment of venous
473 thromboembolism in cancer patients. *Ther Clin Risk Manag.* 2014;10:423–36.
- 474 2. Falanga A, Marchetti M, Vignoli A. Coagulation and cancer: biological and clinical aspects. *J*
475 *Thromb Haemost.* 2013;11(2):223–33.
- 476 3. Lechner D, Weltermann A. Chemotherapy-induced thrombosis: a role for microparticles and
477 tissue factor? *Semin Thromb Hemost.* 2008;34(2):199–203.
- 478 4. Mandala M, Falanga A, Roila F, ESMO Guidelines Working Group. Management of venous
479 thromboembolism (VTE) in cancer patients: ESMO Clinical Practice Guidelines. *Ann Oncol.*
480 2011;22(Supplement 6):vi85–92.
- 481 5. Cohen AT, Katholing A, Rietbrock S, Bamber L, Martinez C. Epidemiology of first and recurrent
482 venous thromboembolism in patients with active cancer. *Thromb Haemost.* 2017;117(01):57–
483 65.
- 484 6. Minister of Health W and S. Letter to the parlement - reimbursement rivaroxaban VTE
485 (Herbeoordeling uitbreiding nadere voorwaarden rivaroxaban (Xarelto®) bij VTE. 2015;
- 486 7. Dutch Internist Society (NIV). Guideline Antithrombotic policy [Internet]. Utrecht; 2015.
- 487 8. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic Therapy
488 for VTE Disease: CHEST Guideline and Expert Panel Report. *Chest.* 2016;149(2):315–52.
- 489 9. Lyman GH, Bohlke K, Khorana AA, Kuderer NM, Lee AY, Arcelus JI, et al. Venous
490 Thromboembolism Prophylaxis and Treatment in Patients With Cancer: American Society of
491 Clinical Oncology Clinical Practice Guideline Update 2014. *J Clin Oncol.* 2015;33(6):654–6.
- 492 10. Hull RD, Pineo GF, Brant RF, Mah AF, Burke N, Dear R, et al. Long-term low-molecular-weight
493 heparin versus usual care in proximal-vein thrombosis patients with cancer. *Am J Med.* 2006
494 Dec;119(12):1062–72.
- 495 11. Lee AYY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M, et al. Low-Molecular-Weight
496 Heparin versus a Coumarin for the Prevention of Recurrent Venous Thromboembolism in
497 Patients with Cancer. *N Engl J Med.* 2003;349(2):146–53.
- 498 12. Meyer G, Marjanovic Z, Valcke J, Lorcerie B, Gruel Y, Solal-Celigny P, et al. Comparison of low-
499 molecular-weight heparin and warfarin for the secondary prevention of venous
500 thromboembolism in patients with cancer: a randomized controlled study. *Arch Intern Med.*
501 162(15):1729–35.
- 502 13. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, et al. The 2018 European
503 Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral
504 anticoagulants in patients with atrial fibrillation. *Eur Heart J.* 2018;
- 505 14. Young AM, Marshall A, Thirlwall J, Chapman O, Lokare A, Hill C, et al. Comparison of an Oral
506 Factor Xa Inhibitor With Low Molecular Weight Heparin in Patients With Cancer With Venous
507 Thromboembolism: Results of a Randomized Trial (SELECT-D). *J Clin Oncol.* 2018;36(20):2017–
508 23.

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3 509 15. Streiff MB, Milentijevic D, McCrae K, Yannicelli D, Fortier J, Nelson WW, et al. Effectiveness and
4 510 safety of anticoagulants for the treatment of venous thromboembolism in patients with cancer.
5 511 *Am J Hematol.* 2018;93(5):664–71.
6 512 16. Hakkaart-van Roijen L, van der Linden N, Bouwmans C, Kanters T, Swan Tan S.
7 513 *Kostenhandleiding: Methodologie van kostenonderzoek en referentieprijzen voor*
8 514 *economische evaluaties in de gezondheidszorg.* Zorginstituut Ned. 2016;1–120.
9 515 17. National Institute of Public Health and the Environment (RIVM). *Cancer numbers and context:*
10 516 *current situation [Internet].* volksgezondheidenzorg.info. 2017. p. 1.
11 517 18. Briggs A, Claxton K, Sculpher M. *Decision modelling for Health Economic Evaluation.* 3rd ed.
12 518 New York: Oxford University Press; 2011. 57–58 p.
13 519 19. Raskob GE, van Es N, Verhamme P, Carrier M, Di Nisio M, Garcia D, et al. Edoxaban for the
14 520 Treatment of Cancer-Associated Venous Thromboembolism. *N Engl J Med.* 2018;378(7):615–
15 521 24.
16 522 20. The Netherlands Cancer Registry. *Survival statistics - all tumours 1961-2015 [Internet].*
17 523 21. Heisen M, Treur MJ, Heemstra HE, Giesen EBW, Postma MJ. Cost-effectiveness analysis of
18 524 rivaroxaban for treatment and secondary prevention of venous thromboembolism in the
19 525 Netherlands. *J Med Econ.* 2017 Aug 3;20(8):813–24.
20 526 22. *Medicijnkosten.nl.* The National Health Care Institute (ZIN) [Internet].
21 527 23. *Summary of Product Characteristics Fragmin.* 2015;
22 528 24. Dutch Statistics. *Length and weight of Dutch population [Internet].* 2017.
23 529 25. de Klerk M, de Boer A, Plaisier I, Schyns P, Kooiker S. *Informele hulp: wie doet er wat? - Rapport*
24 530 *- SCP [Internet].* 2015-35. 2015.
25 531 26. Lloyd AJ, Dewilde S, Noble S, Reimer E, Lee AYY. What Impact Does Venous Thromboembolism
26 532 and Bleeding Have on Cancer Patients' Quality of Life? *Value Heal.* 2018;21(4):449–55.
27 533 27. Roman A, Barbera JA, Castillo MJ, Muñoz R, Escribano P. Health-related quality of life in a
28 534 national cohort of patients with pulmonary arterial hypertension or chronic thromboembolic
29 535 pulmonary hypertension. *Arch Bronconeumol.* 2013;49(5):181–8.
30 536 28. Stevanović J, de Jong LA, Kappelhoff BS, Dvortsin EP, Voorhaar M, Postma MJ. Dabigatran for
31 537 the Treatment and Secondary Prevention of Venous Thromboembolism; A Cost-Effectiveness
32 538 Analysis for the Netherlands. *PLoS One.* 2016;11(10):e0163550.
33 539 29. The Netherlands Cancer Registry. *Prevalence statistics - all tumours [Internet].*
34 540 30. Walker AJ, Card TR, West J, Crooks C, Grainge MJ. Incidence of venous thromboembolism in
35 541 patients with cancer - a cohort study using linked United Kingdom databases. *Eur J Cancer.* 2013
36 542 Apr;49(6):1404–13.
37 543 31. Vedham V, Divi RL, Starks VL, Verma M. Multiple Infections and Cancer: Implications in
38 544 Epidemiology. *Technol Cancer Res Treat.* 2014;13(2):177–94.
39 545 32. Mahé I, Chidiac J, Helfer H, Noble S. Factors influencing adherence to clinical guidelines in the
40 546 management of cancer-associated thrombosis. *J Thromb Haemost.* 2016;14(11):2107–13.
41 547 33. Committee for Medicinal Products for Human Use (CHMP). *Summary of product characteristics*
42 548 *- rivaroxaban 20 mg [Internet].*
43 549 34. Khorana AA, Soff GA, Kakkar AK, Vadhan-Raj S, Riess H, Wun T, et al. Rivaroxaban for
44 550 Thromboprophylaxis in High-Risk Ambulatory Patients with Cancer. *N Engl J Med.* 2019
45 551 Feb;380(8):720–8.
46 552 35. Carrier M, Abou-Nassar K, Mallick R, Tagalakis V, Shivakumar S, Schattner A, et al. Apixaban to
47 553 Prevent Venous Thromboembolism in Patients with Cancer. *N Engl J Med.* 2019;380(8):711–9.
48 554 36. Agnelli G. Direct Oral Anticoagulants for Thromboprophylaxis in Ambulatory Patients with
49 555 Cancer. *N Engl J Med.* 2019;380(8):781–3.
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Author contributions

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3 559 Lisa A. de Jong built the economic model, performed the analyses, and contributed to the design of
4 560 the work, interpretation of the results, writing of the manuscript.
5 561 Annette W.G. van der Velden contributed to the interpretation of the results, writing of the
6 562 manuscript, and critical revision for important intellectual content.
7 563 Marinus van Hulst contributed to the design of the work, interpretation of the results, writing of the
8 564 manuscript, and critical revision for important intellectual content.
9 565 Maarten J. Postma contributed to the design of the work, interpretation of the results, writing of the
10 566 manuscript, and critical revision for important intellectual content.
11 567 All authors approved of the version to be published.
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16 569 **Checklist for the appropriate reporting statement:** This manuscript was written in accordance with
17 570 the CHEERS checklist for reporting economic evaluations of health interventions.
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20 572 **Data sharing statement:** All relevant data are included in the manuscript. The analyses were
21 573 conducted based on publicly available information which is presented and referenced in the
22 574 manuscript.
23
24

25 576 **Word count:** 4,508 (excluding table and figure descriptions and references)
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27

28 578 **Patient consent and ethical approval:** The analyses were conducted based on publicly available
29 579 information which is presented and referenced in the article and Supporting Information files, and did
30 580 therefore not require any patient consent forms or approval from an ethical review board.
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33 582 **Patient and public involvement statement:** It was not appropriate to involve patients or the public in
34 583 the design, or conduct, or reporting, or dissemination plans of our research, because this health
35 584 economic analysis was based on publicly available data and solely concentrated on the analysis of the
36 585 economics consequence of treating cancer patients with rivaroxaban instead of the current standard
37 586 of care.
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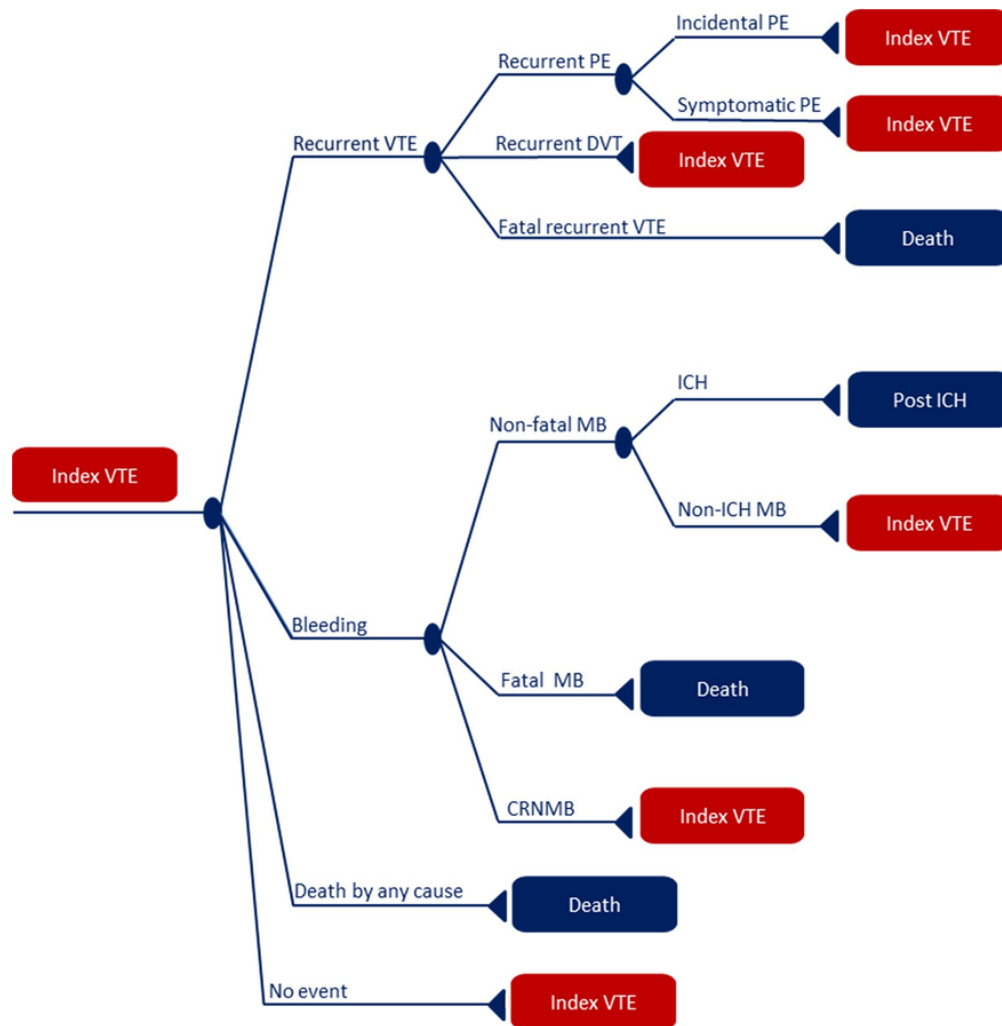
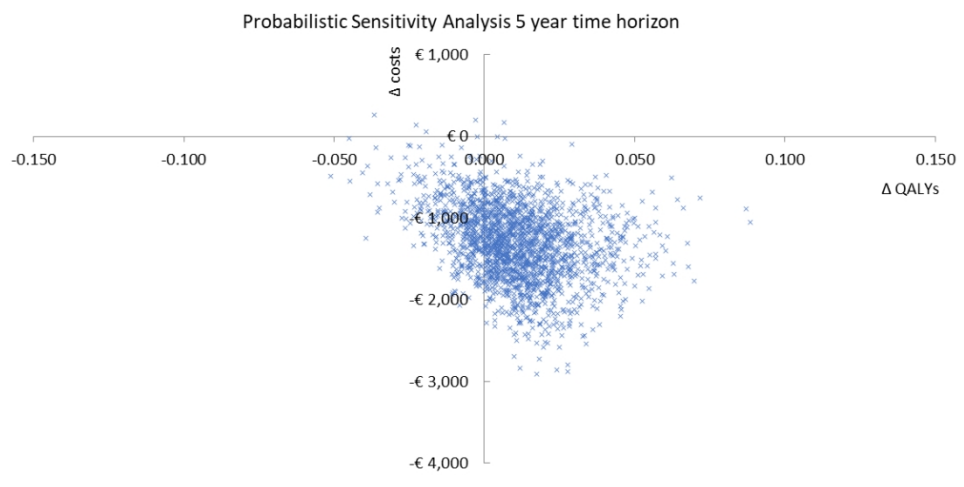


Figure 1. Model outline. All patients enter the model in the 'Index VTE' state and move to other states upon the occurrence of one of the following events: recurrent incidental PE, recurrent symptomatic PE, fatal recurrent VTE, recurrent DVT, ICH, non-ICH MB, fatal MB, CRNMB, or death by any cause. The triangles represent the health state a patient will enter after an event. The blue squares are permanent states, in which a patient will remain until death while not being at risk for other events. The red squares represent a transient state: the patient will re-enter the model in the 'Index VTE' state.

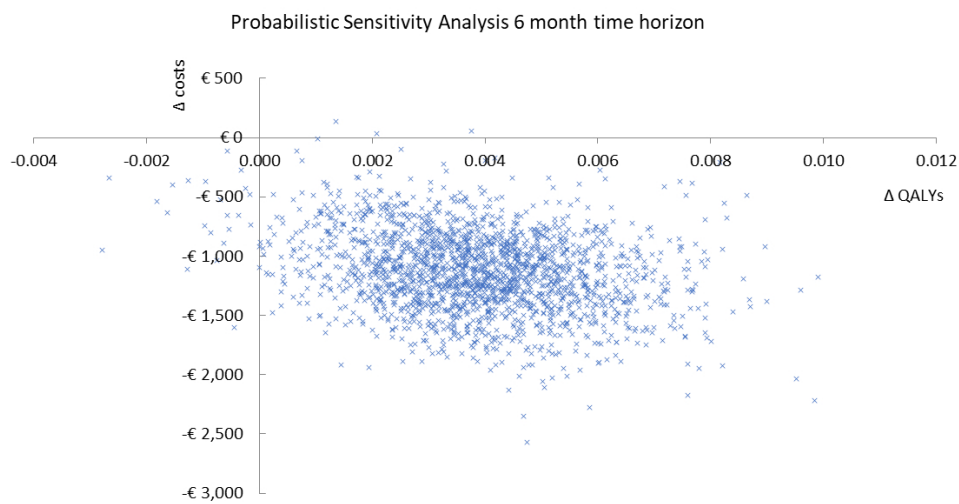
Abbreviations: CRNMB, clinically relevant non-major bleeding; DVT, deep vein thrombosis; ICH, intracranial haemorrhage; MB, major bleeding; PE, pulmonary embolism; VTE, venous thromboembolism

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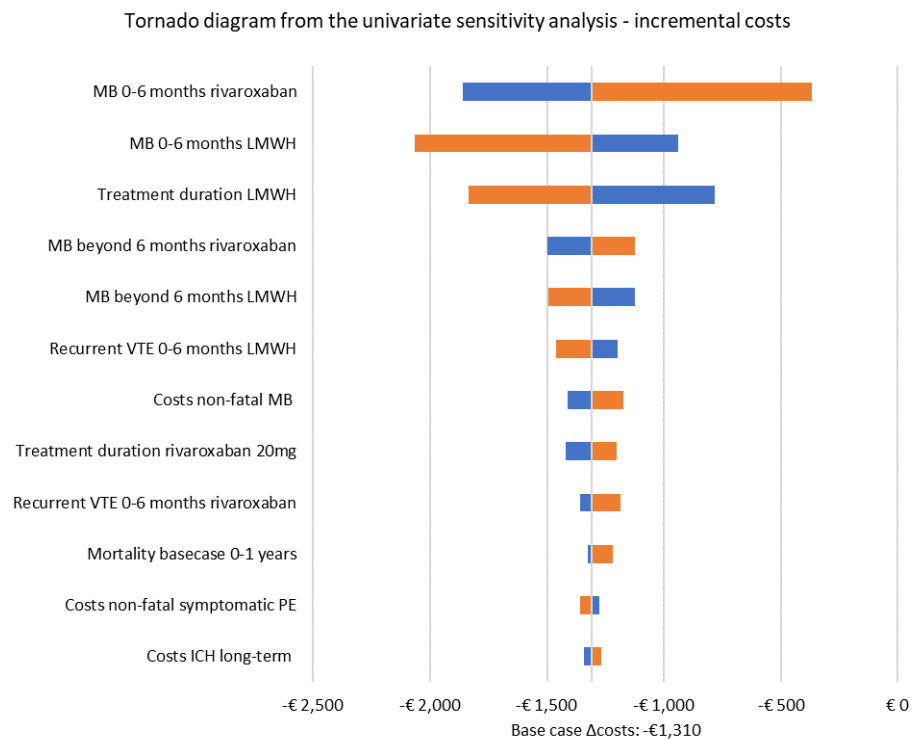


Probabilistic sensitivity analysis of the base case with five year time horizon (base case analysis).
Abbreviation: QALY, quality adjusted life-year

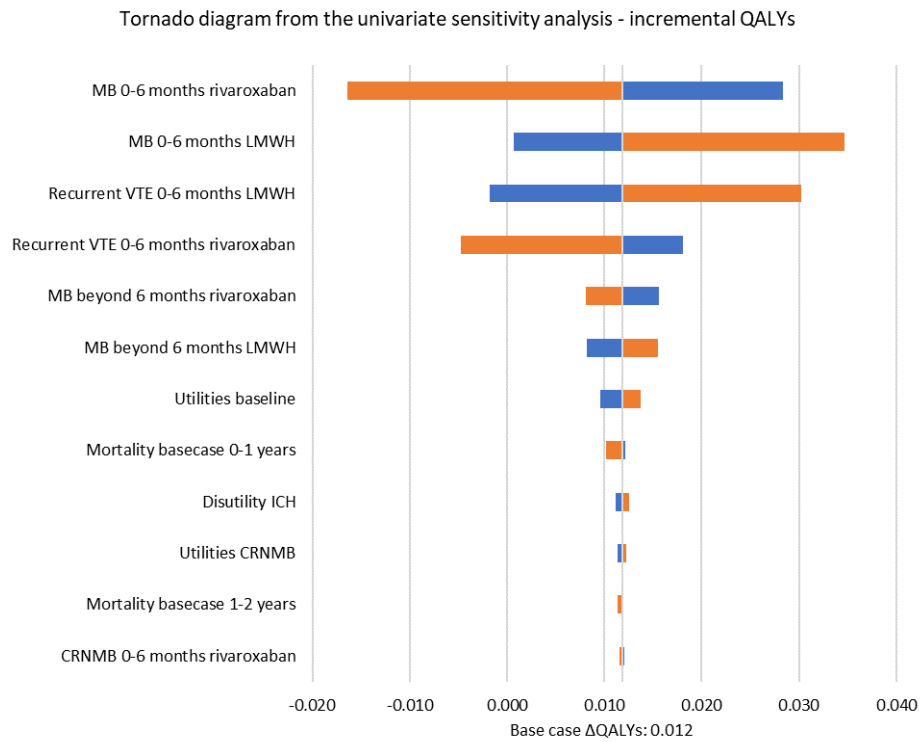


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24 Probabilistic sensitivity analysis with six month time horizon (scenario 4). Abbreviation: QALY, quality
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Tornado diagram from the univariate sensitivity analysis for the base case analysis showing the impact of parameters on the incremental costs. Abbreviations: ICH, intracranial haemorrhage; LMWH, low molecular weight heparin; MB, major bleeding; PE, pulmonary embolism; VTE, venous thromboembolism



Tornado diagram from the univariate sensitivity analysis for the base case analysis showing the impact of parameters on the incremental QALYs. Abbreviations: CRNMB, clinically relevant non-major bleeding; ICH, intracranial haemorrhage; LMWH, low molecular weight heparin; MB, major bleeding; VTE, venous thromboembolism

Supplementary data file – Table S1

Manuscript title: Cost-effectiveness analysis and budget impact of rivaroxaban in cancer patients at risk of recurrent venous thromboembolism

Table S1. Transition probabilities used in the cost-effectiveness model

	Rivaroxaban (95% CI)	LMWH (95% CI)	Distribution	Reference
Recurrent VTE				
0–6 months	0.040 (0.020 – 0.090)	0.110 (0.070 – 0.160)	Beta	[1]
6–12 months	0.040 (0.031 – 0.050)		Beta	[2]
1–2 years	0.034 (0.027 – 0.042)		Beta	[2]
2–3 years	0.021 (0.014 – 0.029)		Beta	[2]
3–4 years	0.016 (0.009 – 0.026)		Beta	[2]
4–5 months	0.013 (0.006 – 0.024)		Beta	[2]
Type of recurrent VTE				
Symptomatic PE	17.4% ($\alpha = 4, \beta = 19$)		Dirichlet	[1]
Incidental PE	30.4% ($\alpha = 7, \beta = 16$)		Dirichlet	[1]
DVT	43.5% ($\alpha = 10, \beta = 13$)		Dirichlet	[1]
Fatal PE	8.7% ($\alpha = 2, \beta = 21$)		Dirichlet	[1]
MB				
0–6 months	0.060 (0.030 – 0.110)	0.040 (0.020 – 0.080)	Beta	[1]
Beyond 6 months treatment	0.008 (0.006 – 0.010)		Beta	[3]
Type of MB				
ICH	10% ($\alpha = 5, \beta = 45$)		Dirichlet	[3]
Non-ICH MB	86% ($\alpha = 43, \beta = 7$)		Dirichlet	[3]
Fatal MB	4% ($\alpha = 2, \beta = 48$)		Dirichlet	[3]
CRNMB				
0–6 months	0.130 (0.090 – 0.190)	0.040 (0.020 – 0.090)	Beta	[1]
Beyond 6 months treatment	0.008 (0.006 – 0.010)		Beta	[3]
PTS				
0–6 months	0.015 (0.011 – 0.019)		Beta	[4]
6–12 months	0.012 (0.009 – 0.015)		Beta	[4]
12–18 months	0.008 (0.006 – 0.010)		Beta	[4]
18–24 months	0.025 (0.023 – 0.019)		Beta	[4]
24–30 months	0.011 (0.008 – 0.014)		Beta	[4]
30–36 months	0.006 (0.005 – 0.008)		Beta	[4]
3–4 years	0.001 (0.0008 – 0.0013)		Beta	[4]
4–5 years	0.001 (0.0008 – 0.0013)		Beta	[4]
CTEPH (annual risk)	0.0057 (0.0002 – 0.012)		Beta	[5]
Mortality (annual risk)				
0–1 years	0.230 (0.200 – 0.390)		Beta	[6]
1–2 years	0.104 (0.088 – 0.180)		Beta	[6]
2–3 years	0.058 (0.055 – 0.120)		Beta	[6]
3–4 years	0.046 (0.043 – 0.068)		Beta	[6]
4–5 years	0.032 (0.030 – 0.073)		Beta	[6]
Relative risk of recurrent VTE, MB, and CRNMB for LMWH versus placebo, used in scenario 5				
Recurrent VTE (any)	5.170		Fixed	[7]
MB	0.242		Fixed	[7]

<i>CRNMB</i>	1.000		Fixed	[7]
Drug-specific distribution of the type of VTE, used in scenario 6				
<i>Symptomatic PE</i>	28.6% ($\alpha = 2, \beta = 5$)	12.5% ($\alpha = 2, \beta = 14$)	Dirichlet	[1]
<i>Incidental PE</i>	14.3% ($\alpha = 1, \beta = 6$)	37.5% ($\alpha = 6, \beta = 10$)	Dirichlet	[1]
<i>DVT</i>	42.9% ($\alpha = 3, \beta = 4$)	43.8% ($\alpha = 7, \beta = 9$)	Dirichlet	[1]
<i>Fatal PE</i>	14.3% ($\alpha = 1, \beta = 6$)	6.3% ($\alpha = 1, \beta = 15$)	Dirichlet	[1]
Drug-specific distribution of the type of MB, used in scenario 6				
<i>ICH</i>	6.1% ($\alpha = 2, \beta = 31$)	17.6% ($\alpha = 3, \beta = 14$)	Dirichlet	[3]
<i>Non-ICH MB</i>	93.9% ($\alpha = 31, \beta = 2$)	70.6% ($\alpha = 12, \beta = 5$)	Dirichlet	[3]
<i>Fatal MB</i>	0% ($\alpha = 0, \beta = 33$)	11.8% ($\alpha = 2, \beta = 15$)	Dirichlet	[3]

Abbreviations: *CI*, confidence interval; *CRNMB*, clinically relevant non-major bleeding; *CTEPH*, chronic thromboembolic pulmonary hypertension; *DVT*, deep vein thrombosis; *ICH*, intracranial haemorrhage; *LMWH*, low-molecular weight heparin; *MB*, major bleeding; *PE*, pulmonary embolism; *PTS*, post-thrombotic syndrome; *SE*, standard error; *VTE*, venous thromboembolism

References

1. Young AM, Marshall A, Thirlwall J, Chapman O, Lokare A, Hill C, et al. Comparison of an Oral Factor Xa Inhibitor With Low Molecular Weight Heparin in Patients With Cancer With Venous Thromboembolism: Results of a Randomized Trial (SELECT-D). *J Clin Oncol*. 2018;36(20):2017–23.
2. Cohen AT, Katholing A, Rietbrock S, Bamber L, Martinez C. Epidemiology of first and recurrent venous thromboembolism in patients with active cancer. *Thromb Haemost*. 2017;117(01):57–65.
3. Raskob GE, van Es N, Verhamme P, Carrier M, Di Nisio M, Garcia D, et al. Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism. *N Engl J Med*. 2018;378(7):615–24.
4. 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(4):423–8.
5. Klok FA, van Kralingen KW, van Dijk APJ, Heyning FH, Vliegen HW, Huisman M V. Prospective cardiopulmonary screening program to detect chronic thromboembolic pulmonary hypertension in patients after acute pulmonary embolism. *Haematologica*. 2010;95(6):970–5.
6. The Netherlands Cancer Registry. Survival statistics - all tumours 1961-2015 [Internet].
7. Napolitano M, Saccullo G, Malato A, Sprini D, Ageno W, Imberti D, et al. Optimal duration of low molecular weight heparin for the treatment of cancer-related deep vein thrombosis: the Cancer-DACUS Study. *J Clin Oncol*. 2014;32(32):3607–12.

Supplementary data file – Table S2

Manuscript title: Cost-effectiveness analysis and budget impact of rivaroxaban in cancer patients at risk of recurrent venous thromboembolism

Table S2. Costs included in the cost-effectiveness model (Euros, 2019)

	Value (95% CI)	Distribution	Reference
Event costs			
Recurrent VTE			
Symptomatic PE	€4,717 (€2,364 – €7,868)	Gamma	[1]
Incidental PE	€0	Fixed	Assumption
DVT	€663 (€464 – €862)	Gamma	[1]
Fatal recurrent VTE ^a	€4,717 (€2,364 – €7,868)	Gamma	[1]
ICH acute care costs	€22,769 (€11,644 – €31,175)	Gamma	[2]
ICH long-term costs (monthly)	€637 (€319 – €1,063)	Gamma	[1]
Non-ICH MB	€10,685 (€5,356 – €17,824)	Gamma	[1]
Fatal MB	€10,685 (€5,356 – €17,824)	Gamma	[1]
CRNMB	€274 (€137 – €457)	Gamma	[1]
PTS	€1,431 (€717 – €2,387)	Gamma	[1]
CTEPH acute care costs	€7,843 (€3,931 – €16,433)	Gamma	[1]
CTEPH long-term costs (monthly)	€89 (€45 – €149)	Gamma	[1]
Treatment costs			
Drug cost (daily)			
<i>LMWH</i> ^b	€9.93	Fixed	[3]
<i>Rivaroxaban 15 mg</i>	€4.58	Fixed	[3]
<i>Rivaroxaban 20 mg</i>	€2.29	Fixed	[3]
Treatment duration (days)			
<i>LMWH</i>	183 (137 – 228)	Gamma	[4]
<i>Rivaroxaban 15 mg</i>	21 (16 – 26)	Gamma	[4]
<i>Rivaroxaban 20 mg</i>	162 (121 – 202)	Gamma	[4]
Renal monitoring ^c	€1.64 (€1.23 – €2.05)	Gamma	[5]
Indirect costs			
Travel costs			
<i>Cost per km</i>	€0.20 (€0.15 – €0.25)	Gamma	[6]
<i>Distance to hospital (km)</i>	7	Fixed	[6]
<i>Distance to GP (km)</i>	1.1	Fixed	[6]
Informal care costs			
<i>PE</i>	€1,515 (€1,136 – €1,894)	Gamma	[7,8]
<i>DVT</i>	€233 (€175 – €291)	Gamma	[7,8]
<i>ICH (acute informal care costs)</i>	€1,515 (€1,136 – €1,894)	Gamma	[7,8]
<i>ICH (long-term informal care costs, monthly)</i>	€626 (€470 – €783)	Gamma	[9]
<i>Non-ICH MB</i>	€758 (€568 – €947)	Gamma	[7,8]
<i>CRNMB</i>	€117 (€87 – €146)	Gamma	[7,8]

Abbreviations: CI, confidence interval; CRNMB, clinically relevant non-major bleeding; CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; GP, general practitioner; ICH, intracranial haemorrhage; LMWH, low-molecular weight heparin; MB, major bleeding; PE, pulmonary embolism; PTS, post-thrombotic syndrome; VTE, venous thromboembolism

^a Assumed to be equal to the costs of non-fatal PE

^b Based on an average weight between 69 and 82 kg.

^c Based on DRG code 070419 and only taken into account for rivaroxaban treated patients

References

1. Heisen M, Treur MJ, Heemstra HE, Giesen EBW, Postma MJ. Cost-effectiveness analysis of rivaroxaban for treatment and secondary prevention of venous thromboembolism in the Netherlands. *J Med Econ.* 2017 Aug 3;20(8):813–24.
2. Baeten S a, van Exel NJ a, Dirks M, Koopmanschap M a, Dippel DW, Niessen LW. Lifetime health effects and medical costs of integrated stroke services - a non-randomized controlled cluster-trial based life table approach. *Cost Eff Resour Alloc.* 2010;8(1):21.
3. Medicijnkosten.nl. The National Health Care Institute (ZIN) [Internet].
4. Young AM, Marshall A, Thirlwall J, Chapman O, Lokare A, Hill C, et al. Comparison of an Oral Factor Xa Inhibitor With Low Molecular Weight Heparin in Patients With Cancer With Venous Thromboembolism: Results of a Randomized Trial (SELECT-D). *J Clin Oncol.* 2018;36(20):2017–23.
5. Dutch Health Authorities. NZa zorgproductapplicatie. Declaration code: 070419. [Internet]. 2018.
6. Roijen LH, Linden N van der, Bouwmans C, Kanters T, Tan SS. Dutch manual for costing studies in health care. Diemen; 2015.
7. Hakkaart-van Roijen L, van der Linden N, Bouwmans C, Kanters T, Swan Tan S. Kostenhandleiding: Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg. Zorginstituut Ned. 2016;1–120.
8. de Klerk M, de Boer A, Plaisier I, Schyns P, Kooiker S. Informele hulp: wie doet er wat? - Rapport - SCP [Internet]. 2015-35. 2015.
9. van den Berg B, Brouwer W, van Exel J, Koopmanschap M, van den Bos GAM, Rutten F. Economic valuation of informal care: lessons from the application of the opportunity costs and proxy good methods. *Soc Sci Med.* 2006;62(4):835–45.

Supplementary data file – Table S3

Manuscript title: Cost-effectiveness analysis and budget impact of rivaroxaban in cancer patients at risk of recurrent venous thromboembolism

Table S3. Utility values included in the cost-effectiveness model

	Value (95% CI)	Distribution	Reference
Utilities			
Index VTE			
0–1 month	0.565 (0.501 – 0.620)	Beta	[1]
1–2 months	0.655 (0.585 – 0.713)	Beta	[1]
2–3 months	0.674 (0.606 – 0.729)	Beta	[1]
3–4 months	0.698 (0.635 – 0.750)	Beta	[1]
4–5 months	0.707 (0.645 – 0.758)	Beta	[1]
5–6 months	0.709 (0.647 – 0.760)	Beta	[1]
Baseline utility 6 months after index VTE	0.715 (0.646 – 0.770)	Beta	[1]
Recurrent VTE			
DVT	0.605 (0.514 – 0.678)	Beta	[1]
Non-fatal symptomatic PE	0.621 (0.477 – 0.725)	Beta	[1]
Non-fatal incidental PE	0.664 (0.615 – 0.707)	Beta	[1]
Fatal PE	0.456 (0.268 – 0.595)	Beta	[1]
Non-ICH MB	0.593 (0.461 – 0.693)	Beta	[1]
CRNMB	0.622 (0.568 – 0.669)	Beta	[1]
Utility decrements			
Recurrent VTE within first six months after index VTE			
DVT	0.040 (0.000 – 0.158)	Beta	[1]
Symptomatic PE	0.024 (0.000 – 0.195)	Beta	[1]
Incidental PE	0.189 (0.021 – 0.404)	Beta	[1]
ICH	0.380 (0.285 – 0.475)	Beta	[2]
Severe PTS (<6 months after diagnosis)	0.186 (0.090 – 0.280)	Beta	[1]
Severe PTS (>6 months after diagnosis)	0.070 (0.053 – 0.088)	Beta	[2]
CTEPH			
0-1 year	0.194 (0.071 – 0.303)	Beta	[3]
1–4 years	0.109 (0.000 – 0.244)	Beta	[3]
4–7 years	0.079 (0.000 – 0.277)	Beta	[3]
>7 years	0.065 (0.000 – 0.164)	Beta	[3]

Abbreviations: CI, confidence interval; CRNMB, clinically relevant non-major bleeding; CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; ICH, intracranial haemorrhage; MB, major bleeding; PE, pulmonary embolism; PTS, post-thrombotic syndrome; VTE, venous thromboembolism

References

- Lloyd AJ, Dewilde S, Noble S, Reimer E, Lee AYY. What Impact Does Venous Thromboembolism and Bleeding Have on Cancer Patients' Quality of Life? *Value Heal*. 2018;21(4):449–55.
- Stevanović J, de Jong LA, Kappelhoff BS, Dvortsin EP, Voorhaar M, Postma MJ. Dabigatran for the Treatment and Secondary Prevention of Venous Thromboembolism; A Cost-Effectiveness Analysis for the Netherlands. *PLoS One*. 2016;11(10):e0163550.
- Roman A, Barbera JA, Castillo MJ, Muñoz R, Escribano P. Health-related quality of life in a national cohort of patients with pulmonary arterial hypertension or chronic thromboembolic

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3 pulmonary hypertension. Arch Bronconeumol. 2013;49(5):181–8.
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CHEERS checklist—Items to include when reporting economic evaluations of health interventions

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as “cost-effectiveness analysis”, and describe the interventions compared.	Page 1, line 9-10
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Page 1, line 34-64
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	Page 4, line 91-120
		Present the study question and its relevance for health policy or practice decisions.	Page 4, line 121-126
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Page 5, line 149-151 Page 5, line 179
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Page 4, line 130-140
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Page 5, line 135-137
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Page 4, line 130-132
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Page 5, line 152-154
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Page 8, line 241 Page 9, line 264
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Page 4, line 133-140
Measurement of effectiveness	11a	<i>Single study-based estimates:</i> Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	
	11b	<i>Synthesis-based estimates:</i> Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	Page 6, line 184-210
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	
Estimating resources and costs	13a	<i>Single study-based economic evaluation:</i> Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
	13b	<i>Model-based economic evaluation:</i> Describe approaches and data sources used to estimate	Page 8, line 213-253

Section/item	Item No	Recommendation	Reported on page No/ line No
		resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Page 8, line 246
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Page 5, line 143-176
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Page 5, line 162-166 Page 8, line 230-240
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Page 7, line 190-201 Page 10, line 284-301
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Page 6, line 201-210 Page 8, line 241-253 Page 9, line 264-271 Page 10, line 276-278
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Page 11, line 320-323 Page 14, line 393-398
Characterising uncertainty	20a	<i>Single study-based economic evaluation:</i> Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	
	20b	<i>Model-based economic evaluation:</i> Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Page 13, line 354-389
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	Page 12, line 311-333
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Page 11, line 323-351
Other			

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Section/item	Item No	Recommendation	Reported on page No/ line No
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Page 3, line 79
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Page 3, line 81-84

For consistency, the CHEERS statement checklist format is based on the format of the CONSORT statement checklist

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BMJ Open

Cost-effectiveness analysis and budget impact of rivaroxaban compared with dalteparin in cancer patients at risk of recurrent venous thromboembolism

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Primary Subject Heading:	Health economics
Secondary Subject Heading:	Cardiovascular medicine, Health economics
Keywords:	Anticoagulation < HAEMATOLOGY, ONCOLOGY, Thromboembolism < CARDIOLOGY, HEALTH ECONOMICS

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3 1 Cost-effectiveness analysis and budget impact of rivaroxaban compared with dalteparin in cancer
4 2 patients at risk of recurrent venous thromboembolism

5 3
6 4 Short title: Economic evaluation of rivaroxaban in cancer patients

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33 31 **Author contributions:**

34 32 LA de Jong contributed to the design, interpretation of the data, modelling, drafting the manuscript
35 33 and revisions. M van Hulst, MJ Postma and AWG van der Velden contributed to the design,
36 34 interpretation of the data, validation of the model and drafting the manuscript.

Abstract

Objectives: We aim to calculate the cost-effectiveness and budget impact of rivaroxaban compared with dalteparin in cancer patients at risk of recurrent venous thromboembolism (VTE).

Setting: The analyses were performed for the Dutch healthcare setting. We built a Markov model to calculate the cost-effectiveness from a societal perspective over a five-year time horizon.

Participants: A hypothetical cohort of 1,000 cancer patients with VTE entered the model with baseline characteristics based on the SELECT-D trial.

Intervention: Six months treatment with rivaroxaban (15 mg twice daily for first three weeks followed by 20 mg once daily) was compared with six months treatment with dalteparin (200 IU/kg daily during month one followed by 150 IU/kg daily).

Primary and secondary outcome measures: The primary outcome of the cost-effectiveness analysis was the incremental cost-effectiveness ratio (ICER). The robustness of the model was evaluated in probabilistic and univariate sensitivity analyses. A budget impact analysis was performed to calculate the total annual financial consequences for the society.

Results: In the base case and all scenarios, rivaroxaban were cost-saving while also slightly improving the patient's health, resulting in economically dominant ICERs. In the probabilistic sensitivity analysis, 77.8% and 98.7% of the simulations showed rivaroxaban to be cost-saving and more effective for a five year and six-month time horizon, respectively. Rivaroxaban can save up to €11,326,763 (confidence interval: €5,164,254–€17,363,231) in approximately 8,000 cancer patients with VTE per year compared with dalteparin based on a one-year time horizon.

Conclusions: Treatment with rivaroxaban is economically dominant over dalteparin in cancer patients at risk for recurrent VTE in the Netherlands. The use of rivaroxaban instead of a LMWH can save up to ten million euros per year, primarily driven by the difference in drug costs.

Strengths and limitations of this study

- This analysis includes both cost-effectiveness and budget impact analyses, presenting the economic impact on a patient as well as on a population level.
- Markov tunnel states were used to model the occurrence of time-dependent events.
- Various additional scenarios were used to analyse the effect of different assumptions and clinical situations.
- We assumed a six-month treatment duration for all patients, while in clinical practice the treatment duration may vary between patients.
- Due to lack of data, the productivity losses were not taken into account.

Funding statement: This work was supported by Bayer Pharma Netherlands. The sponsor was involved with the start of the project, but they were not involved in the identification of data, design, conduct, and reporting of the analysis. Award/grant number: not applicable.

Competing interests: LA De Jong, M van Hulst and AWG van der Velden declare that they have no competing interest with relation to subject. Postma MJ has received research grants from various pharmaceutical companies, including but not limiting to Bayer, Pfizer, Bristol-Myers Squibb, GSK, Roche and Novartis.

77 Introduction

78 Venous thromboembolism (VTE), comprising both pulmonary embolism (PE) and deep vein
79 thrombosis (DVT), is a major challenge in patients with cancer [1]. In addition to the characteristics of
80 the cancer itself, cancer therapy (chemotherapy and cancer surgery) has effects on the patient's
81 coagulation system and therefore increases the risk of VTE and bleeding [2,3]. VTE in cancer patients
82 can cause unnecessary hospitalizations, interruption or postponement of cancer treatment, and
83 increased mortality, leading to decreased quality of life and increased costs.

84 VTE is treated with anticoagulation therapy, and this is continued as prophylaxis for recurrence
85 over a longer period because of the high risk of recurrence during the first months after the initial VTE
86 [4]. Vitamin K antagonists (VKAs) or direct oral anticoagulants (DOACs) are indicated for the treatment
87 and prevention of VTE in the general population [5]. DOACs, are a relatively new class of
88 anticoagulants. Apixaban, dabigatran, edoxaban and rivaroxaban are the four DOACs that are currently
89 registered for the prevention of recurrent VTE in Europe. DOACs have a more beneficial efficacy/safety
90 ratio, do not require routine measurements of the INR, and show fewer food-drug and drug-drug
91 interactions compared with VKAs [6,7].

92 The guidelines recommend against the use of VKAs in cancer patients because of potential
93 drug interactions, liver dysfunction, and malnutrition, all of which lead to fluctuations of the
94 international normalized ratio (INR) and could result in negative patient outcomes [8–11]. Moreover,
95 trials in cancer patients with VTE have shown that LMWH is more effective in the prevention of
96 recurrent VTE compared with VKA, without increasing bleeding risk [12–14]. Therefore, the guidelines
97 recommend at least 6 months of therapeutic treatment with a daily subcutaneous injection of low
98 molecular weight heparin (LMWH, e.g., dalteparin) in cancer patients [8–11]. However, recently,
99 DOACs rivaroxaban and edoxaban were also added as treatment options for the prevention of
100 recurrent VTE in cancer patients. This recommendation was based on the results from the SELECT-D
101 and HOKUSAI VTE Cancer trials [15,16].

102 The SELECT-D is a multicenter, randomized, clinical pilot trial in the UK; it is a head-to-head
103 comparison of rivaroxaban and dalteparin in 406 patients with active cancer who had experienced a
104 symptomatic PE, incidental PE, or symptomatic DVT [15]. Incidental PEs are non-symptomatic PEs that
105 are incidentally found during tumour imaging. The trial researchers found that rivaroxaban reduces
106 the recurrence of VTE (six month cumulative VTE recurrence rate: 4% versus 11%) at the cost of an
107 increased risk of bleeding (six month cumulative major bleeding [MB] rate: 6% versus 4%; six month
108 cumulative clinically relevant non-major bleeding [CRNMB] rate: 13% versus 4%) compared with
109 dalteparin. These results were comparable to those of a large retrospective study by Streiff et al. [17].

110 Based on the results of these studies and the fact that DOACs can be orally administered (unlike
111 the subcutaneously injected LMWHs), a greater utilisation of DOACs for VTE in cancer patients might
112 be expected. Since the introduction of DOACs there has been an ongoing discussion about the
113 economic impact of these drugs. By designing an economic model based on the SELECT-D trial, we aim
114 to evaluate the cost-effectiveness and budget impact of rivaroxaban compared with dalteparin in
115 cancer patients at risk of recurrent VTE in the Netherlands.

118 Methods

119 The economic model comparing rivaroxaban with dalteparin was designed based on the SELECT-D trial
120 [15], since this study presented the most comprehensive results reflecting recurrent VTE and bleeding

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3 121 complications per event type (symptomatic PE, incidental PE, and DVT) or severity (MB and CRNMB).
4 122 The primary outcome of the cost-effectiveness analysis is the incremental cost-effectiveness ratio
5 123 (ICER); this is calculated by dividing the incremental costs by the incremental health effects, expressed
6 124 in quality adjusted life-years (QALYs). In accordance with Dutch costing guidelines for economic
7 125 evaluations in healthcare, the ICER was calculated from a societal perspective, which incorporates
8 126 direct as well as indirect costs both inside and outside the healthcare sector[18]. We performed
9 127 sensitivity and scenario analyses to test the robustness of the model. Additionally, we conducted a
10 128 budget impact analysis to reflect the annual financial consequences of the use of rivaroxaban in cancer
11 129 patients at risk of recurrent VTE in the Netherlands. The analysis was carried out early 2019. The
12 130 analyses were conducted based on publicly available information which is presented and referenced
13 131 in the article and Supporting Information files, and did therefore not require any patient consent forms
14 132 or approval from an ethical review board.
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23 135 Model outline

24 136 We developed a decision-tree-based Markov model using Microsoft Excel 2016 to calculate the ICER.
25 137 Figure 1 shows a schematic representation of the model, with the disease course being represented
26 138 by separate health states. A hypothetical cohort of 1,000 cancer patients with VTE entered the model
27 139 with incidental PE, symptomatic PE, or DVT, represented by the 'index VTE' health state. According to
28 140 the guidelines, patients with incidental PE should be treated identically to those with symptomatic PE
29 141 [8,10]. Patient characteristics were based on the SELECT-D trial protocol (Table 1) [15]. The SELECT-D
30 142 population is representative for the Dutch cancer population, based on age, tumour type, and gender
31 143 distribution [19]. Patients move through various health states in the model during the follow-up time
32 144 of five years. Five years was used because overall survival was assumed to be low after five years since
33 145 the majority (58%) of the SELECT-D trial population had metastatic cancer [15]. We included the
34 146 following health states in our model (see legend of Figure 1 for abbreviations): 'recurrent incidental
35 147 PE', 'recurrent symptomatic PE', 'fatal recurrent VTE', 'recurrent DVT', 'ICH', 'non-ICH MB', 'fatal MB',
36 148 'CRNMB', 'death by any cause', and 'no event'. Patients were assumed to remain in these states for
37 149 one cycle, after which they moved back to the 'index VTE' state or the chronic, debilitating 'post-ICH'
38 150 state, in which they remained until death without being at risk for any further complications. The cycle
39 151 length was one month. Markov tunnel states (one-month post-VTE, two months post-VTE, ..., 60
40 152 months post VTE) were used to implement time-dependency. These temporary states can only be
41 153 visited once, which allows time-dependent future transitions, costs, and health-related quality of life
42 154 dependent on how long the patient has gone without a recurrent VTE event [20]. The chronic
43 155 complications post-thrombotic syndrome (PTS) and chronic thromboembolic pulmonary hypertension
44 156 (CTEPH) were modelled in the background. This means that PTS or CTEPH could occur at any time in
45 157 the model, regardless of the health state the patient is in. Costs and health effects of these events
46 158 were taken into account. However, only the severe cases of PTS were modelled, since the costs of
47 159 minor PTS are considered negligible. For these chronic complications we also used tunnel states since
48 160 the risks of PTS and CTEPH were also time-dependent.
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164 **Figure 1. Model outline.** All patients enter the model in the 'Index VTE' state and move to other states upon the occurrence
165 of one of the following events: recurrent incidental PE, recurrent symptomatic PE, fatal recurrent VTE, recurrent DVT, ICH,

166 non-ICH MB, fatal MB, CRNMB, or death by any cause. The triangles represent the health state a patient will enter after an
 167 event. The blue squares are permanent states, in which a patient will remain until death while not being at risk for other
 168 events. The red squares represent a transient state: the patient will re-enter the model in the 'Index VTE' state.
 169 *Abbreviations: CRNMB, clinically relevant non-major bleeding; DVT, deep vein thrombosis; ICH, intracranial haemorrhage;*
 170 *MB, major bleeding; PE, pulmonary embolism; VTE, venous thromboembolism*

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173 **Table 1. Patient characteristics of the hypothetical cohort of 1,000 cancer patients at risk of recurrent VTE.**

Unit	Value	Reference
Age (years)	67	[15]
Proportion male	53%	[15]
BMI (kg/m ²)	25.6	[15]
Type of cancer		
<i>Early or locally advanced cancer</i>	39%	[15]
<i>Metastatic cancer</i>	58%	[15]
<i>Haematologic malignancy</i>	2%	[15]
Distribution of PE and DVT		
<i>% index VTE that is symptomatic PE</i>	20%	[15]
<i>% index VTE that is incidental PE</i>	53%	[15]
<i>% index VTE that is DVT</i>	27%	[15]

174 *Abbreviations: BMI, body mass index; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism*

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177 Transition probabilities

178 Transition probabilities were used to calculate the number of patients in each health state per one-
 179 month cycle. Table S1 summarizes all event rates presented in six-month risks. The event rates were
 180 translated into monthly transition probabilities with the following formula:

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$$182 \quad P = 1 - \exp \{ -rt \}$$

183 Where P is the transition probability, r is the event rate, and t is the cycle length (one month) [20].

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185 Event rates of recurrent VTE, MB, and CRNMB in the first six months of treatment were based on the
 186 SELECT-D trial [15]. If patients did not experience a recurrent event during this period, anticoagulation
 187 treatment was discontinued. Recurrent VTE rates after treatment discontinuation were based on a
 188 retrospective study in active-cancer patients experiencing a VTE [4]. Upon the occurrence of a non-
 189 fatal recurrent VTE, patients were assigned to another six months treatment, with corresponding event
 190 rates. Bleeding risks after treatment discontinuation were based on the outcomes of the cancer
 191 population of the HOKUSAI VTE Cancer trial (which followed patients after edoxaban discontinuation
 192 for an additional six months) because these data is not reported for the SELECT-D trial [16]. The
 193 HOKUSAI VTE Cancer trial was also used to determine the distribution of ICH, non-ICH, and fatal
 194 bleeding. The distributions among the different types of VTE (incidental PE, symptomatic PE, DVT, and
 195 fatal PE) and MB (ICH, non-ICH, fatal MB) were calculated based on the total number of events in both
 196 arms (rivaroxaban and dalteparin) together and assumed it to be treatment-independent, since the
 197 total number of events in the trials was low. The distributions of the types of VTE event were based on
 198 the number of recurrent VTE events observed in the SELECT-D trial in the lower extremities and
 199 pulmonary embolisms— other locations of VTE events (brachial, subclavian, jugular, renal plus inferior
 200 vena cava, or the extrahepatic vein) were excluded [15]. Mortality rates (death by any cause) were
 201 based on Dutch cancer mortality data from the Netherlands Cancer Registry [21]. In the sensitivity

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3 202 analysis, all transition probabilities were varied over beta distributions. For percentages of the type of
4 203 recurrent VTE and MB, a Dirichlet distribution was used in the sensitivity analysis. As recommended by
5 204 the Dutch guidelines for economic evaluation of healthcare, the distributions were based on Briggs et
6 205 al., who described the use of distributions around model input parameters (e.g., distributions limited
7 206 to positive values (costs) or even confined between 0-1 (probabilities)) [18,20].
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209 Costs

210 All cost parameters are standardised to 2019 Euros, and summarised in Table S2. Event-related
211 healthcare costs were based on a previous Dutch cost-effectiveness study for rivaroxaban in the
212 general VTE population [22]. Costs of fatal recurrent VTE were assumed to be similar to those of non-
213 fatal symptomatic PE. We assumed no event-related healthcare costs for patients with incidental PE,
214 because these embolisms were found incidentally and did therefore not require physician visits.
215 However, since patients with incidental PE should be treated identically to those with symptomatic PE,
216 we did take medication costs into account. Costs for ICH and CTEPH consisted of acute care costs during
217 the first month after diagnosis, followed by long-term care costs until the patient moved to the 'death'
218 state. Costs of a fatal MB were assumed to be equal to those of non-fatal non-ICH MB.

219 Drug costs were retrieved from the national medication costs database [23]. For rivaroxaban these
220 costs were based on 15 mg twice daily for three weeks followed by 20 mg once daily. Drug costs of
221 dalteparin were based on 200 IU/kg daily during month one followed by 150 IU/kg daily in months two
222 to six [15,24]. Based on an average body mass index of 25.6 from the SELECT-D trial and an average
223 height of 1.72 m for the Dutch population, we calculated that the average weight was between 69 and
224 82 kg, which corresponds with a dose of 15,000 IU daily during month one followed by 12,500 IU daily
225 in months two to six [15,25]. Rivaroxaban users were assumed to require an annual check-up of their
226 renal function [6]. We included one-time costs for an injection instruction by a home-caregiver.
227 Administration costs were only accounted to patients with early or locally advanced cancer (39%),
228 since patients with metastatic cancer or haematologic malignancies often already have home care or
229 an informal caregiver who can administer the dalteparin injection. Similarly, informal care costs were
230 only taken into account for this same subgroup.

231 Based on a previously published report on informal care in the Netherlands, we made a distinction
232 between intensive (26 hours per week) and non-intensive (8 hours per week) informal care [26]. This
233 was multiplied by the average duration and tariff for informal care, obtained from the Dutch cost
234 manual [27]. To prevent double counting, we did not include informal care costs for the chronic
235 complications. Travel costs were taken into account for renal monitoring visits and upon the
236 occurrence of a DVT or CRNMB. Costs related to forgone leisure activity were not taken into account
237 since there is no data available on the impact of a VTE or bleeding on leisure losses in cancer patients.
238 Moreover, the starting age of the population in the model was 67 years (which is the Dutch retirement
239 age) based on the average age of the SELECT-D trial and the fact that the majority (58%) of the patients
240 in the SELECT-D trial had metastatic cancer may indicate a low employment rate.

241 Costs were discounted at an annual rate of 4% [18]. In the sensitivity analysis, the costs were varied
242 with gamma distributions corresponding to the 95% confidence interval (CI) [18,20], as indicated in
243 Table S2.
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246 Utilities

247 Utility scores, used to calculate the QALYs, were derived from a sub-analysis from the CATCH study
 248 assessing the EQ-5D scores associated with VTE and recurrent VTE in cancer patients (Table S3) [28].
 249 The CATCH study assessed the effectiveness of six months of treatment with tinzaparin versus warfarin
 250 for the treatment of acute venous thromboembolism in patients with active cancer. It was chosen
 251 because it aligns well with our population and events of interest. Utility decrements for CTEPH were
 252 based on a study assessing EQ-5D VAS scores in CTEPH patients up to 5 years after their initial diagnosis
 253 [29]. Utility decrements for ICH and long-term PTS (>6months after diagnosis) were obtained from a
 254 previous cost-effectiveness study [30]. QALYs related to fatal events, such as death to any cause, fatal
 255 PE and fatal MB, were assumed to be 0. QALYs were discounted at 1.5% per annum according to Dutch
 256 guidelines [18]. In the sensitivity analyses, utility scores were varied over their 95% CI with a beta
 257 distribution [18,20].

260 Sensitivity analysis

261 Sensitivity analyses were conducted to check the robustness of the model results to uncertainty and
 262 known variations in key input parameters. In the probabilistic sensitivity analysis, all input parameters
 263 were varied simultaneously over their 95% CI. If the 95% CI was unavailable and calculating the 95% CI
 264 based on the number of events was not possible, the 95% CI was calculated based on a 25% standard
 265 error. The ICER was calculated with 2,000 iterations and plotted in a cost-effectiveness plane. A
 266 univariate sensitivity analysis was conducted to show the influence of an individual parameter on the
 267 ICER. The 12 most influencing parameters were presented in a tornado diagram.

270 Scenario analysis

271 We conducted several scenario analyses to show the effect on the outcomes of different (clinical)
 272 situations (Table 2).

275 **Table 2. Overview of the scenario analyses.**

Scenario	Description	Details
Base case	5-year time horizon from societal perspective	-
1	6-month time horizon from societal perspective	The follow-up period of the SELECT-D trial was six months; therefore, outcomes beyond six months had to be extrapolated based on other publications.
2	Base case analysis from healthcare payer's perspective	In the Netherlands, guidelines advise to calculate the ICER from a societal perspective, while in countries such as the UK or Belgium, the healthcare payer's perspective is preferred. To make results comparable to other countries we also calculated the base case ICER from a healthcare payer's perspective, by excluding the indirect costs.
3	Base case analysis with dalteparin dose of 12,500 IU	The costs of dalteparin vary with the patient's weight. For the base case analysis, we assumed an average weight between 69 and 82 kg. In scenarios 3 and 4 we calculated the base case ICER with the costs of dalteparin based on weight categories of 57–68 kg (12,500 IE daily during month one followed by 10,000 IE daily in month two to six) and 83–98 kg (18,000 IE daily during month one followed by 15,000 IE daily in month two to six), respectively.
4	Base case analysis with dalteparin dose of 18,000 IU	

5	Scenario 1 with treatment duration based on Streiff et al.	This scenario was similar to scenario 1, except for the treatment period which was based on a study of Streiff et al., who—comparable to SELECT-D—compared rivaroxaban to LMWH for the prevention of recurrent VTE in cancer patients [15]. They found an average treatment duration of one month and three months for LMWH and rivaroxaban, respectively.
6	Base case analysis using drug-specific distributions for the types of VTE and MB	Due to low numbers of VTE and MB events observed in the SELECT-D trial [14] and HOKUSAI VTE Cancer [16] trials, respectively, we calculated the distribution of the types of VTE and MB in the base case analysis based on the total number of events and assumed it to be equal for both drugs. In this scenario we assess the effect of this assumption on the cost-effectiveness results by using the drug-specific distributions of the types of VTE and MB based on the results of the SELECT-D and HOKUSAI VTE Cancer trials [14,19].

Abbreviations: IU, international units; MB, major bleeding; VTE, venous thromboembolism.

Budget impact

A budget impact analysis was conducted to estimate the total annual financial consequences of the implementation of rivaroxaban for the treatment and prevention of VTE in cancer patients within the Dutch healthcare setting. The budget impact was calculated from a societal perspective using the costs calculations from the cost-effectiveness model with a one-year time horizon. We extracted from the model the costs (event-related, treatment, and indirect costs) per patient with a cut-off point of one year for rivaroxaban and dalteparin. The difference in cost per patient was multiplied by the annual number of cancer patients with VTE in the Netherlands. The incidence of VTE in cancer patients and the total number of Dutch cancer patients were used to calculate the yearly number of cancer patients with VTE. The Netherlands Cancer Registry estimated a total of 579,781 cancer patients in 2017 [31]. The incidence of VTE in cancer patients was 13.9 per 1,000 person-years, based on a cohort study of linked UK databases [32]. The outcome of the budget impact analysis was presented as the total budget impact per year, including a subdivision of the costs per type (event-related costs, treatment costs and indirect costs) and corresponding 95% CIs derived from PSA.

Results

Cost-effectiveness analysis

Table 3 represents the deterministic results of the base case and scenario analyses. In each scenario, rivaroxaban was economically dominant—meaning that it simultaneously confers better clinical and quality-of-life outcomes at less cost—over dalteparin. As such, a numerical ICER is not presented because it has no meaning. Despite the fact that every scenario shows an improvement in the patient's health, the difference in QALYs was very low (incremental QALYs of 0.012 over 5 years' time horizon, which equals 4.4 quality-adjusted life days, in the base case analysis). In the base case analysis, rivaroxaban saved €1,376 per patient compared with dalteparin. The scenario calculating the cost-effectiveness over a six-month time horizon resulted in cost-savings of €1,312 per patient (scenario 1). There was increased cost-savings compared with the societal perspective when calculated from a healthcare payer's perspective (scenario 2). In scenarios 3 and 4 we assessed the effect of variations in the patient's weight (and thus dalteparin dosing) on the ICER. Compared with the base case analysis, there was decreased cost-savings with a lower dalteparin dose and increased cost-savings with a higher dalteparin dose, both still resulting in dominant ICERs. When comparing three months of rivaroxaban

310 treatment to one month of dalteparin treatment, we found incremental QALYs of 0.016 and cost-
 311 savings of €702 per patient (scenario 5). We assessed the effect of using drug-specific distributions of
 312 the types of VTE and MB, resulting in cost-savings of €1,815 and incremental QALYs of 0.037 (scenario
 313 6).

314 The number of events and the corresponding average costs per patient in the base case analysis and
 315 scenario 4 (base case analysis with a time horizon of 6 months) are presented in Table 4. Rivaroxaban
 316 is associated with a lower number of recurrent VTE events, preventing on average €131 and €108 in
 317 costs per patient over five years and over six months, respectively. On the other hand, rivaroxaban
 318 causes more bleeding events, especially in the treatment period. ICH and non-ICH MB have the highest
 319 incremental event costs per patient. Treatment costs are higher for dalteparin compared with
 320 rivaroxaban, with incremental costs of €1,721 and €1,468 in the five-year and the six-month time
 321 horizon, respectively. The differences in indirect costs for rivaroxaban compared with dalteparin were
 322 €19 and -€2 for the five-year and the six-month time horizon, respectively.

325 **Table 3. Deterministic results per patient of the base case and scenario analyses in a cohort of 1,000 cancer patients**
 326 **(2019, Euros).**

	Costs	QALYs	Δ Costs	Δ QALYs	ICER
Base case analysis - 5-year time horizon from societal perspective					
Rivaroxaban	€3,139	2.459	-€1,476	0.012	Dominant
Dalteparin	€4,615	2.448			
Scenario 1 – 6-month time horizon from societal perspective					
Rivaroxaban	€1,361	0.304	-€1,312	0.004	Dominant
Dalteparin	€2,673	0.300			
Scenario 2 – base case analysis from healthcare payer’s perspective					
Rivaroxaban	€2,942	2.459	-€1,496	0.012	Dominant
Dalteparin	€4,438	2.448			
Scenario 3 – base case analysis with dalteparin dose of 12,500 IU					
Rivaroxaban	€3,139	2.459	-€1,079	0.012	Dominant
Dalteparin	€4,218	2.448			
Scenario 4 – base case analysis with dalteparin dose of 18,000 IU					
Rivaroxaban	€3,139	2.459	-€1,898	0.012	Dominant
Dalteparin	€5,037	2.448			
Scenario 5 – scenario 1 with treatment duration based on Streiff et al.					
Rivaroxaban	€1,299	0.289	-€702	0.016	Dominant
Dalteparin	€2,001	0.273			
Scenario 6 – base case analysis using drug-specific distributions for the types of VTE and MB					
Rivaroxaban	€3,065	2.463	-€1,815	0.037	Dominant
Dalteparin	€4,880	2.425			

327 *Abbreviations: ICER, incremental cost-effectiveness ratio; IU, international units; MB, major bleeding; QALY, quality adjusted*
 328 *life-years; VTE, venous thromboembolism.*

330 **Table 4. Number of events and costs per event per patient in a cohort of 1,000 cancer patients (2019, Euros).**

	Base case (5-year time horizon)					
	Rivaroxaban		Dalteparin		Incremental	
	Number of events	Costs per patient	Number of events	Costs per patient	Number of events	Costs per patient
Event costs						
Recurrent VTE	191	€311.85	275	€442.92	-84	-€131
Non-fatal symptomatic recurrent PE	33	€168.36	48	€239.13	-15	-€71

Non-fatal incidental recurrent PE	58	-	84	-	-26	
Non-fatal recurrent DVT	83	€59.31	120	€84.23	-37	-€25
Fatal recurrent VTE	17	€84.18	24	€119.56	-7	-€35
ICH	11	€550.70	9	€438.40	2	€112
Non-ICH MB	98	€1,106.87	79	€902.47	19	€204
Fatal MB	5	€51.48	4	€41.98	1	€10
CRNMB	197	€56.28	92	€26.93	105	€29
PTS	61	€92.72	61	€92.37	0	€0
CTEPH	20	€223.79	20	€222.83	0	€1
Total event costs		€2,705.54		€2,610.83		€95
Treatment costs		€548.83		€2,270.33		-€1,721
Indirect costs		€196.31		€177.08		€19
Scenario 1 (6-month time horizon)						
	Rivaroxaban		Dalteparin		Incremental	
	Number of events	Costs per patient	Number of events	Costs per patient	Number of events	Costs per patient
Event costs						
Recurrent VTE	38	€58.95	109	€166.96	-70	-€108
Non-fatal symptomatic recurrent PE	7	€31.82	19	€90.14	-12	-€58
Non-fatal incidental recurrent PE	12	-	33	-	-21	-
Non-fatal recurrent DVT	17	€11.21	47	€31.75	-31	-€21
Fatal recurrent VTE	3	€15.91	9	€45.07	-6	-€29
ICH	6	€142.82	4	€94.25	2	€49
Non-ICH MB	50	€539.38	33	€355.95	17	€183
Fatal MB	2	€25.09	2	€16.56	1	€9
CRNMB	130	€35.99	38	€10.62	91	€25
PTS	14	€20.59	14	€20.56	0	€0
CTEPH	3	€21.96	3	€21.93	0	€0
Total event costs		€903.72		€2,639.25		-€1,736
Treatment costs		€479.40		€1,947.45		-€1,468
Indirect costs		€36.50		€38.39		-€2

Abbreviations: CRNMB, clinically relevant non-major bleeding; CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; ICH, intracranial haemorrhage; MB, major bleeding; PE, pulmonary embolism; PTS, post thrombotic syndrome; VTE, venous thromboembolism

In the probabilistic sensitivity analysis, we assessed the robustness of the model over a five-year time horizon (base case) and a six-month time horizon (scenario 1). The results are presented in cost-effectiveness planes in Figure 2 and Figure S1. In the base case analysis, rivaroxaban was in the majority (77.8%) of the 2,000 iterations cost-saving and more effective compared with dalteparin. In 22.2% of the iterations rivaroxaban is considered cost-saving but less effective compared with dalteparin. In scenario 1, rivaroxaban was in almost all (98.7%) the iterations cost-saving and more effective compared with dalteparin.

The influence of the individual input parameters on the base case incremental costs and QALYs are analysed in the univariate sensitivity analysis. The tornado diagrams (Figure 3 and Figure 4) present the 12 input parameters with the highest impact in the base case analysis. The risk of MB for both rivaroxaban and dalteparin, treatment duration of dalteparin, and recurrent VTE risks during the first six months after a VTE had the highest influence on the incremental costs. Similarly, the risk of MB and recurrent VTE in the first six months for rivaroxaban and dalteparin showed the highest influence on the incremental QALYs. Similar results were found in the univariate sensitivity analysis of scenario 1 (Figure S2 and Figure S3).

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Figure 2. Probabilistic sensitivity analysis of the base case with five-year time horizon (base case analysis). The red mark represents the deterministic incremental cost-effectiveness ratio. Abbreviation: QALY, quality adjusted life-year

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Figure 3. Tornado diagram from the univariate sensitivity analysis for the base case analysis showing the impact of parameters on the incremental costs. Abbreviations: ICH, intracranial haemorrhage; MB, major bleeding; PE, pulmonary embolism; VTE, venous thromboembolism

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Figure 4. Tornado diagram from the univariate sensitivity analysis for the base case analysis showing the impact of parameters on the incremental QALYs. Abbreviations: CRNMB, clinically relevant non-major bleeding; ICH, intracranial haemorrhage; MB, major bleeding; VTE, venous thromboembolism

Budget impact

The results of the budget impact analysis are presented in Table 5. The replacement of LMWHs (including dalteparin) with rivaroxaban can lead to cost-savings of a maximum of €11,326,763 (€5,164,254–€17,363,231) over approximately 8,000 cancer patients with VTE based on a one-year time horizon. A reduction in treatment costs can lead to savings of up to €12.6 million. Event-related costs and indirect costs slightly increase by €1,234,467 (€-2,103,366–€5,231,955) and €2,101 (€-173,830–€184,677), respectively, when LMWHs are replaced by rivaroxaban.

Table 5. Budget impact over one-year time horizon in the Netherlands.

Event-related costs	€1,234,467 (€-2,103,366–€5,231,955)
Treatment costs	€-12,559,130 (€-17,327,405–€-8,149,498)
Indirect costs	€-2,101 (€-173,830–€184,677)
Budget impact	€-11,326,763 (€-17,363,231–€-5,164,254)

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Discussion

Thrombosis treatment is a challenge in cancer patients. According to the guidelines, LMWHs and DOACs edoxaban and rivaroxaban are the preferred treatment for the prevention of recurrent VTE in cancer patients [8–11]. We have assessed the cost-effectiveness and budget impact of rivaroxaban in cancer patients at risk of recurrent VTE based on the SELECT-D trial [15]. We conclude that, in the Netherlands, rivaroxaban is a cost-saving treatment option with a small health benefit per patient over five years compared with dalteparin. In sensitivity analyses our model appeared to be robust.

The cost-savings were mainly driven by the difference in treatment costs. It should be noted that this is specifically the case for the Netherlands, and may differ in other countries. On the other hand, both the cost-effectiveness and budget impact analyses showed that the event-related costs and indirect costs increase with the use of rivaroxaban compared with dalteparin. A total of 84 VTE-related events were prevented over five years, leading to an average cost-saving of €131 per patient. This is line with findings from a recent study that assessed the VTE-related healthcare costs in cancer patients,

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3 396 which found that rivaroxaban treated patients had a significantly lower total VTE-related costs relative
4 397 to patients treated with LMWH [33]. Although the cost difference between the rivaroxaban and LWMH
5 398 cohorts was even greater with \$12,004 per patient per year.

7 399 On the other hand, MB events were more frequent with rivaroxaban compared with dalteparin
8 400 (11 ICH and 98 non-ICH versus 9 ICH and 79 non-ICH, respectively). MB events are very burdensome
9 401 and frequently severely disabling, leading to high acute and long-term direct and indirect costs. This
10 402 explains why the indirect costs were higher for rivaroxaban than for dalteparin in the base case
11 403 scenario. Moreover, there was no data available on leisure activity losses caused by the occurrence of
12 404 a VTE event in patients who are already burdened with cancer. Therefore, the indirect costs might have
13 405 been underestimated, possibly leading to lower cost-saving results. The indirect costs account for €196
14 406 to €177 per patient over five years—approximately 4-6% of the total cost—however, they do not have
15 407 a major influence on the differences between the two drugs (€19 and -€2 for the five-year and 6-month
16 408 time horizon, respectively). This suggests that, although the indirect costs might have been
17 409 underestimated, rivaroxaban is still likely to be cost-saving compared with dalteparin.

21 410 As mentioned, the main driver of the cost-savings is the difference in treatment costs. In the
22 411 cost-effectiveness analysis, we estimated that more than €1,700 per patient over a five-year period
23 412 can be saved on treatment costs, compared with dalteparin. Moreover, in the scenario analysis we
24 413 varied the price of dalteparin based on weight. Although the lowest dose (12,500 IU daily during month
25 414 one followed by 10,000 IU in months two to six based on weight class 57–68 kg) had a lower price,
26 415 €8.06 versus €9.93, the ICER remained cost-saving. Rivaroxaban users were assumed to require an
27 416 annual check-up of their renal function. However, cancer patients (especially those with metastatic
28 417 cancer) are at higher risk for renal impairment and may be tested much more frequently [34]. This may
29 418 have caused an overestimation of the costs of rivaroxaban, and therefore underestimated the total
30 419 cost-savings of rivaroxaban compared with dalteparin.

34 420 In the budget impact analysis, we calculated that rivaroxaban replacing LMWH (including
35 421 dalteparin) leads to cost-savings of a maximum of €11,326,763 within one year over a total of 8,000
36 422 cancer patients. This is the absolute maximum, since it is not possible to treat each patient with
37 423 rivaroxaban from a clinical perspective. In practice, the market share of rivaroxaban will be lower—
38 424 despite the fact that there are three other DOACs that could be prescribed—because there are some
39 425 clinical considerations that should be taken into account. Firstly, although DOACs have far fewer drug
40 426 interactions than VKAs, it should be noted that rivaroxaban is metabolized by CYP3A4 enzymes [1].
41 427 Cancer patients, especially those with haematological cancer, are at high risk for opportunistic and
42 428 fungal infections, for which they are often treated with CYP3A4 inhibitors or inducers [35]. For this
43 429 reason, prescription of rivaroxaban for the prevention of recurrent VTE in cancer patients must be
44 430 done carefully [1]. This interaction does not play a role in LMWH treatment.

48 431 Secondly, the balance between the risk of thrombosis and the risk of bleeding should always
49 432 be a consideration in the prescription of anticoagulants. For example, DOACs are not advised in
50 433 patients with GI tumours, due to a higher risk of GI bleeding [8–11]. Some prediction scores for primary
51 434 prevention have been developed to predict thrombosis risk in cancer patients, since thrombosis
52 435 prophylaxis is most effective in patients with an increased VTE risk. Unfortunately, for cancer these
53 436 scores have still not been shown to reliably identify patients with the highest risk [36]. Predictive scores
54 437 for bleeding, such as the HAS-BLED score used for atrial fibrillation patients, are also needed.

57 438 A third consideration is the oral administration of rivaroxaban. Although it is less burdensome
58 439 than the LMWH injections, oral administration can be problematic in patients with anorexia and
59 440 vomiting, which is often seen as a side effect in cancer therapy [15]. Moreover, low food intake might

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3 441 influence the metabolism of rivaroxaban resulting in lower bioavailability [37]. Lastly, adherence is
4 442 always a point of discussion, but since adherence to current guidelines is often low [36], we feel that
5 443 adherence might even increase due to the more patient-friendly administration.

7 444 Our analysis is not without limitations. It should also be noted that 58% of the patients included
8 445 in the SELECT-D trial were having metastatic cancer, and thus results and conclusions pertain mostly
9 446 to severely ill patients. Also, the majority (53%) of the initial VTE events were incidental PE, related to
11 447 computed tomography imaging for tumour status [15]. Additionally, as with all cost-effectiveness
12 448 models some assumptions need to be made due to lack of data.

13 449 We assumed that patients were treated with anticoagulation over six months, which is in line
14 450 with the guidelines [8–11]. Previous studies have shown that adherence to these guidelines is poor
16 451 [36]. As seen in the study by Streiff et al, in practice, treatment with LMWH is often not six months,
17 452 presumably due to the fact that LMWH injections are burdensome, there are concerns about the
18 453 bleeding risk, and the complexity of the treatment of cancer patients [36]. However, this
20 454 recommended treatment period was also not achieved in many patients treated with rivaroxaban,
21 455 which resulted in an average duration of three months. We conducted a scenario analysis (scenario 5)
22 456 to assess this difference in treatment duration (one month of LMWH versus three months of
23 457 rivaroxaban). These results favoured rivaroxaban, because the incremental QALYs increased while still
25 458 being cost-saving. On the other hand, there are also some clinical situations in which the treatment
26 459 period might be longer than six months: for example, in patients with a recurrent VTE event, patients
27 460 with an active malignancy, or patients receiving cancer treatment for their malignancy beyond six
29 461 months. Moreover, in the Netherlands anticoagulation is often continued after six months of initial
30 462 treatment in case the cancer is still active. Unfortunately, we were unable to assess the effect of
31 463 continued anticoagulation treatment due to lack of data. However, since rivaroxaban is associated with
33 464 cost-saving results during the first six months, it is to be expected that during a longer treatment period
34 465 the cost-savings and health gains will accrue even more compared with dalteparin.

35 466 In the univariate sensitivity analysis, we have shown that the risk of MB and VTE for both
36 467 rivaroxaban and dalteparin have a high influence on the incremental costs and QALYs. In the SELECT-
38 468 D trial [15], the incidence of symptomatic and fatal PE events was relatively higher in patients treated
39 469 with rivaroxaban. However, due to low numbers of VTE observed in the SELECT-D trial [15], we
40 470 calculated the distribution of the type of VTE based on the total number of events and assumed it to
42 471 be equal for both drugs. This may have led to an overestimation of the effect of rivaroxaban compared
43 472 with dalteparin, since symptomatic and fatal PE events have a higher impact on the costs and the
44 473 patient's health compared to DVT and incidental PE. On the other hand, we used this same approach
45 474 to calculate the distributions of the types of MB from the HOKUSAI VTE Cancer trial [16], in which the
47 475 patients treated with dalteparin had relatively more severe MB events compared with the NOAC
48 476 edoxaban (ICH: 17.6% versus 6.1%, respectively). This results in an underestimation of the number of
49 477 MBs in dalteparin-treated patients. We assessed the effect of using drug-specific distributions of the
51 478 type of VTE and MB in scenario six, showing an increase in incremental cost-savings and QALYs
52 479 compared to the base case analysis. Therefore, we conclude that our approach of using equal
53 480 distributions of the types of VTE and MB for rivaroxaban and dalteparin is conservative.

54 481 This study focuses on the secondary prevention of VTE, based on the results of the SELECT-D
56 482 and, partially, the HOKUSAI VTE Cancer trials. However, recently, apixaban was also assessed in cancer
57 483 patients at risk of recurrent VTE and found to be non-inferior compared to dalteparin [38,39].
58 484 Moreover, the AVERT and CASSINI trials have shown that apixaban and rivaroxaban are also effective
59 485 as a primary prophylaxis of VTE in cancer patients compared with a placebo [40–42]. Based on these

486 two studies, clinicians may consider DOAC prophylaxis in some of their cancer patients [42]. Therefore,
487 future research is needed to assess if DOACs are also cost-effective for the primary prevention of VTE.

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490 Conclusion

491 Treatment with rivaroxaban is dominant (cost-saving while slightly improving the patient's
492 health) over dalteparin in cancer patients at risk for recurrent VTE in the Netherlands. The use of
493 rivaroxaban instead of LMWH can save more than eleven million euros per year, which is primarily
494 driven by the difference in treatment costs. Since treatment with rivaroxaban is economically
495 dominant compared with dalteparin and its oral administration is more convenient than daily
496 subcutaneous injection, we feel that certain cancer patients can benefit from DOAC treatment.

499 References

- 500 1. Gerotziapas GT, Mahé I, Elalamy I. Therapeutics and Clinical Risk Management Dovepress New
501 orally active anticoagulant agents for the prevention and treatment of venous
502 thromboembolism in cancer patients. *Ther Clin Risk Manag.* 2014;10:423–36.
- 503 2. Falanga A, Marchetti M, Vignoli A. Coagulation and cancer: Biological and clinical aspects. *J*
504 *Thromb Haemost.* 2013;11(2):223–33.
- 505 3. Lechner D, Weltermann A. Chemotherapy-induced thrombosis: a role for microparticles and
506 tissue factor? *Semin Thromb Hemost.* 2008;34(2):199–203.
- 507 4. Cohen AT, Katholing A, Rietbrock S, Bamber L, Martinez C. Epidemiology of first and recurrent
508 venous thromboembolism in patients with active cancer. *Thromb Haemost.* 2017;117(01):57–
509 65.
- 510 5. Minister of Health W and S. Letter to the parlement - reimbursement rivaroxaban VTE
511 (Herbeoordeling uitbreiding nadere voorwaarden rivaroxaban (Xarelto®) bij VTE. 2015;
- 512 6. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, et al. The 2018 European
513 Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral
514 anticoagulants in patients with atrial fibrillation. *Eur Heart J.* 2018;
- 515 7. Mandala M, Falanga A, Roila F, ESMO Guidelines Working Group. Management of venous
516 thromboembolism (VTE) in cancer patients: ESMO Clinical Practice Guidelines. *Ann Oncol.*
517 2011;22(Supplement 6):vi85–92.
- 518 8. Key NS, Khorana AA, Kuderer NM, Bohlke K, Lee AYY, Arcelus JJ, et al. Venous
519 thromboembolism prophylaxis and treatment in patients with cancer: ASCO clinical practice
520 guideline update. *J Clin Oncol.* 2020;38(5):496–520.
- 521 9. Farge D, Frere C, Connors JM, Ay C, Khorana AA, Munoz A, et al. 2019 International Clinical
522 Practice Guidelines for the Treatment and Prophylaxis of Venous Thromboembolism in
523 Patients With Cancer. *Lancet Oncol.* 2019;20(10):e566–81.
- 524 10. Konstantinides S V., Meyer G, Bueno H, Galié N, Gibbs JSR, Ageno W, et al. 2019 ESC
525 Guidelines for the diagnosis and management of acute pulmonary embolism developed in
526 collaboration with the European respiratory society (ERS). *Eur Heart J.* 2020;41(4):543–603.
- 527 11. Streiff MB, Holmstrom B, Angelini D, Ashrani A, Bockenstedt PL, Chesney C, et al. NCCN
528 Guidelines® insights cancer-associated venous thromboembolic disease, version 2.2018
529 featured updates to the NCCN guidelines. *JNCCN J Natl Compr Cancer Netw.*
530 2018;16(11):1289–303.
- 531 12. Hull RD, Pineo GF, Brant RF, Mah AF, Burke N, Dear R, et al. Long-term low-molecular-weight
532 heparin versus usual care in proximal-vein thrombosis patients with cancer. *Am J Med.* 2006

- 1
2
3 533 Dec;119(12):1062–72.
- 4 534 13. Lee AYY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M, et al. Low-Molecular-Weight
5 535 Heparin versus a Coumarin for the Prevention of Recurrent Venous Thromboembolism in
6 536 Patients with Cancer. *N Engl J Med*. 2003;349(2):146–53.
- 7 537 14. Meyer G, Marjanovic Z, Valcke J, Lorcerie B, Gruel Y, Solal-Celigny P, et al. Comparison of low-
8 538 molecular-weight heparin and warfarin for the secondary prevention of venous
9 539 thromboembolism in patients with cancer: a randomized controlled study. *Arch Intern Med*.
10 540 162(15):1729–35.
- 11 541 15. Young AM, Marshall A, Thirlwall J, Chapman O, Lokare A, Hill C, et al. Comparison of an Oral
12 542 Factor Xa Inhibitor With Low Molecular Weight Heparin in Patients With Cancer With Venous
13 543 Thromboembolism: Results of a Randomized Trial (SELECT-D). *J Clin Oncol*. 2018;36(20):2017–
14 544 23.
- 15 545 16. Raskob GE, van Es N, Verhamme P, Carrier M, Di Nisio M, Garcia D, et al. Edoxaban for the
16 546 Treatment of Cancer-Associated Venous Thromboembolism. *N Engl J Med*. 2018;378(7):615–
17 547 24.
- 18 548 17. Streiff MB, Milentijevic D, McCrae K, Yannicelli D, Fortier J, Nelson WW, et al. Effectiveness
19 549 and safety of anticoagulants for the treatment of venous thromboembolism in patients with
20 550 cancer. *Am J Hematol*. 2018;93(5):664–71.
- 21 551 18. Dutch Institute National Health Care (Zorginstituut Nederland). Richtlijn voor het uitvoeren
22 552 van economische evaluaties in de gezondheidszorg (Protocol for the execution of economic
23 553 evaluation in healthcare). 29-02-2016. 2016;(november):120.
- 24 554 19. National Institute of Public Health and the Environment (RIVM). Cancer numbers and context:
25 555 current situation [Internet]. *volksgezondheidszorg.info*. 2017. p. 1.
- 26 556 20. Briggs A, Claxton K, Sculpher M. Decision modelling for Health Economic Evaluation. 3rd ed.
27 557 New York: Oxford University Press; 2011. 57–58 p.
- 28 558 21. The Netherlands Cancer Registry. Survival statistics - all tumours 1961-2015 [Internet].
29 559 22. Heisen M, Treur MJ, Heemstra HE, Giesen EBW, Postma MJ. Cost-effectiveness analysis of
30 560 rivaroxaban for treatment and secondary prevention of venous thromboembolism in the
31 561 Netherlands. *J Med Econ*. 2017 Aug 3;20(8):813–24.
- 32 562 23. Medicijnkosten.nl. The National Health Care Institute (ZIN) [Internet].
33 563 24. Summary of Product Characteristics Fragmin. 2015;
34 564 25. Dutch Statistics. Length and weight of Dutch population [Internet]. 2017.
- 35 565 26. de Klerk M, de Boer A, Plaisier I, Schyns P, Kooiker S. Informele hulp: wie doet er wat? -
36 566 Rapport - SCP [Internet]. 2015-35. 2015.
- 37 567 27. Hakkaart-van Roijen L, van der Linden N, Bouwmans C, Kanters T, Swan Tan S.
38 568 Kostenhandleiding: Methodologie van kostenonderzoek en referentieprijzen voor
39 569 economische evaluaties in de gezondheidszorg. *Zorginstituut Ned*. 2016;1–120.
- 40 570 28. Lloyd AJ, Dewilde S, Noble S, Reimer E, Lee AYY. What Impact Does Venous
41 571 Thromboembolism and Bleeding Have on Cancer Patients' Quality of Life? *Value Heal*.
42 572 2018;21(4):449–55.
- 43 573 29. Roman A, Barbera JA, Castillo MJ, Muñoz R, Escribano P. Health-related quality of life in a
44 574 national cohort of patients with pulmonary arterial hypertension or chronic thromboembolic
45 575 pulmonary hypertension. *Arch Bronconeumol*. 2013;49(5):181–8.
- 46 576 30. Stevanović J, de Jong LA, Kappelhoff BS, Dvortsin EP, Voorhaar M, Postma MJ. Dabigatran for
47 577 the Treatment and Secondary Prevention of Venous Thromboembolism; A Cost-Effectiveness
48 578 Analysis for the Netherlands. *PLoS One*. 2016;11(10):e0163550.
- 49 579 31. The Netherlands Cancer Registry. Prevalence statistics - all tumours [Internet].
50 580 32. Walker AJ, Card TR, West J, Crooks C, Grainge MJ. Incidence of venous thromboembolism in
51 581 patients with cancer - a cohort study using linked United Kingdom databases. *Eur J Cancer*.
52 582 2013 Apr;49(6):1404–13.
- 53 583 33. Streiff M, Milentijevic D, McCrae KR, Laliberté F, Lejeune D, Lefebvre P, et al. Healthcare
54 584 resource utilization and costs associated with venous thromboembolism in cancer patients

- 1
2
3 585 treated with anticoagulants. *J Med Econ*. 2019;22(11):1134–40.
- 4 586 34. Aapro M, Launay-Vacher V. Importance of monitoring renal function in patients with cancer.
5 587 *Cancer Treat Rev*. 2012;38(3):235–40.
- 6 588 35. Vedham V, Divi RL, Starks VL, Verma M. Multiple Infections and Cancer: Implications in
7 589 Epidemiology. *Technol Cancer Res Treat*. 2014;13(2):177–94.
- 8 590 36. Mahé I, Chidiac J, Helfer H, Noble S. Factors influencing adherence to clinical guidelines in the
9 591 management of cancer-associated thrombosis. *J Thromb Haemost*. 2016;14(11):2107–13.
- 10 592 37. Committee for Medicinal Products for Human Use (CHMP). Summary of product
11 593 characteristics - rivaroxaban 20 mg [Internet].
- 12 594 38. Agnelli G, Becattini C, Meyer G, Muñoz A, Huisman M V., Connors JM, et al. Apixaban for the
13 595 treatment of venous thromboembolism associated with cancer. *N Engl J Med*.
14 596 2020;382(17):1599–607.
- 15 597 39. McBane RD, Wysokinski WE, Le-Rademacher JG, Zemla T, Ashrani A, Tafur A, et al. Apixaban
16 598 and dalteparin in active malignancy-associated venous thromboembolism: The ADAM VTE
17 599 trial. *J Thromb Haemost*. 2020;18(2):411–21.
- 18 600 40. Khorana AA, Soff GA, Kakkar AK, Vadhan-Raj S, Riess H, Wun T, et al. Rivaroxaban for
19 601 Thromboprophylaxis in High-Risk Ambulatory Patients with Cancer. *N Engl J Med*. 2019
20 602 Feb;380(8):720–8.
- 21 603 41. Carrier M, Abou-Nassar K, Mallick R, Tagalakis V, Shivakumar S, Schattner A, et al. Apixaban to
22 604 Prevent Venous Thromboembolism in Patients with Cancer. *N Engl J Med*. 2019;380(8):711–9.
- 23 605 42. Agnelli G. Direct Oral Anticoagulants for Thromboprophylaxis in Ambulatory Patients with
24 606 Cancer. *N Engl J Med*. 2019;380(8):781–3.
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609 Author contributions

31 610 Lisa A. de Jong built the economic model, performed the analyses, and contributed to the design of
32 611 the work, interpretation of the results, writing of the manuscript.

33 612 Annette W.G. van der Velden contributed to the interpretation of the results, writing of the
34 613 manuscript, and critical revision for important intellectual content.

35 614 Marinus van Hulst contributed to the design of the work, interpretation of the results, writing of the
36 615 manuscript, and critical revision for important intellectual content.

37 616 Maarten J. Postma contributed to the design of the work, interpretation of the results, writing of the
38 617 manuscript, and critical revision for important intellectual content.

39 618 All authors approved of the version to be published.

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44 620 **Checklist for the appropriate reporting statement:** This manuscript was written in accordance with
45 621 the CHEERS checklist for reporting economic evaluations of health interventions.

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48 623 **Data sharing statement:** All relevant data are included in the manuscript. The analyses were
49 624 conducted based on publicly available information which is presented and referenced in the
50 625 manuscript.

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53 627 **Word count:** 4,508 (excluding table and figure descriptions and references)

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56 629 **Patient consent and ethical approval:** The analyses were conducted based on publicly available
57 630 information which is presented and referenced in the article and Supporting Information files, and did
58 631 therefore not require any patient consent forms or approval from an ethical review board.

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3 633 **Patient and public involvement statement:** It was not appropriate to involve patients or the public in
4 634 the design, or conduct, or reporting, or dissemination plans of our research, because this health
5 635 economic analysis was based on publicly available data and solely concentrated on the analysis of the
6 636 economics consequence of treating cancer patients with rivaroxaban instead of the current standard
7 637 of care.
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For peer review only

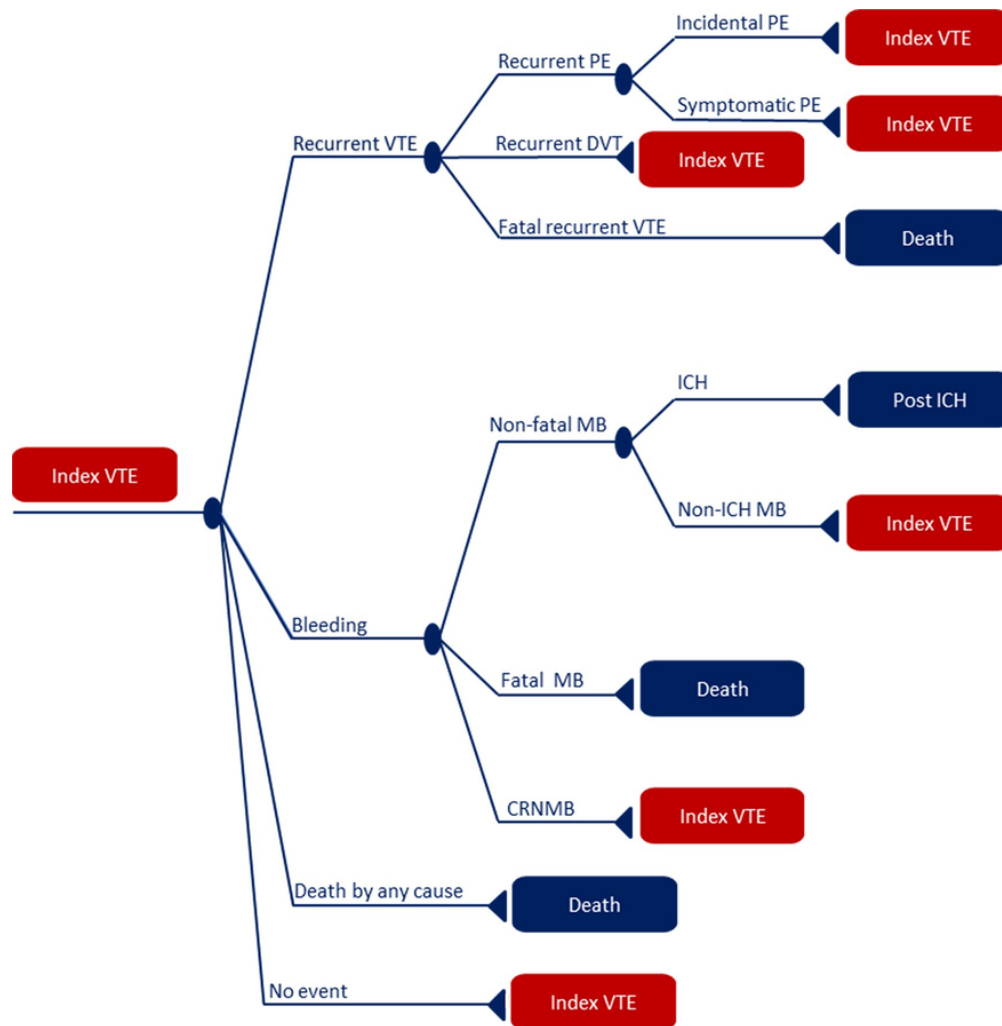
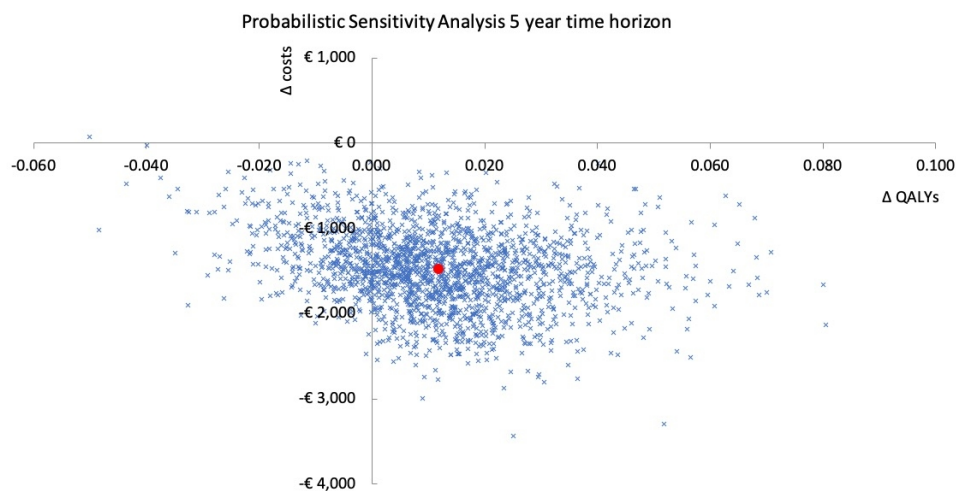


Figure 1. Model outline. All patients enter the model in the 'Index VTE' state and move to other states upon the occurrence of one of the following events: recurrent incidental PE, recurrent symptomatic PE, fatal recurrent VTE, recurrent DVT, ICH, non-ICH MB, fatal MB, CRNMB, or death by any cause. The triangles represent the health state a patient will enter after an event. The blue squares are permanent states, in which a patient will remain until death while not being at risk for other events. The red squares represent a transient state: the patient will re-enter the model in the 'Index VTE' state.

Abbreviations: CRNMB, clinically relevant non-major bleeding; DVT, deep vein thrombosis; ICH, intracranial haemorrhage; MB, major bleeding; PE, pulmonary embolism; VTE, venous thromboembolism

74x75mm (300 x 300 DPI)



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Figure 2. Probabilistic sensitivity analysis of the base case with five-year time horizon (base case analysis). The red mark represents the deterministic incremental cost-effectiveness ratio. Abbreviation: QALY, quality adjusted life-year

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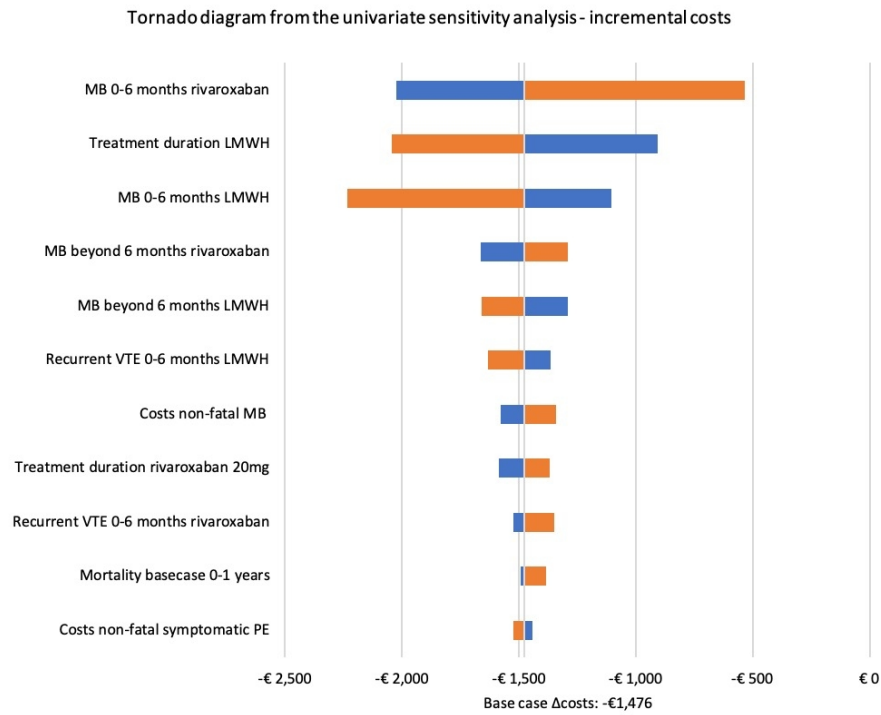


Figure 3. Tornado diagram from the univariate sensitivity analysis for the base case analysis showing the impact of parameters on the incremental costs. Abbreviations: ICH, intracranial haemorrhage; MB, major bleeding; PE, pulmonary embolism; VTE, venous thromboembolism

194x143mm (144 x 144 DPI)

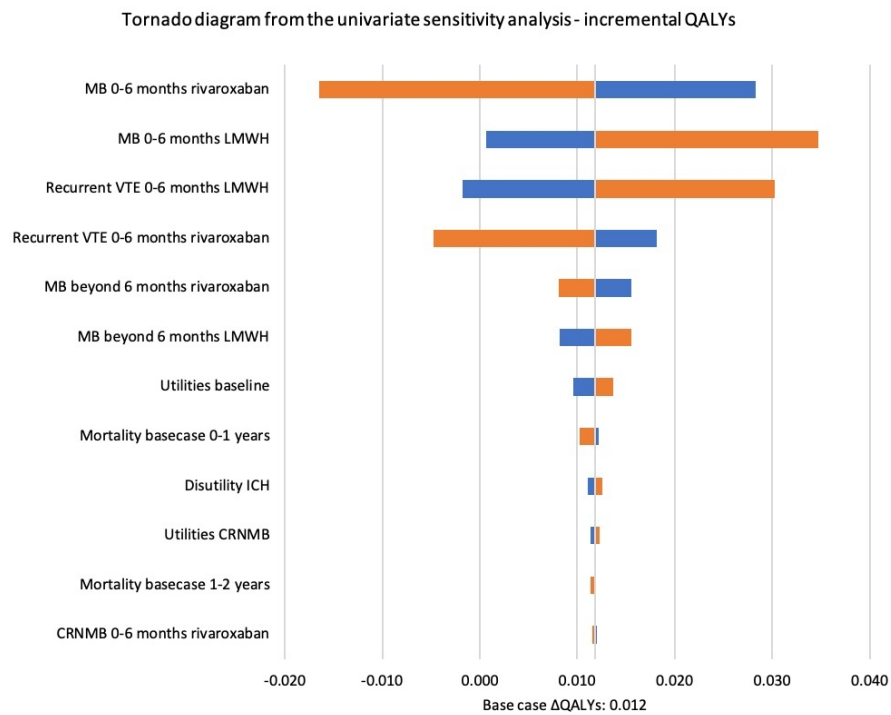


Figure 4. Tornado diagram from the univariate sensitivity analysis for the base case analysis showing the impact of parameters on the incremental QALYs. Abbreviations: CRNMB, clinically relevant non-major bleeding; ICH, intracranial haemorrhage; MB, major bleeding; VTE, venous thromboembolism

194x143mm (144 x 144 DPI)

Supplementary data file – Table S1

Manuscript title: Cost-effectiveness analysis and budget impact of rivaroxaban in cancer patients at risk of recurrent venous thromboembolism

Table S1. Transition probabilities used in the cost-effectiveness model

	Rivaroxaban (95% CI)	LMWH (95% CI)	Distribution	Reference
Recurrent VTE				
0–6 months	0.040 (0.020 – 0.090)	0.110 (0.070 – 0.160)	Beta	[1]
6–12 months	0.040 (0.031 – 0.050)		Beta	[2]
1–2 years	0.034 (0.027 – 0.042)		Beta	[2]
2–3 years	0.021 (0.014 – 0.029)		Beta	[2]
3–4 years	0.016 (0.009 – 0.026)		Beta	[2]
4–5 months	0.013 (0.006 – 0.024)		Beta	[2]
Type of recurrent VTE				
Symptomatic PE	17.4% ($\alpha = 4, \beta = 19$)		Dirichlet	[1]
Incidental PE	30.4% ($\alpha = 7, \beta = 16$)		Dirichlet	[1]
DVT	43.5% ($\alpha = 10, \beta = 13$)		Dirichlet	[1]
Fatal PE	8.7% ($\alpha = 2, \beta = 21$)		Dirichlet	[1]
MB				
0–6 months	0.060 (0.030 – 0.110)	0.040 (0.020 – 0.080)	Beta	[1]
Beyond 6 months treatment	0.008 (0.006 – 0.010)		Beta	[3]
Type of MB				
ICH	10% ($\alpha = 5, \beta = 45$)		Dirichlet	[3]
Non-ICH MB	86% ($\alpha = 43, \beta = 7$)		Dirichlet	[3]
Fatal MB	4% ($\alpha = 2, \beta = 48$)		Dirichlet	[3]
CRNMB				
0–6 months	0.130 (0.090 – 0.190)	0.040 (0.020 – 0.090)	Beta	[1]
Beyond 6 months treatment	0.008 (0.006 – 0.010)		Beta	[3]
PTS				
0–6 months	0.015 (0.011 – 0.019)		Beta	[4]
6–12 months	0.012 (0.009 – 0.015)		Beta	[4]
12–18 months	0.008 (0.006 – 0.010)		Beta	[4]
18–24 months	0.025 (0.023 – 0.019)		Beta	[4]
24–30 months	0.011 (0.008 – 0.014)		Beta	[4]
30–36 months	0.006 (0.005 – 0.008)		Beta	[4]
3–4 years	0.001 (0.0008 – 0.0013)		Beta	[4]
4–5 years	0.001 (0.0008 – 0.0013)		Beta	[4]
CTEPH (annual risk)	0.0057 (0.0002 – 0.012)		Beta	[5]
Mortality (annual risk)				
0–1 years	0.230 (0.200 – 0.390)		Beta	[6]
1–2 years	0.104 (0.088 – 0.180)		Beta	[6]
2–3 years	0.058 (0.055 – 0.120)		Beta	[6]
3–4 years	0.046 (0.043 – 0.068)		Beta	[6]
4–5 years	0.032 (0.030 – 0.073)		Beta	[6]
Relative risk of recurrent VTE, MB, and CRNMB for LMWH versus placebo, used in scenario 5				
Recurrent VTE (any)	5.170		Fixed	[7]
MB	0.242		Fixed	[7]
CRNMB	1.000		Fixed	[7]

Drug-specific distribution of the type of VTE, used in scenario 6				
<i>Symptomatic PE</i>	28.6% ($\alpha = 2, \beta = 5$)	12.5% ($\alpha = 2, \beta = 14$)	Dirichlet	[1]
<i>Incidental PE</i>	14.3% ($\alpha = 1, \beta = 6$)	37.5% ($\alpha = 6, \beta = 10$)	Dirichlet	[1]
<i>DVT</i>	42.9% ($\alpha = 3, \beta = 4$)	43.8% ($\alpha = 7, \beta = 9$)	Dirichlet	[1]
<i>Fatal PE</i>	14.3% ($\alpha = 1, \beta = 6$)	6.3% ($\alpha = 1, \beta = 15$)	Dirichlet	[1]
Drug-specific distribution of the type of MB, used in scenario 6				
<i>ICH</i>	6.1% ($\alpha = 2, \beta = 31$)	17.6% ($\alpha = 3, \beta = 14$)	Dirichlet	[3]
<i>Non-ICH MB</i>	93.9% ($\alpha = 31, \beta = 2$)	70.6% ($\alpha = 12, \beta = 5$)	Dirichlet	[3]
<i>Fatal MB</i>	0% ($\alpha = 0, \beta = 33$)	11.8% ($\alpha = 2, \beta = 15$)	Dirichlet	[3]

Abbreviations: CI, confidence interval; CRNMB, clinically relevant non-major bleeding; CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; ICH, intracranial haemorrhage; LMWH, low-molecular weight heparin; MB, major bleeding; PE, pulmonary embolism; PTS, post-thrombotic syndrome; SE, standard error; VTE, venous thromboembolism

References

1. Young AM, Marshall A, Thirlwall J, Chapman O, Lokare A, Hill C, et al. Comparison of an Oral Factor Xa Inhibitor With Low Molecular Weight Heparin in Patients With Cancer With Venous Thromboembolism: Results of a Randomized Trial (SELECT-D). *J Clin Oncol*. 2018;36(20):2017–23.
2. Cohen AT, Katholing A, Rietbrock S, Bamber L, Martinez C. Epidemiology of first and recurrent venous thromboembolism in patients with active cancer. *Thromb Haemost*. 2017;117(01):57–65.
3. Raskob GE, van Es N, Verhamme P, Carrier M, Di Nisio M, Garcia D, et al. Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism. *N Engl J Med*. 2018;378(7):615–24.
4. 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(4):423–8.
5. Klok FA, van Kralingen KW, van Dijk APJ, Heyning FH, Vliegen HW, Huisman M V. Prospective cardiopulmonary screening program to detect chronic thromboembolic pulmonary hypertension in patients after acute pulmonary embolism. *Haematologica*. 2010;95(6):970–5.
6. The Netherlands Cancer Registry. Survival statistics - all tumours 1961-2015 [Internet].
7. Napolitano M, Saccullo G, Malato A, Sprini D, Ageno W, Imberti D, et al. Optimal duration of low molecular weight heparin for the treatment of cancer-related deep vein thrombosis: the Cancer-DACUS Study. *J Clin Oncol*. 2014;32(32):3607–12.

Supplementary data file – Table S2

Manuscript title: Cost-effectiveness analysis and budget impact of rivaroxaban in cancer patients at risk of recurrent venous thromboembolism

Table S2. Costs included in the cost-effectiveness model (Euros, 2019)

	Value (95% CI)	Distribution	Reference
Event costs			
Recurrent VTE			
Symptomatic PE	€4,717 (€2,364 – €7,868)	Gamma	[1]
Incidental PE	€0	Fixed	Assumption
DVT	€663 (€464 – €862)	Gamma	[1]
Fatal recurrent VTE ^a	€4,717 (€2,364 – €7,868)	Gamma	[1]
ICH acute care costs	€22,769 (€11,644 – €31,175)	Gamma	[2]
ICH long-term costs (monthly)	€637 (€319 – €1,063)	Gamma	[1]
Non-ICH MB	€10,685 (€5,356 – €17,824)	Gamma	[1]
Fatal MB	€10,685 (€5,356 – €17,824)	Gamma	[1]
CRNMB	€274 (€137 – €457)	Gamma	[1]
PTS	€1,431 (€717 – €2,387)	Gamma	[1]
CTEPH acute care costs	€7,843 (€3,931 – €16,433)	Gamma	[1]
CTEPH long-term costs (monthly)	€89 (€45 – €149)	Gamma	[1]
Treatment costs			
Drug cost (daily)			
LMWH ^b	€9.93	Fixed	[3]
Rivaroxaban 15 mg	€4.58	Fixed	[3]
Rivaroxaban 20 mg	€2.29	Fixed	[3]
Treatment duration (days)			
LMWH	183 (137 – 228)	Gamma	[4]
Rivaroxaban 15 mg	21 (16 – 26)	Gamma	[4]
Rivaroxaban 20 mg	162 (121 – 202)	Gamma	[4]
LMWH administration costs			
Costs for home caregiver (per hour)	€59.34 (€44.51 – €74.18)	Gamma	[5]
Duration of at home administration (hour)	0.25 (0.19 – 0.31)	Gamma	Assumption
Hospitalisation duration PE (days) ^c	6.6 (5.0 – 8.3)	Gamma	[6]
Renal monitoring ^c	€1.64 (€1.23 – €2.05)	Gamma	[7]
Indirect costs			
Travel costs			
Cost per km	€0.20 (€0.15 – €0.25)	Gamma	[8]
Distance to hospital (km)	7	Fixed	[8]
Distance to GP (km)	1.1	Fixed	[8]
Informal care costs			
PE	€1,515 (€1,136 – €1,894)	Gamma	[5,9]
DVT	€233 (€175 – €291)	Gamma	[5,9]
ICH (acute informal care costs)	€1,515 (€1,136 – €1,894)	Gamma	[5,9]
ICH (long-term informal care costs, monthly)	€626 (€470 – €783)	Gamma	[10]
Non-ICH MB	€758 (€568 – €947)	Gamma	[5,9]
CRNMB	€117 (€87 – €146)	Gamma	[5,9]

Abbreviations: CI, confidence interval; CRNMB, clinically relevant non-major bleeding; CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; GP, general practitioner; ICH, intracranial haemorrhage; LMWH, low-molecular weight heparin; MB, major bleeding; PE, pulmonary embolism; PTS, post-thrombotic syndrome; VTE, venous thromboembolism

^aAssumed to be equal to the costs of non-fatal PE

^bBased on an average weight between 69 and 82 kg.

^cBased on DRG code 070419 and only taken into account for rivaroxaban treated patients

References

1. Heisen M, Treur MJ, Heemstra HE, Giesen EBW, Postma MJ. Cost-effectiveness analysis of rivaroxaban for treatment and secondary prevention of venous thromboembolism in the Netherlands. *J Med Econ*. 2017 Aug 3;20(8):813–24.
2. Baeten S a, van Exel NJ a, Dirks M, Koopmanschap M a, Dippel DW, Niessen LW. Lifetime health effects and medical costs of integrated stroke services - a non-randomized controlled cluster-trial based life table approach. *Cost Eff Resour Alloc*. 2010;8(1):21.
3. Medicijnkosten.nl. The National Health Care Institute (ZIN) [Internet].
4. Young AM, Marshall A, Thirlwall J, Chapman O, Lokare A, Hill C, et al. Comparison of an Oral Factor Xa Inhibitor With Low Molecular Weight Heparin in Patients With Cancer With Venous Thromboembolism: Results of a Randomized Trial (SELECT-D). *J Clin Oncol*. 2018;36(20):2017–23.
5. Hakkaart-van Roijen L, van der Linden N, Bouwmans C, Kanters T, Swan Tan S. Kostenhandleiding: Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg. Zorginstituut Ned. 2016;1–120.
6. van Bellen B, Bamber L, Correa de Carvalho F, Prins M, Wang M, Lensing AWA. Reduction in the length of stay with rivaroxaban as a single-drug regimen for the treatment of deep vein thrombosis and pulmonary embolism. *Curr Med Res Opin*. 2014;30(5):829–37.
7. Dutch Health Authorities. NZa zorgproductapplicatie. Declaration code: 070419. [Internet]. 2018.
8. Roijen LH, Linden N van der, Bouwmans C, Kanters T, Tan SS. Dutch manual for costing studies in health care. Diemen; 2015.
9. de Klerk M, de Boer A, Plaisier I, Schyns P, Kooiker S. Informele hulp: wie doet er wat? - Rapport - SCP [Internet]. 2015-35. 2015.
10. van den Berg B, Brouwer W, van Exel J, Koopmanschap M, van den Bos GAM, Rutten F. Economic valuation of informal care: lessons from the application of the opportunity costs and proxy good methods. *Soc Sci Med*. 2006;62(4):835–45.

Supplementary data file – Table S3

Manuscript title: Cost-effectiveness analysis and budget impact of rivaroxaban in cancer patients at risk of recurrent venous thromboembolism

Table S3. Utility values included in the cost-effectiveness model

	Value (95% CI)	Distribution	Reference
Utilities			
Index VTE			
0–1 month	0.565 (0.501 – 0.620)	Beta	[1]
1–2 months	0.655 (0.585 – 0.713)	Beta	[1]
2–3 months	0.674 (0.606 – 0.729)	Beta	[1]
3–4 months	0.698 (0.635 – 0.750)	Beta	[1]
4–5 months	0.707 (0.645 – 0.758)	Beta	[1]
Baseline utility 6 months after index VTE	0.715 (0.646 – 0.770)	Beta	[1]
Recurrent VTE			
DVT	0.605 (0.514 – 0.678)	Beta	[1]
Non-fatal symptomatic PE	0.621 (0.477 – 0.725)	Beta	[1]
Non-fatal incidental PE	0.664 (0.615 – 0.707)	Beta	[1]
Non-ICH MB	0.593 (0.461 – 0.693)	Beta	[1]
CRNMB	0.622 (0.568 – 0.669)	Beta	[1]
Utility decrements			
Recurrent VTE within first six months after index VTE			
DVT	0.040 (0.000 – 0.158)	Beta	[1]
Symptomatic PE	0.024 (0.000 – 0.195)	Beta	[1]
Incidental PE	0.189 (0.021 – 0.404)	Beta	[1]
ICH			
Severe PTS (<6 months after diagnosis)	0.186 (0.090 – 0.280)	Beta	[1]
Severe PTS (>6 months after diagnosis)	0.070 (0.053 – 0.088)	Beta	[2]
CTEPH			
0-1 year	0.194 (0.071 – 0.303)	Beta	[3]
1–4 years	0.109 (0.000 – 0.244)	Beta	[3]
4–5 years	0.079 (0.000 – 0.277)	Beta	[3]

Abbreviations: CI, confidence interval; CRNMB, clinically relevant non-major bleeding; CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; ICH, intracranial haemorrhage; MB, major bleeding; PE, pulmonary embolism; PTS, post-thrombotic syndrome; VTE, venous thromboembolism

References

- Lloyd AJ, Dewilde S, Noble S, Reimer E, Lee AYY. What Impact Does Venous Thromboembolism and Bleeding Have on Cancer Patients' Quality of Life? *Value Heal*. 2018;21(4):449–55.
- Stevanović J, de Jong LA, Kappelhoff BS, Dvortsin EP, Voorhaar M, Postma MJ. Dabigatran for the Treatment and Secondary Prevention of Venous Thromboembolism; A Cost-Effectiveness Analysis for the Netherlands. *PLoS One*. 2016;11(10):e0163550.
- Roman A, Barbera JA, Castillo MJ, Muñoz R, Escribano P. Health-related quality of life in a national cohort of patients with pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension. *Arch Bronconeumol*. 2013;49(5):181–8.

Supplementary data file – Figure S1

Manuscript title: Cost-effectiveness analysis and budget impact of rivaroxaban in cancer patients at risk of recurrent venous thromboembolism

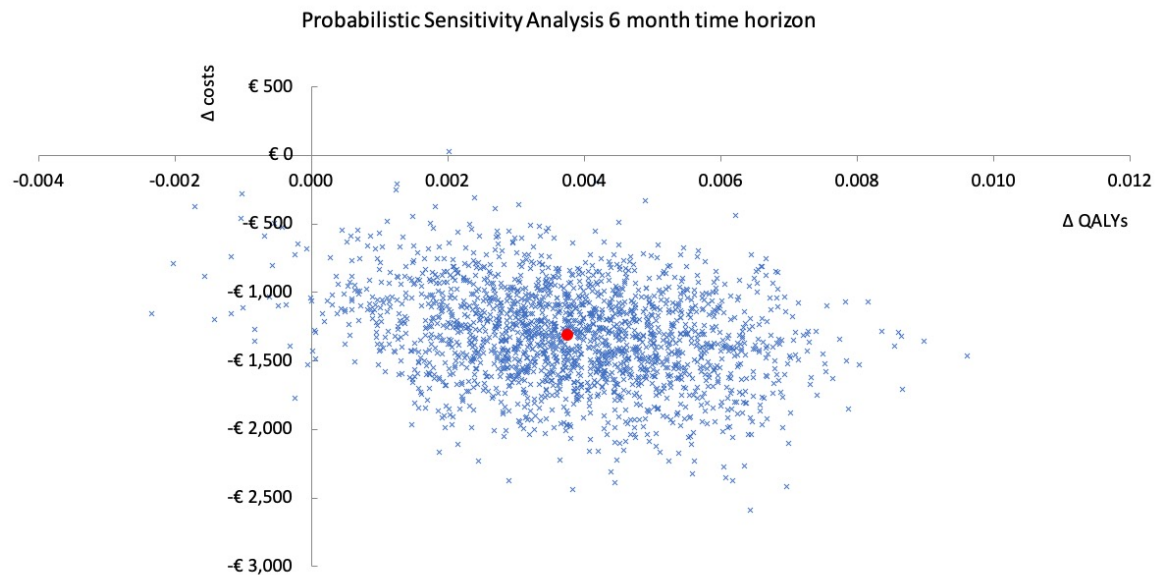


Figure S1. Probabilistic sensitivity analysis with six-month time horizon (scenario 1). The red mark represents the deterministic incremental cost-effectiveness ratio. Abbreviation: QALY, quality adjusted life-year

Supplementary data file – Figure S2

Manuscript title: Cost-effectiveness analysis and budget impact of rivaroxaban in cancer patients at risk of recurrent venous thromboembolism

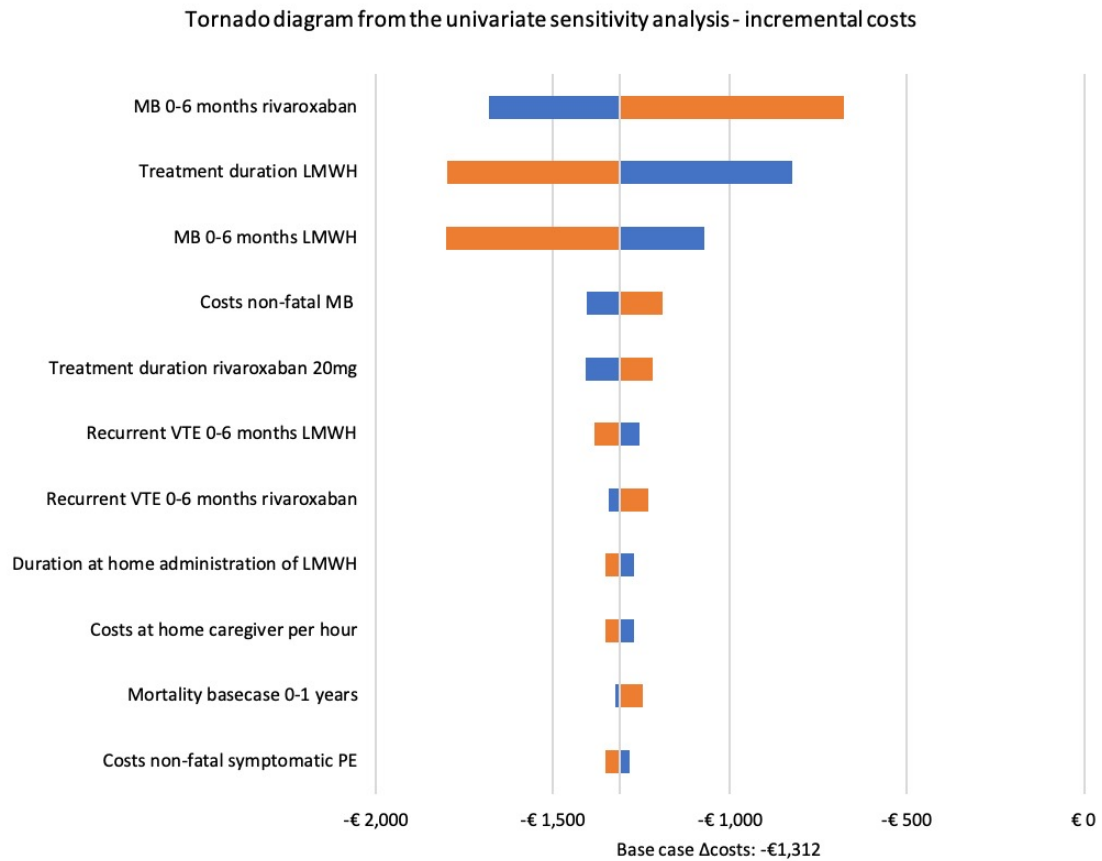


Figure S2. Tornado diagram from the univariate sensitivity analysis for scenario 1 showing the impact of parameters on the incremental costs. Abbreviations: MB, major bleeding; PE, pulmonary embolism; VTE, venous thromboembolism

Supplementary data file – Figure S3

Manuscript title: Cost-effectiveness analysis and budget impact of rivaroxaban in cancer patients at risk of recurrent venous thromboembolism

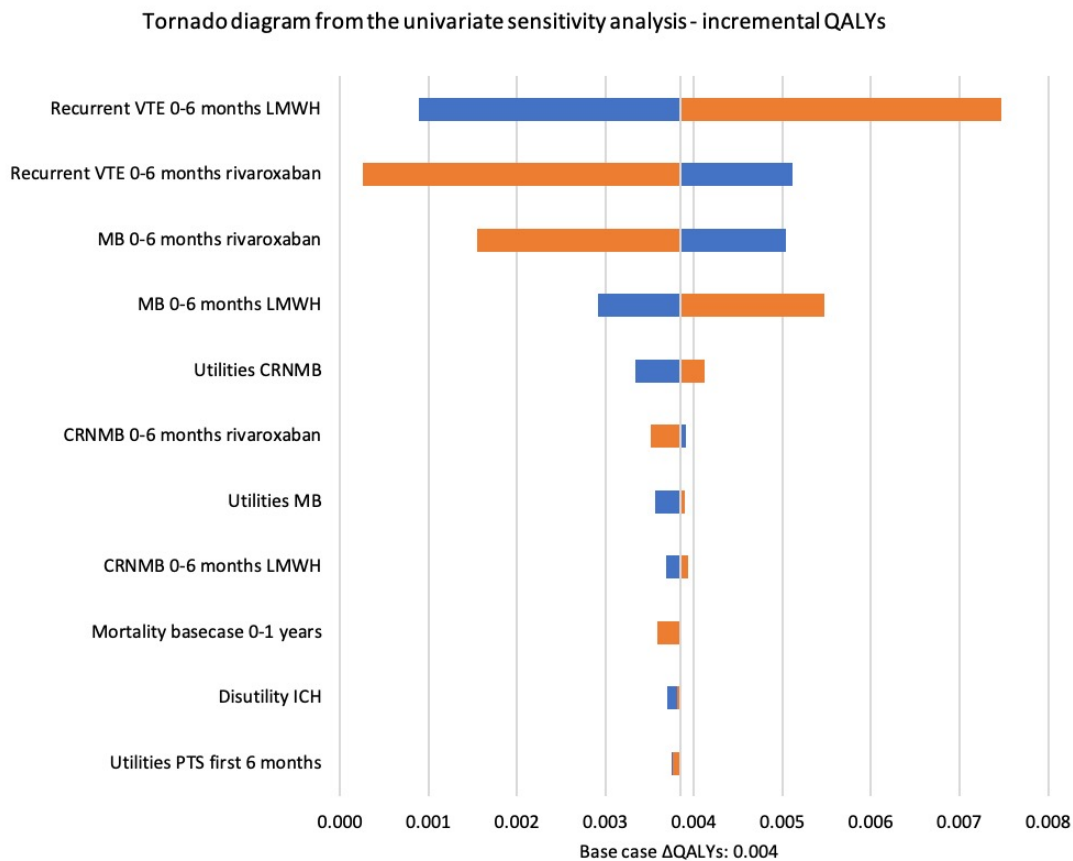


Figure S3. Tornado diagram from the univariate sensitivity analysis for scenario 1 showing the impact of parameters on the incremental QALYs. Abbreviations: CRNMB, clinically relevant non-major bleeding; ICH, intracranial haemorrhage; MB, major bleeding; PE, pulmonary embolism; VTE, venous thromboembolism

CHEERS checklist—Items to include when reporting economic evaluations of health interventions

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as “cost-effectiveness analysis”, and describe the interventions compared.	Page 1, line 9-10
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Page 1, line 34-64
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	Page 4, line 91-120
		Present the study question and its relevance for health policy or practice decisions.	Page 4, line 121-126
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Page 5, line 149-151 Page 5, line 179
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Page 4, line 130-140
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Page 5, line 135-137
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Page 4, line 130-132
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Page 5, line 152-154
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Page 8, line 241 Page 9, line 264
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Page 4, line 133-140
Measurement of effectiveness	11a	<i>Single study-based estimates:</i> Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	
	11b	<i>Synthesis-based estimates:</i> Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	Page 6, line 184-210
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	
Estimating resources and costs	13a	<i>Single study-based economic evaluation:</i> Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
	13b	<i>Model-based economic evaluation:</i> Describe approaches and data sources used to estimate	Page 8, line 213-253

Section/item	Item No	Recommendation	Reported on page No/ line No
		resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Page 8, line 246
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Page 5, line 143-176
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Page 5, line 162-166 Page 8, line 230-240
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Page 7, line 190-201 Page 10, line 284-301
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Page 6, line 201-210 Page 8, line 241-253 Page 9, line 264-271 Page 10, line 276-278
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Page 11, line 320-323 Page 14, line 393-398
Characterising uncertainty	20a	<i>Single study-based economic evaluation:</i> Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	
	20b	<i>Model-based economic evaluation:</i> Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Page 13, line 354-389
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	Page 12, line 311-333
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Page 11, line 323-351
Other			

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Section/item	Item No	Recommendation	Reported on page No/ line No
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Page 3, line 79
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Page 3, line 81-84

For consistency, the CHEERS statement checklist format is based on the format of the CONSORT statement checklist

For peer review only

BMJ Open

Cost-effectiveness analysis and budget impact of rivaroxaban compared with dalteparin in cancer patients at risk of recurrent venous thromboembolism

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Date Submitted by the Author:	13-Oct-2020
Complete List of Authors:	de Jong, Lisa; University of Groningen, Unit of Pharmacotherapy, - Epidemiology and -Economics van der Velden, Annette; Martini Hospital, Department of Internal Medicine Hulst, Marinus; Martini Hospital, Department of Clinical Pharmacy and Toxicology; University Medical Centre Groningen, Department of Health Sciences Postma, Maarten; University Medical Centre Groningen, Department of Health Sciences; University of Groningen, Department of Economics, Econometrics & Finance
Primary Subject Heading:	Health economics
Secondary Subject Heading:	Cardiovascular medicine, Health economics
Keywords:	Anticoagulation < HAEMATOLOGY, ONCOLOGY, Thromboembolism < CARDIOLOGY, HEALTH ECONOMICS

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3 1 Cost-effectiveness analysis and budget impact of rivaroxaban compared with dalteparin in cancer
4 2 patients at risk of recurrent venous thromboembolism

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7 4 Short title: Economic evaluation of rivaroxaban in cancer patients
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34 31 **Author contributions:**

35 32 LA de Jong contributed to the design, interpretation of the data, modelling, drafting the manuscript
36 33 and revisions. M van Hulst, MJ Postma and AWG van der Velden contributed to the design,
37 34 interpretation of the data, validation of the model and drafting the manuscript.
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Abstract

Objectives: In the SELECT-D trial, rivaroxaban showed relatively low venous thromboembolism (VTE) recurrence but higher bleeding compared with dalteparin in cancer patients. We aim to calculate the cost-effectiveness and budget impact of rivaroxaban compared with dalteparin in cancer patients at risk of recurrent VTE.

Setting: We built a Markov model to calculate the cost-effectiveness from a societal perspective over a five-year time horizon for the Dutch healthcare setting.

Participants: A hypothetical cohort of 1,000 cancer patients with VTE entered the model with baseline characteristics based on the SELECT-D trial.

Intervention: Six months treatment with rivaroxaban (15 mg twice daily for first three weeks followed by 20 mg once daily) was compared with six months treatment with dalteparin (200 IU/kg daily during month one followed by 150 IU/kg daily).

Primary and secondary outcome measures: The primary outcome of the cost-effectiveness analysis was the incremental cost-effectiveness ratio (ICER). The robustness of the model was evaluated in probabilistic and univariate sensitivity analyses. A budget impact analysis was performed to calculate the total annual financial consequences for a societal perspective in the Netherlands.

Results: In the base case and all scenarios, rivaroxaban were cost-saving while also slightly improving the patient's health, resulting in economically dominant ICERs. In the probabilistic sensitivity analysis, 77.8% and 98.7% of the simulations showed rivaroxaban to be cost-saving and more effective for a five-year and six-month time horizon, respectively. Rivaroxaban can save up to €11,326,763 (confidence interval: €5,164,254–€17,363,231) in approximately 8,000 cancer patients with VTE per year compared with dalteparin based on a one-year time horizon.

Conclusions: Treatment with rivaroxaban is economically dominant over dalteparin in cancer patients at risk for recurrent VTE in the Netherlands. The use of rivaroxaban instead of dalteparin can save over ten million euros per year, primarily driven by the difference in drug costs.

Strengths and limitations of this study

- This analysis used sophisticated pharmacoeconomic modelling methods to conduct cost-effectiveness and budget impact analyses, presenting the economic impact on a patient as well as on a population level.
- Our model is based on timely, robust data from the important SELECT-D trial.
- Various additional scenarios were used to analyse the effect of different assumptions and clinical situations.
- We assumed a six-month treatment duration for all patients, while in clinical practice the treatment duration may vary between patients.
- Due to lack of data, the productivity losses were not taken into account.

Funding statement: This work was supported by Bayer Pharma Netherlands. The sponsor was involved with the start of the project, but they were not involved in the identification of data, design, conduct, and reporting of the analysis. Award/grant number: not applicable.

Competing interests: LA De Jong, M van Hulst and AWG van der Velden declare that they have no competing interest with relation to subject. Postma MJ has received research grants from various pharmaceutical companies, including but not limiting to Bayer, Pfizer, Bristol-Myers Squibb, GSK, Roche and Novartis.

80 Introduction

81 Venous thromboembolism (VTE), comprising both pulmonary embolism (PE) and deep vein
82 thrombosis (DVT), is a major challenge in patients with cancer [1]. In addition to the characteristics of
83 the cancer itself, cancer therapy (chemotherapy and cancer surgery) has effects on the patient's
84 coagulation system and therefore increases the risk of VTE and bleeding [2,3]. VTE in cancer patients
85 can cause unnecessary hospitalizations, interruption or postponement of cancer treatment, and
86 increased mortality, leading to decreased quality of life and increased costs.

87 VTE is treated with anticoagulation therapy, and this is continued as prophylaxis for recurrence
88 over a longer period because of the high risk of recurrence during the first months after the initial VTE
89 [4]. Vitamin K antagonists (VKAs) or direct oral anticoagulants (DOACs) are indicated for the treatment
90 and prevention of VTE in the general population [5]. DOACs, are a relatively new class of
91 anticoagulants. Apixaban, dabigatran, edoxaban and rivaroxaban are the four DOACs that are currently
92 registered for the prevention of recurrent VTE in Europe. DOACs have a more beneficial efficacy/safety
93 ratio, do not require routine measurements of the INR, and show fewer food-drug and drug-drug
94 interactions compared with VKAs [6,7].

95 The guidelines recommend against the use of VKAs in cancer patients because of potential
96 drug interactions, liver dysfunction, and malnutrition, all of which lead to fluctuations of the
97 international normalized ratio (INR) and could result in negative patient outcomes [8–11]. Moreover,
98 trials in cancer patients with VTE have shown that LMWH is more effective in the prevention of
99 recurrent VTE compared with VKA, without increasing bleeding risk [12–14]. Therefore, the guidelines
100 recommend at least 6 months of therapeutic treatment with a daily subcutaneous injection of low
101 molecular weight heparin (LMWH, e.g., dalteparin) in cancer patients [8–11]. However, recently,
102 DOACs rivaroxaban and edoxaban were also added as treatment options for the prevention of
103 recurrent VTE in cancer patients. This recommendation was based on the results from the SELECT-D
104 and HOKUSAI VTE Cancer trials [15,16].

105 The SELECT-D is a multicenter, randomized, clinical pilot trial in the UK; it is a head-to-head
106 comparison of rivaroxaban and dalteparin in 406 patients with active cancer who had experienced a
107 symptomatic PE, incidental PE, or symptomatic DVT [15]. Incidental PEs are non-symptomatic PEs that
108 are incidentally found during tumour imaging. The trial researchers found that rivaroxaban reduces
109 the recurrence of VTE (six month cumulative VTE recurrence rate: 4% versus 11%) at the cost of an
110 increased risk of bleeding (six month cumulative major bleeding [MB] rate: 6% versus 4%; six month
111 cumulative clinically relevant non-major bleeding [CRNMB] rate: 13% versus 4%) compared with
112 dalteparin. These results were comparable to those of a large retrospective study by Streiff et al. [17].

113 Based on the results of these studies and the fact that DOACs can be orally administered (unlike
114 the subcutaneously injected LMWHs), a greater utilisation of DOACs for VTE in cancer patients might
115 be expected. Since the introduction of DOACs there has been an ongoing discussion about the
116 economic impact of these drugs. To help guide this discussion and inform decision making in this area,
117 we designed and developed an economic model based on the SELECT-D trial to evaluate the cost-
118 effectiveness and budget impact of rivaroxaban compared with dalteparin in cancer patients at risk of
119 recurrent VTE in the Netherlands.

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122 Methods

123 The economic model comparing rivaroxaban with dalteparin was designed based on the SELECT-D trial
124 [15], since this study presented the most comprehensive results reflecting recurrent VTE and bleeding
125 complications per event type (symptomatic PE, incidental PE, and DVT) or severity (MB and CRNMB).
126 The primary outcome of the cost-effectiveness analysis is the incremental cost-effectiveness ratio
127 (ICER); this is calculated by dividing the incremental costs by the incremental health effects, expressed
128 in quality adjusted life-years (QALYs). In accordance with Dutch costing guidelines for economic
129 evaluations in healthcare, the ICER was calculated from a societal perspective, which incorporates
130 direct as well as indirect costs both inside and outside the healthcare sector[18]. We performed
131 sensitivity and scenario analyses to test the robustness of the model. Additionally, we conducted a
132 budget impact analysis to reflect the annual financial consequences of the use of rivaroxaban in cancer
133 patients at risk of recurrent VTE in the Netherlands. The analysis was carried out early 2019. The
134 analyses were conducted based on publicly available information which is presented and referenced
135 in the article and Supporting Information files, and did therefore not require any patient consent forms
136 or approval from an ethical review board.

139 Model outline

140 We developed a decision-tree-based Markov model using Microsoft Excel 2016 to calculate the ICER.
141 Figure 1 shows a schematic representation of the model, with the disease course being represented
142 by separate health states. A hypothetical cohort of 1,000 cancer patients with VTE entered the model
143 with incidental PE, symptomatic PE, or DVT, represented by the 'index VTE' health state. According to
144 the guidelines, patients with incidental PE should be treated identically to those with symptomatic PE
145 [8,10]. Patient characteristics were based on the SELECT-D trial protocol (Table 1) [15]. The SELECT-D
146 population is representative for the Dutch cancer population, based on age, tumour type, and gender
147 distribution [19]. Patients move through various health states in the model during the follow-up time
148 of five years. Five years was used because overall survival was assumed to be low after five years since
149 the majority (58%) of the SELECT-D trial population had metastatic cancer [15]. We included the
150 following health states in our model (see legend of Figure 1 for abbreviations): 'recurrent incidental
151 PE', 'recurrent symptomatic PE', 'fatal recurrent VTE', 'recurrent DVT', 'ICH', 'non-ICH MB', 'fatal MB',
152 'CRNMB', 'death by any cause', and 'no event'. Patients were assumed to remain in these states for
153 one cycle, after which they moved back to the 'index VTE' state or the chronic, debilitating 'post-ICH'
154 state, in which they remained until death without being at risk for any further complications. The cycle
155 length was one month. Markov tunnel states (one-month post-VTE, two months post-VTE, ..., 60
156 months post VTE) were used to implement time-dependency. These temporary states can only be
157 visited once, which allows time-dependent future transitions, costs, and health-related quality of life
158 dependent on how long the patient has gone without a recurrent VTE event [20]. The chronic
159 complications post-thrombotic syndrome (PTS) and chronic thromboembolic pulmonary hypertension
160 (CTEPH) were modelled in the background. This means that PTS or CTEPH could occur at any time in
161 the model, regardless of the health state the patient is in. Costs and health effects of these events
162 were taken into account. However, only the severe cases of PTS were modelled, since the costs of
163 minor PTS are considered negligible. For these chronic complications we also used tunnel states since
164 the risks of PTS and CTEPH were also time-dependent.

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Figure 1. Model outline. All patients enter the model in the ‘Index VTE’ state and move to other states upon the occurrence of one of the following events: recurrent incidental PE, recurrent symptomatic PE, fatal recurrent VTE, recurrent DVT, ICH, non-ICH MB, fatal MB, CRNMB, or death by any cause. The triangles represent the health state a patient will enter after an event. The blue squares are permanent states, in which a patient will remain until death while not being at risk for other events. The red squares represent a transient state: the patient will re-enter the model in the ‘Index VTE’ state.
Abbreviations: CRNMB, clinically relevant non-major bleeding; DVT, deep vein thrombosis; ICH, intracranial haemorrhage; MB, major bleeding; PE, pulmonary embolism; VTE, venous thromboembolism

Table 1. Patient characteristics of the hypothetical cohort of 1,000 cancer patients at risk of recurrent VTE.

Unit	Value	Reference
Age (years)	67	[15]
Proportion male	53%	[15]
BMI (kg/m ²)	25.6	[15]
Type of cancer		
<i>Early or locally advanced cancer</i>	39%	[15]
<i>Metastatic cancer</i>	58%	[15]
<i>Haematologic malignancy</i>	2%	[15]
Distribution of PE and DVT		
<i>% index VTE that is symptomatic PE</i>	20%	[15]
<i>% index VTE that is incidental PE</i>	53%	[15]
<i>% index VTE that is DVT</i>	27%	[15]

Abbreviations: BMI, body mass index; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism

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Transition probabilities

Transition probabilities were used to calculate the number of patients in each health state per one-month cycle. Table S1 summarizes all event rates presented in six-month risks. The event rates were translated into monthly transition probabilities with the following formula:

$$P = 1 - \exp \{ -rt \}$$

Where P is the transition probability, r is the event rate, and t is the cycle length (one month) [20].

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Event rates of recurrent VTE, MB, and CRNMB in the first six months of treatment were based on the SELECT-D trial [15]. If patients did not experience a recurrent event during this period, anticoagulation treatment was discontinued. Recurrent VTE rates after treatment discontinuation were based on a retrospective study in active-cancer patients experiencing a VTE [4]. Upon the occurrence of a non-fatal recurrent VTE, patients were assigned to another six months treatment, with corresponding event rates. Bleeding risks after treatment discontinuation were based on the outcomes of the cancer population of the HOKUSAI VTE Cancer trial (which followed patients after edoxaban discontinuation for an additional six months) because these data are not reported for the SELECT-D trial [16]. The HOKUSAI VTE Cancer trial was also used to determine the distribution of ICH, non-ICH, and fatal bleeding. The distributions among the different types of VTE (incidental PE, symptomatic PE, DVT, and fatal PE) and MB (ICH, non-ICH, fatal MB) were calculated based on the total number of events in both arms (rivaroxaban and dalteparin) together and assumed it to be treatment-independent, since the

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3 201 total number of events in the trials was low. The distributions of the types of VTE event were based on
4 202 the number of recurrent VTE events observed in the SELECT-D trial in the lower extremities and
5 203 pulmonary embolisms— other locations of VTE events (brachial, subclavian, jugular, renal plus inferior
6 204 vena cava, or the extrahepatic vein) were excluded [15]. Mortality rates (death by any cause) were
7 205 based on Dutch cancer mortality data from the Netherlands Cancer Registry [21]. In the sensitivity
8 206 analysis, all transition probabilities were varied over beta distributions. For percentages of the type of
9 207 recurrent VTE and MB, a Dirichlet distribution was used in the sensitivity analysis. As recommended by
10 208 the Dutch guidelines for economic evaluation of healthcare, the distributions were based on Briggs et
11 209 al., who described the use of distributions around model input parameters (e.g., distributions limited
12 210 to positive values (costs) or even confined between 0-1 (probabilities)) [18,20].
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19 213 Costs

20 214 All cost parameters are standardised to 2019 Euros, and summarised in Table S2. Event-related
21 215 healthcare costs were based on a previous Dutch cost-effectiveness study for rivaroxaban in the
22 216 general VTE population [22]. Costs of fatal recurrent VTE were assumed to be similar to those of non-
23 217 fatal symptomatic PE. We assumed no event-related healthcare costs for patients with incidental PE,
24 218 because these embolisms were found incidentally and did therefore not require physician visits.
25 219 However, since patients with incidental PE should be treated identically to those with symptomatic PE,
26 220 we did take medication costs into account. Costs for ICH and CTEPH consisted of acute care costs during
27 221 the first month after diagnosis, followed by long-term care costs until the patient moved to the 'death'
28 222 state. Costs of a fatal MB were assumed to be equal to those of non-fatal non-ICH MB.
29 223 Drug costs were retrieved from the national medication costs database [23]. For rivaroxaban these
30 224 costs were based on 15 mg twice daily for three weeks followed by 20 mg once daily. Drug costs of
31 225 dalteparin were based on 200 IU/kg daily during month one followed by 150 IU/kg daily in months two
32 226 to six [15,24]. Based on an average body mass index of 25.6 from the SELECT-D trial and an average
33 227 height of 1.72 m for the Dutch population, we calculated that the average weight was between 69 and
34 228 82 kg, which corresponds with a dose of 15,000 IU daily during month one followed by 12,500 IU daily
35 229 in months two to six [15,25]. Rivaroxaban users were assumed to require an annual check-up of their
36 230 renal function [6]. We included one-time costs for an injection instruction by a home-caregiver.
37 231 Administration costs were only accounted to patients with early or locally advanced cancer (39%),
38 232 since patients with metastatic cancer or haematologic malignancies often already have home care or
39 233 an informal caregiver who can administer the dalteparin injection. Similarly, informal care costs were
40 234 only taken into account for this same subgroup.
41 235 Based on a previously published report on informal care in the Netherlands, we made a distinction
42 236 between intensive (26 hours per week) and non-intensive (8 hours per week) informal care [26]. This
43 237 was multiplied by the average duration and tariff for informal care, obtained from the Dutch cost
44 238 manual [27]. To prevent double counting, we did not include informal care costs for the chronic
45 239 complications. Travel costs were taken into account for renal monitoring visits and upon the
46 240 occurrence of a DVT or CRNMB. Costs related to forgone leisure activity were not taken into account
47 241 since there are no data available on the impact of a VTE or bleeding on leisure losses in cancer patients.
48 242 Moreover, the starting age of the population in the model was 67 years (which is the Dutch retirement
49 243 age) based on the average age of the SELECT-D trial and the fact that the majority (58%) of the patients
50 244 in the SELECT-D trial had metastatic cancer may indicate a low employment rate.
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245 Costs were discounted at an annual rate of 4% [18]. In the sensitivity analysis, the costs were varied
 246 with gamma distributions corresponding to the 95% confidence interval (CI) [18,20], as indicated in
 247 Table S2.

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250 Utilities

251 Utility scores, used to calculate the QALYs, were derived from a sub-analysis from the CATCH study
 252 assessing the EQ-5D scores associated with VTE and recurrent VTE in cancer patients (Table S3) [28].
 253 The CATCH study assessed the effectiveness of six months of treatment with tinzaparin versus warfarin
 254 for the treatment of acute venous thromboembolism in patients with active cancer. It was chosen
 255 because it aligns well with our population and events of interest. Utility decrements for CTEPH were
 256 based on a study assessing EQ-5D VAS scores in CTEPH patients up to 5 years after their initial diagnosis
 257 [29]. Utility decrements for ICH and long-term PTS (>6 months after diagnosis) were obtained from a
 258 previous cost-effectiveness study [30]. QALYs related to fatal events, such as death due to any cause,
 259 fatal PE and fatal MB, were assumed to be 0. QALYs were discounted at 1.5% per annum according to
 260 Dutch guidelines [18]. In the sensitivity analyses, utility scores were varied over their 95% CI with a
 261 beta distribution [18,20].

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264 Sensitivity analysis

265 Sensitivity analyses were conducted to check the robustness of the model results to uncertainty and
 266 known variations in key input parameters. In the probabilistic sensitivity analysis, all input parameters
 267 were varied simultaneously over their 95% CI. If the 95% CI was unavailable and calculating the 95% CI
 268 based on the number of events was not possible, the 95% CI was calculated based on a 25% standard
 269 error. The ICER was calculated with 2,000 iterations and plotted in a cost-effectiveness plane. A
 270 univariate sensitivity analysis was conducted to show the influence of an individual parameter on the
 271 ICER. The 10 most influencing parameters were presented in a tornado diagram.

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274 Scenario analysis

275 We conducted several scenario analyses to show the effect on the outcomes of different (clinical)
 276 situations (Table 2).

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279 **Table 2. Overview of the scenario analyses.**

Scenario	Description	Details
Base case	5-year time horizon from societal perspective	-
1	6-month time horizon from societal perspective	The follow-up period of the SELECT-D trial was six months; therefore, outcomes beyond six months had to be extrapolated based on other publications.
2	Base case analysis from healthcare payer's perspective	In the Netherlands, guidelines advise to calculate the ICER from a societal perspective, while in countries such as the UK or Belgium, the healthcare payer's perspective is preferred. To make results comparable to other countries we also calculated the base case ICER from a healthcare payer's perspective, by excluding the indirect costs.

3	Base case analysis with dalteparin dose of 12,500 IU	The costs of dalteparin vary with the patient's weight. For the base case analysis, we assumed an average weight between 69 and 82 kg. In scenarios 3 and 4 we calculated the base case ICER with the costs of dalteparin based on weight categories of 57–68 kg (12,500 IE daily during month one followed by 10,000 IE daily in month two to six) and 83–98 kg (18,000 IE daily during month one followed by 15,000 IE daily in month two to six), respectively.
4	Base case analysis with dalteparin dose of 18,000 IU	
5	Scenario 1 with treatment duration based on Streiff et al. [17]	This scenario was similar to scenario 1, except for the treatment period which was based on a study of Streiff et al., who—comparable to SELECT-D—compared rivaroxaban to LMWH for the prevention of recurrent VTE in cancer patients [17]. They found an average treatment duration of one month and three months for LMWH and rivaroxaban, respectively.
6	Base case analysis using drug-specific distributions for the types of VTE and MB	Due to low numbers of VTE and MB events observed in the SELECT-D trial [15] and HOKUSAI VTE Cancer [16] trials, respectively, we calculated the distribution of the types of VTE and MB in the base case analysis based on the total number of events and assumed it to be equal for both drugs. In this scenario we assess the effect of this assumption on the cost-effectiveness results by using the drug-specific distributions of the types of VTE and MB based on the results of the SELECT-D and HOKUSAI VTE Cancer trials [15,16].

Abbreviations: IU, international units; MB, major bleeding; VTE, venous thromboembolism.

Budget impact

A budget impact analysis was conducted to estimate the total annual financial consequences of the implementation of rivaroxaban for the treatment and prevention of VTE in cancer patients within the Dutch healthcare setting. The budget impact was calculated from a societal perspective using the costs calculations from the cost-effectiveness model with a one-year time horizon. We extracted from the model the costs (event-related, treatment, and indirect costs) per patient with a cut-off point of one year for rivaroxaban and dalteparin. The difference in cost per patient was multiplied by the annual number of cancer patients with VTE in the Netherlands. The incidence of VTE in cancer patients and the total number of Dutch cancer patients were used to calculate the yearly number of cancer patients with VTE. The Netherlands Cancer Registry estimated a total of 579,781 cancer patients in 2017 [31]. The incidence of VTE in cancer patients was 13.9 per 1,000 person-years, based on a cohort study of linked UK databases [32]. Based on these numbers we calculated a total of approximately 8,000 cancer patients with VTE per year in the Netherlands. The outcome of the budget impact analysis was presented as the total budget impact per year, including a subdivision of the costs per type (event-related costs, treatment costs and indirect costs) and corresponding 95% CIs derived from PSA.

Results

Cost-effectiveness analysis

Table 3 represents the deterministic results of the base case and scenario analyses. In each scenario, rivaroxaban was economically dominant—meaning that it simultaneously confers better clinical and quality-of-life outcomes at less cost—compared with dalteparin. As such, a numerical ICER is not presented because it has no meaning. Despite the fact that every scenario shows an improvement in the patient's health, the difference in QALYs was very low (incremental QALYs of 0.012 over 5 years' time horizon, which equals 4.4 quality-adjusted life days, in the base case analysis). In the base case analysis, rivaroxaban saved €1,376 per patient compared with dalteparin. The scenario calculating the

309 cost-effectiveness over a six-month time horizon resulted in cost-savings of €1,312 per patient
 310 (scenario 1). There was increased cost-savings compared with the societal perspective when calculated
 311 from a healthcare payer's perspective (scenario 2). In scenarios 3 and 4 we assessed the effect of
 312 variations in the patient's weight (and thus dalteparin dosing) on the ICER. Compared with the base
 313 case analysis, there was decreased cost-savings with a lower dalteparin dose and increased cost-
 314 savings with a higher dalteparin dose, both still resulting in dominant ICERs. When comparing three
 315 months of rivaroxaban treatment to one month of dalteparin treatment, we found incremental QALYs
 316 of 0.016 and cost-savings of €702 per patient (scenario 5). We assessed the effect of using drug-specific
 317 distributions of the types of VTE and MB, resulting in cost-savings of €1,815 and incremental QALYs of
 318 0.037 (scenario 6).

319 The number of events and the corresponding average costs per patient in the base case analysis and
 320 scenario 4 (base case analysis with a time horizon of 6 months) are presented in Table 4. Rivaroxaban
 321 is associated with a lower number of recurrent VTE events, preventing on average €131 and €108 in
 322 costs per patient over five years and over six months, respectively. On the other hand, rivaroxaban
 323 causes more bleeding events, especially in the treatment period. ICH and non-ICH MB have the highest
 324 incremental event costs per patient. Treatment costs are higher for dalteparin compared with
 325 rivaroxaban, with incremental costs of €1,721 and €1,468 in the five-year and the six-month time
 326 horizon, respectively. The differences in indirect costs for rivaroxaban compared with dalteparin were
 327 €19 and -€2 for the five-year and the six-month time horizon, respectively.

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330 **Table 3. Deterministic results per patient of the base case and scenario analyses in a cohort of 1,000 cancer patients**
 331 **(2019, Euros).**

	Costs	QALYs	Δ Costs	Δ QALYs	ICER
Base case analysis - 5-year time horizon from societal perspective					
Rivaroxaban	€3,139	2.459	-€1,476	0.012	Rivaroxaban dominant
Dalteparin	€4,615	2.448			
Scenario 1 – 6-month time horizon from societal perspective					
Rivaroxaban	€1,361	0.304	-€1,312	0.004	Rivaroxaban dominant
Dalteparin	€2,673	0.300			
Scenario 2 – base case analysis from healthcare payer's perspective					
Rivaroxaban	€2,942	2.459	-€1,496	0.012	Rivaroxaban dominant
Dalteparin	€4,438	2.448			
Scenario 3 – base case analysis with dalteparin dose of 12,500 IU					
Rivaroxaban	€3,139	2.459	-€1,079	0.012	Rivaroxaban dominant
Dalteparin	€4,218	2.448			
Scenario 4 – base case analysis with dalteparin dose of 18,000 IU					
Rivaroxaban	€3,139	2.459	-€1,898	0.012	Rivaroxaban dominant
Dalteparin	€5,037	2.448			
Scenario 5 – scenario 1 with treatment duration based on Streiff et al. [17]					
Rivaroxaban	€1,299	0.289	-€702	0.016	Rivaroxaban dominant
Dalteparin	€2,001	0.273			
Scenario 6 – base case analysis using drug-specific distributions for the types of VTE and MB					
Rivaroxaban	€3,065	2.463	-€1,815	0.037	Rivaroxaban dominant
Dalteparin	€4,880	2.425			

332 *Abbreviations: ICER, incremental cost-effectiveness ratio; IU, international units; MB, major bleeding; QALY, quality adjusted*
 333 *life-years; VTE, venous thromboembolism.*

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336 Table 4. Number of events and costs per event per patient in a cohort of 1,000 cancer patients (2019, Euros).

Base case (5-year time horizon)						
	Rivaroxaban		Dalteparin		Incremental	
	Number of events	Costs per patient	Number of events	Costs per patient	Number of events	Costs per patient
Event costs						
Recurrent VTE	191	€311.85	275	€442.92	-84	-€131
Non-fatal symptomatic recurrent PE	33	€168.36	48	€239.13	-15	-€71
Non-fatal incidental recurrent PE	58	-	84	-	-26	
Non-fatal recurrent DVT	83	€59.31	120	€84.23	-37	-€25
Fatal recurrent VTE	17	€84.18	24	€119.56	-7	-€35
ICH	11	€550.70	9	€438.40	2	€112
Non-ICH MB	98	€1,106.87	79	€902.47	19	€204
Fatal MB	5	€51.48	4	€41.98	1	€10
CRNMB	197	€56.28	92	€26.93	105	€29
PTS	61	€92.72	61	€92.37	0	€0
CTEPH	20	€223.79	20	€222.83	0	€1
Total event costs		€2,705.54		€2,610.83		€95
Treatment costs		€548.83		€2,270.33		-€1,721
Indirect costs		€196.31		€177.08		€19
Scenario 1 (6-month time horizon)						
	Rivaroxaban		Dalteparin		Incremental	
	Number of events	Costs per patient	Number of events	Costs per patient	Number of events	Costs per patient
Event costs						
Recurrent VTE	38	€58.95	109	€166.96	-70	-€108
Non-fatal symptomatic recurrent PE	7	€31.82	19	€90.14	-12	-€58
Non-fatal incidental recurrent PE	12	-	33	-	-21	-
Non-fatal recurrent DVT	17	€11.21	47	€31.75	-31	-€21
Fatal recurrent VTE	3	€15.91	9	€45.07	-6	-€29
ICH	6	€142.82	4	€94.25	2	€49
Non-ICH MB	50	€539.38	33	€355.95	17	€183
Fatal MB	2	€25.09	2	€16.56	1	€9
CRNMB	130	€35.99	38	€10.62	91	€25
PTS	14	€20.59	14	€20.56	0	€0
CTEPH	3	€21.96	3	€21.93	0	€0
Total event costs		€903.72		€2,639.25		-€1,736
Treatment costs		€479.40		€1,947.45		-€1,468
Indirect costs		€36.50		€38.39		-€2

337 Abbreviations: CRNMB, clinically relevant non-major bleeding; CTEPH, chronic thromboembolic pulmonary hypertension;
338 DVT, deep vein thrombosis; ICH, intracranial haemorrhage; MB, major bleeding; PE, pulmonary embolism; PTS, post
339 thrombotic syndrome; VTE, venous thromboembolism

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342 In the probabilistic sensitivity analysis, we assessed the robustness of the model over a five-year time
343 horizon (base case) and a six-month time horizon (scenario 1). The results are presented in cost-
344 effectiveness planes in Figure 2 and Figure S1. In the base case analysis, rivaroxaban was in the majority
345 (77.8%) of the 2,000 iterations cost-saving and more effective compared with dalteparin. In 22.2% of
346 the iterations rivaroxaban was cost-saving but less effective compared with dalteparin. In scenario 1,
347 rivaroxaban was in almost all (98.7%) the iterations cost-saving and more effective compared with
348 dalteparin.

349 The influence of the individual input parameters on the base case incremental costs and QALYs are
350 analysed in the univariate sensitivity analysis. The tornado diagrams (Figure 3 and Figure 4) present

the 10 input parameters with the highest impact in the base case analysis. The risk of MB for both rivaroxaban and dalteparin, treatment duration of dalteparin, and recurrent VTE risks during the first six months after a VTE had the highest influence on the incremental costs. Similarly, the risk of MB and recurrent VTE in the first six months for rivaroxaban and dalteparin showed the highest influence on the incremental QALYs. Similar results were found in the univariate sensitivity analysis of scenario 1 (Figure S2 and Figure S3).

Figure 2. Probabilistic sensitivity analysis of the base case with five-year time horizon (base case analysis). The red mark represents the deterministic incremental cost-effectiveness ratio. Abbreviation: QALY, quality adjusted life-year

Figure 3. Tornado diagram from the univariate sensitivity analysis for the base case analysis showing the impact of parameters on the incremental costs. Abbreviations: ICH, intracranial haemorrhage; MB, major bleeding; PE, pulmonary embolism; VTE, venous thromboembolism

Figure 4. Tornado diagram from the univariate sensitivity analysis for the base case analysis showing the impact of parameters on the incremental QALYs. Abbreviations: CRNMB, clinically relevant non-major bleeding; ICH, intracranial haemorrhage; MB, major bleeding; VTE, venous thromboembolism

Budget impact

The results of the budget impact analysis are presented in Table 5. The replacement of LMWHs (including dalteparin) with rivaroxaban can lead to cost-savings of a maximum of €11,326,763 (€5,164,254–€17,363,231) over approximately 8,000 cancer patients with VTE based on a one-year time horizon. A reduction in treatment costs can lead to savings of up to €12.6 million. Event-related costs and indirect costs slightly increase by €1,234,467 (€-2,103,366–€5,231,955) and €2,101 (€-173,830–€184,677), respectively, when LMWHs are replaced by rivaroxaban.

Table 5. Budget impact (95% CI) over one-year time horizon in the Netherlands.

Event-related costs	€1,234,467 (€-2,103,366–€5,231,955)
Treatment costs	€-12,559,130 (€-17,327,405–€-8,149,498)
Indirect costs	€-2,101 (€-173,830–€184,677)
Budget impact	€-11,326,763 (€-17,363,231–€-5,164,254)

Abbreviation: CI, confidence interval

Discussion

Thrombosis treatment is a challenge in cancer patients. According to the guidelines, LMWHs and DOACs edoxaban and rivaroxaban are the preferred treatment for the prevention of recurrent VTE in cancer patients [8–11]. We have assessed the cost-effectiveness and budget impact of rivaroxaban in cancer patients at risk of recurrent VTE based on the SELECT-D trial [15]. We conclude that, in the Netherlands, rivaroxaban is a cost-saving treatment option with a small health benefit per patient over

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3 394 five years compared with dalteparin. Comprehensive sensitivity analyses confirm that results
4 395 generated by our model are robust.

5 396 The cost-savings associated with rivaroxaban were mainly driven by the difference in
6 397 treatment costs. It should be noted that this is specifically the case for the Netherlands, and may differ
7 398 in other countries. The VTE recurrence and MB risks also showed to have a high influence on the
8 399 incremental costs and QALYs in the univariate sensitivity analysis. The SELECT-D trial showed a
9 400 relatively low VTE recurrence but higher bleeding (especially CRNMB) compared with dalteparin. This
10 401 cost-effectiveness model allowed to address the question if the reduction in VTE recurrence outweighs
11 402 the increase in bleeding events.

12 403 A total of 84 VTE-related events were prevented over five years, leading to an average cost-
13 404 saving of €131 per patient. This is line with findings from a recent study that assessed the VTE-related
14 405 healthcare costs in cancer patients, which found that rivaroxaban treated patients had a significantly
15 406 lower total VTE-related costs relative to patients treated with LMWH [33]. Although the cost difference
16 407 between the rivaroxaban and dalteparin cohorts was even greater with \$12,004 per patient per year.

17 408 On the other hand, MB events were more frequent with rivaroxaban compared with dalteparin
18 409 (11 ICH and 98 non-ICH versus 9 ICH and 79 non-ICH, respectively). MB events are very burdensome
19 410 and frequently severely disabling, leading to high acute and long-term direct and indirect costs. In line
20 411 with the findings from the SELECT-D trial, CRNMB events were much more frequent with rivaroxaban
21 412 compared with dalteparin (197 and 92, respectively). Although the difference between rivaroxaban
22 413 and dalteparin in CRNMB (105 events over 5-year time horizon) is greater than for MB (20 events over
23 414 5-year time horizon), the influence on the incremental costs and QALYs were lower because CRNMB is
24 415 relatively less burdensome.

25 416 The indirect costs were higher for rivaroxaban than for dalteparin in the base case scenario.
26 417 This can be explained by the increased number of MB events with rivaroxaban compared with
27 418 dalteparin. Moreover, there were no data available on leisure activity losses caused by the occurrence
28 419 of a VTE event in patients who are already burdened with cancer. Therefore, the indirect costs might
29 420 have been underestimated, possibly leading to lower cost-savings. The indirect costs account for €196
30 421 to €177 per rivaroxaban and dalteparin patient, respectively, over five years—approximately 4-6% of
31 422 the total cost—however, they do not have a major influence on the differences between the two drugs
32 423 (€19 and -€2 for the five-year and 6-month time horizon, respectively). This suggests that, although
33 424 the indirect costs might have been underestimated, rivaroxaban is still likely to be cost-saving
34 425 compared with dalteparin.

35 426 As mentioned, the main driver of the cost-savings is the difference in treatment costs. In the
36 427 cost-effectiveness analysis, we estimated that more than €1,700 per patient over a five-year period
37 428 can be saved on treatment costs, compared with dalteparin. Moreover, in the scenario analysis we
38 429 varied the price of dalteparin based on weight. Although the lowest dose (12,500 IU daily during month
39 430 one followed by 10,000 IU in months two to six based on weight class 57–68 kg) had a lower price,
40 431 €8.06 versus €9.93, the ICER remained cost-saving. Rivaroxaban users were assumed to require an
41 432 annual check-up of their renal function. However, cancer patients (especially those with metastatic
42 433 cancer) are at higher risk for renal impairment and may be tested much more frequently [34]. This may
43 434 have caused an overestimation of the costs of rivaroxaban, and therefore reduced the cost-savings
44 435 estimate of rivaroxaban compared with dalteparin.

45 436 In the budget impact analysis, we calculated that rivaroxaban replacing LMWH (including
46 437 dalteparin) leads to cost-savings of €11,326,763 within one year over a total of 8,000 cancer patients.
47 438 This is the absolute maximum, since it is not possible to treat each patient with rivaroxaban from a

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3 439 clinical perspective. In practice, the market share of rivaroxaban will be lower—despite the fact that
4 440 there are three other DOACs that could be prescribed—because there are some clinical considerations
5 441 that should be taken into account. Firstly, although DOACs have far fewer drug interactions than VKAs,
6 442 it should be noted that rivaroxaban is metabolized by CYP3A4 enzymes [1]. Cancer patients, especially
7 443 those with haematological cancer, are at high risk for opportunistic and fungal infections, for which
8 444 they are often treated with CYP3A4 inhibitors or inducers [35]. For this reason, prescription of
9 445 rivaroxaban for the prevention of recurrent VTE in cancer patients must be done carefully [1]. This
10 446 interaction does not play a role in LWMH treatment.

11 447 Secondly, the balance between the risk of thrombosis and the risk of bleeding should always
12 448 be a consideration in the prescription of anticoagulants. For example, DOACs are not advised in
13 449 patients with GI tumours, due to a higher risk of GI bleeding [8–11]. Some prediction scores for primary
14 450 prevention have been developed to predict thrombosis risk in cancer patients, since thrombosis
15 451 prophylaxis is most effective in patients with an increased VTE risk. Unfortunately, for cancer these
16 452 scores have still not been shown to reliably identify patients with the highest risk [36]. Predictive scores
17 453 for bleeding, such as the HAS-BLED score used for atrial fibrillation patients, are also needed.

18 454 A third consideration is the oral administration of rivaroxaban. Although it is less burdensome
19 455 than the LMWH injections, oral administration can be problematic in patients with anorexia and
20 456 vomiting, which is often seen as a side effect in cancer therapy [15]. Moreover, low food intake might
21 457 influence the metabolism of rivaroxaban resulting in lower bioavailability [37]. Lastly, adherence is
22 458 always a point of discussion, but since adherence to current guidelines is often low [36], we feel that
23 459 adherence to rivaroxaban might be relatively high than LMWHs due to the more patient-friendly
24 460 administration.

25 461 Our analysis is not without limitations. It should also be noted that 58% of the patients included
26 462 in the SELECT-D trial had metastatic cancer, and thus results and conclusions pertain mostly to severely
27 463 ill patients. Also, the majority (53%) of the initial VTE events were incidental PE, related to computed
28 464 tomography imaging for tumour status [15]. Additionally, as with all cost-effectiveness models some
29 465 assumptions were required due to lack of data.

30 466 We assumed that patients were treated with anticoagulation over six months, which is in line
31 467 with the guidelines [8–11]. Previous studies have shown that adherence to these guidelines is poor
32 468 [36]. As seen in the study by Streiff et al [17], in practice, treatment with LMWH is often not six months,
33 469 presumably due to the fact that LMWH injections are burdensome, there are concerns about the
34 470 bleeding risk, and the complexity of the treatment of cancer patients [36]. However, this
35 471 recommended treatment period was also not achieved in many patients treated with rivaroxaban,
36 472 which resulted in an average duration of three months. We conducted a scenario analysis (scenario 5)
37 473 to assess this difference in treatment duration (one month of LMWH versus three months of
38 474 rivaroxaban). These results favoured rivaroxaban, because the incremental QALYs increased while still
39 475 being cost-saving. On the other hand, there are also some clinical situations in which the treatment
40 476 period might be longer than six months: for example, in patients with a recurrent VTE event, patients
41 477 with an active malignancy, or patients receiving cancer treatment for their malignancy beyond six
42 478 months. Moreover, in the Netherlands anticoagulation is often continued after six months of initial
43 479 treatment in case the cancer is still active. Unfortunately, we were unable to assess the effect of
44 480 continued anticoagulation treatment due to lack of data. However, since rivaroxaban is associated with
45 481 cost-saving results during the first six months, it is to be expected that during a longer treatment period
46 482 the cost-savings and health gains will accrue even more compared with dalteparin.

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3 483 In the univariate sensitivity analysis, we have shown that the risk of MB and VTE for both
4 484 rivaroxaban and dalteparin have a high influence on the incremental costs and QALYs. In the SELECT-
5 485 D trial [15], the incidence of symptomatic and fatal PE events was relatively higher in patients treated
6 486 with rivaroxaban. However, due to low numbers of VTE observed in the SELECT-D trial [15], we
7 487 calculated the distribution of the type of VTE based on the total number of events and assumed it to
8 488 be equal for both drugs. This may have led to an overestimation of the effect of rivaroxaban compared
9 489 with dalteparin, since symptomatic and fatal PE events have a higher impact on the costs and the
10 490 patient's health compared to DVT and incidental PE. On the other hand, we used this same approach
11 491 to calculate the distributions of the types of MB from the HOKUSAI VTE Cancer trial [16], in which the
12 492 patients treated with dalteparin had relatively more severe MB events compared with the NOAC
13 493 edoxaban (ICH: 17.6% versus 6.1%, respectively). This results in an underestimation of the number of
14 494 MBs in dalteparin-treated patients. We assessed the effect of using drug-specific distributions of the
15 495 type of VTE and MB in scenario six, showing an increase in incremental cost-savings and QALYs
16 496 compared to the base case analysis. Therefore, we conclude that our approach of using equal
17 497 distributions of the types of VTE and MB for rivaroxaban and dalteparin is conservative.

18 498 This study focuses on the secondary prevention of VTE, based on the results of the SELECT-D
19 499 and, partially, the HOKUSAI VTE Cancer trials. However, recently, apixaban was also assessed in cancer
20 500 patients at risk of recurrent VTE and found to be non-inferior compared to dalteparin [38,39].
21 501 Moreover, the AVERT and CASSINI trials have shown that apixaban and rivaroxaban are also effective
22 502 as a primary prophylaxis of VTE in cancer patients compared with a placebo [40–42]. Based on these
23 503 two studies, clinicians may consider DOAC prophylaxis in some of their cancer patients [42]. Therefore,
24 504 future research is needed to assess if DOACs are also cost-effective for the primary prevention of VTE.

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34 35 507 Conclusion

36 508 Treatment with rivaroxaban is dominant (cost-saving while slightly improving the patient's
37 509 health and quality of life) over dalteparin in cancer patients at risk for recurrent VTE in the Netherlands.
38 510 The use of rivaroxaban instead of LMWH (including dalteparin) can save more than eleven million
39 511 euros per year, which is primarily driven by the difference in treatment costs. Since treatment with
40 512 rivaroxaban is economically dominant compared with dalteparin and its oral administration is more
41 513 convenient than daily subcutaneous injection, it is logical that certain cancer patients can benefit from
42 514 DOAC treatment and provide savings to the healthcare system.

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50 517 References

- 51 518 1. Gerotziafas GT, Mahé I, Elalamy I. Therapeutics and Clinical Risk Management Dovepress New
52 519 orally active anticoagulant agents for the prevention and treatment of venous
53 520 thromboembolism in cancer patients. *Ther Clin Risk Manag.* 2014;10:423–36.
54 521 2. Falanga A, Marchetti M, Vignoli A. Coagulation and cancer: Biological and clinical aspects. *J*
55 522 *Thromb Haemost.* 2013;11(2):223–33.
56 523 3. Lechner D, Weltermann A. Chemotherapy-induced thrombosis: a role for microparticles and
57 524 tissue factor? *Semin Thromb Hemost.* 2008;34(2):199–203.
58 525 4. Cohen AT, Katholing A, Rietbrock S, Bamber L, Martinez C. Epidemiology of first and recurrent
59 526 venous thromboembolism in patients with active cancer. *Thromb Haemost.* 2017;117(01):57–

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3 527 65.
4 528 5. Minister of Health W and S. Letter to the parlement - reimbursement rivaroxaban VTE
5 529 (Herbeoordeling uitbreiding nadere voorwaarden rivaroxaban (Xarelto®) bij VTE. 2015;
6 530 6. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, et al. The 2018 European
7 531 Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral
8 532 anticoagulants in patients with atrial fibrillation. *Eur Heart J*. 2018;
9 533 7. Mandala M, Falanga A, Roila F, ESMO Guidelines Working Group. Management of venous
10 534 thromboembolism (VTE) in cancer patients: ESMO Clinical Practice Guidelines. *Ann Oncol*.
11 535 2011;22(Supplement 6):vi85–92.
12 536 8. Key NS, Khorana AA, Kuderer NM, Bohlke K, Lee AYY, Arcelus JJ, et al. Venous
13 537 thromboembolism prophylaxis and treatment in patients with cancer: ASCO clinical practice
14 538 guideline update. *J Clin Oncol*. 2020;38(5):496–520.
15 539 9. Farge D, Frere C, Connors JM, Ay C, Khorana AA, Munoz A, et al. 2019 International Clinical
16 540 Practice Guidelines for the Treatment and Prophylaxis of Venous Thromboembolism in
17 541 Patients With Cancer. *Lancet Oncol*. 2019;20(10):e566–81.
18 542 10. Konstantinides S V., Meyer G, Bueno H, Galié N, Gibbs JSR, Agno W, et al. 2019 ESC
19 543 Guidelines for the diagnosis and management of acute pulmonary embolism developed in
20 544 collaboration with the European respiratory society (ERS). *Eur Heart J*. 2020;41(4):543–603.
21 545 11. Streiff MB, Holmstrom B, Angelini D, Ashrani A, Bockenstedt PL, Chesney C, et al. NCCN
22 546 Guidelines® insights cancer-associated venous thromboembolic disease, version 2.2018
23 547 featured updates to the NCCN guidelines. *JNCCN J Natl Compr Cancer Netw*.
24 548 2018;16(11):1289–303.
25 549 12. Hull RD, Pineo GF, Brant RF, Mah AF, Burke N, Dear R, et al. Long-term low-molecular-weight
26 550 heparin versus usual care in proximal-vein thrombosis patients with cancer. *Am J Med*. 2006
27 551 Dec;119(12):1062–72.
28 552 13. Lee AYY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M, et al. Low-Molecular-Weight
29 553 Heparin versus a Coumarin for the Prevention of Recurrent Venous Thromboembolism in
30 554 Patients with Cancer. *N Engl J Med*. 2003;349(2):146–53.
31 555 14. Meyer G, Marjanovic Z, Valcke J, Lorcerie B, Gruel Y, Solal-Celigny P, et al. Comparison of low-
32 556 molecular-weight heparin and warfarin for the secondary prevention of venous
33 557 thromboembolism in patients with cancer: a randomized controlled study. *Arch Intern Med*.
34 558 162(15):1729–35.
35 559 15. Young AM, Marshall A, Thirlwall J, Chapman O, Lokare A, Hill C, et al. Comparison of an Oral
36 560 Factor Xa Inhibitor With Low Molecular Weight Heparin in Patients With Cancer With Venous
37 561 Thromboembolism: Results of a Randomized Trial (SELECT-D). *J Clin Oncol*. 2018;36(20):2017–
38 562 23.
39 563 16. Raskob GE, van Es N, Verhamme P, Carrier M, Di Nisio M, Garcia D, et al. Edoxaban for the
40 564 Treatment of Cancer-Associated Venous Thromboembolism. *N Engl J Med*. 2018;378(7):615–
41 565 24.
42 566 17. Streiff MB, Milentijevic D, McCrae K, Yannicelli D, Fortier J, Nelson WW, et al. Effectiveness
43 567 and safety of anticoagulants for the treatment of venous thromboembolism in patients with
44 568 cancer. *Am J Hematol*. 2018;93(5):664–71.
45 569 18. Dutch Institute National Health Care (Zorginstituut Nederland). Richtlijn voor het uitvoeren
46 570 van economische evaluaties in de gezondheidszorg (Protocol for the execution of economic
47 571 evaluation in healthcare). 29-02-2016. 2016;(november):120.
48 572 19. National Institute of Public Health and the Environment (RIVM). Cancer numbers and context:
49 573 current situation [Internet]. *volksgezondheidszorg.info*. 2017. p. 1.
50 574 20. Briggs A, Claxton K, Sculpher M. Decision modelling for Health Economic Evaluation. 3rd ed.
51 575 New York: Oxford University Press; 2011. 57–58 p.
52 576 21. The Netherlands Cancer Registry. Survival statistics - all tumours 1961-2015 [Internet].
53 577 22. Heisen M, Treur MJ, Heemstra HE, Giesen EBW, Postma MJ. Cost-effectiveness analysis of
54 578 rivaroxaban for treatment and secondary prevention of venous thromboembolism in the

- 1
2
3 579 Netherlands. *J Med Econ*. 2017 Aug 3;20(8):813–24.
- 4 580 23. Medicijnkosten.nl. The National Health Care Institute (ZIN) [Internet].
- 5 581 24. Summary of Product Characteristics Fragmin. 2015;
- 6 582 25. Dutch Statistics. Length and weight of Dutch population [Internet]. 2017.
- 7 583 26. de Klerk M, de Boer A, Plaisier I, Schyns P, Kooiker S. *Informele hulp: wie doet er wat? - Rapport - SCP* [Internet]. 2015-35. 2015.
- 8 584
- 9 585 27. Hakkaart-van Roijen L, van der Linden N, Bouwmans C, Kanters T, Swan Tan S.
- 10 586 *Kostenhandleiding: Methodologie van kostenonderzoek en referentieprijzen voor*
- 11 587 *economische evaluaties in de gezondheidszorg*. Zorginstituut Ned. 2016;1–120.
- 12 588 28. Lloyd AJ, Dewilde S, Noble S, Reimer E, Lee AYY. What Impact Does Venous
- 13 589 Thromboembolism and Bleeding Have on Cancer Patients' Quality of Life? *Value Heal*.
- 14 590 2018;21(4):449–55.
- 15 591 29. Roman A, Barbera JA, Castillo MJ, Muñoz R, Escribano P. Health-related quality of life in a
- 16 592 national cohort of patients with pulmonary arterial hypertension or chronic thromboembolic
- 17 593 pulmonary hypertension. *Arch Bronconeumol*. 2013;49(5):181–8.
- 18 594 30. Stevanović J, de Jong LA, Kappelhoff BS, Dvortsin EP, Voorhaar M, Postma MJ. Dabigatran for
- 19 595 the Treatment and Secondary Prevention of Venous Thromboembolism; A Cost-Effectiveness
- 20 596 Analysis for the Netherlands. *PLoS One*. 2016;11(10):e0163550.
- 21 597 31. The Netherlands Cancer Registry. Prevalence statistics - all tumours [Internet].
- 22 598 32. Walker AJ, Card TR, West J, Crooks C, Grainge MJ. Incidence of venous thromboembolism in
- 23 599 patients with cancer - a cohort study using linked United Kingdom databases. *Eur J Cancer*.
- 24 600 2013 Apr;49(6):1404–13.
- 25 601 33. Streiff M, Milentijevic D, McCrae KR, Laliberté F, Lejeune D, Lefebvre P, et al. Healthcare
- 26 602 resource utilization and costs associated with venous thromboembolism in cancer patients
- 27 603 treated with anticoagulants. *J Med Econ*. 2019;22(11):1134–40.
- 28 604 34. Apro M, Launay-Vacher V. Importance of monitoring renal function in patients with cancer.
- 29 605 *Cancer Treat Rev*. 2012;38(3):235–40.
- 30 606 35. Vedham V, Divi RL, Starks VL, Verma M. Multiple Infections and Cancer: Implications in
- 31 607 *Epidemiology*. *Technol Cancer Res Treat*. 2014;13(2):177–94.
- 32 608 36. Mahé I, Chidiac J, Helfer H, Noble S. Factors influencing adherence to clinical guidelines in the
- 33 609 management of cancer-associated thrombosis. *J Thromb Haemost*. 2016;14(11):2107–13.
- 34 610 37. Committee for Medicinal Products for Human Use (CHMP). Summary of product
- 35 611 characteristics - rivaroxaban 20 mg [Internet].
- 36 612 38. Agnelli G, Becattini C, Meyer G, Muñoz A, Huisman M V., Connors JM, et al. Apixaban for the
- 37 613 treatment of venous thromboembolism associated with cancer. *N Engl J Med*.
- 38 614 2020;382(17):1599–607.
- 39 615 39. McBane RD, Wysokinski WE, Le-Rademacher JG, Zemla T, Ashrani A, Tafur A, et al. Apixaban
- 40 616 and dalteparin in active malignancy-associated venous thromboembolism: The ADAM VTE
- 41 617 trial. *J Thromb Haemost*. 2020;18(2):411–21.
- 42 618 40. Khorana AA, Soff GA, Kakkar AK, Vadhan-Raj S, Riess H, Wun T, et al. Rivaroxaban for
- 43 619 Thromboprophylaxis in High-Risk Ambulatory Patients with Cancer. *N Engl J Med*. 2019
- 44 620 Feb;380(8):720–8.
- 45 621 41. Carrier M, Abou-Nassar K, Mallick R, Tagalakis V, Shivakumar S, Schattner A, et al. Apixaban to
- 46 622 Prevent Venous Thromboembolism in Patients with Cancer. *N Engl J Med*. 2019;380(8):711–9.
- 47 623 42. Agnelli G. Direct Oral Anticoagulants for Thromboprophylaxis in Ambulatory Patients with
- 48 624 Cancer. *N Engl J Med*. 2019;380(8):781–3.
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Author contributions

Lisa A. de Jong built the economic model, performed the analyses, and contributed to the design of the work, interpretation of the results, writing of the manuscript.

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3 630 Annette W.G. van der Velden contributed to the interpretation of the results, writing of the
4 631 manuscript, and critical revision for important intellectual content.

5 632 Marinus van Hulst contributed to the design of the work, interpretation of the results, writing of the
6 633 manuscript, and critical revision for important intellectual content.

7 634 Maarten J. Postma contributed to the design of the work, interpretation of the results, writing of the
8 635 manuscript, and critical revision for important intellectual content.

9 636 All authors approved of the version to be published.

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13 638 **Checklist for the appropriate reporting statement:** This manuscript was written in accordance with
14 639 the CHEERS checklist for reporting economic evaluations of health interventions.

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17 641 **Data sharing statement:** All relevant data are included in the manuscript. The analyses were
18 642 conducted based on publicly available information which is presented and referenced in the
19 643 manuscript.

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22 645 **Word count:** 5,061 (excluding table and figure descriptions and references)

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25 647 **Patient consent and ethical approval:** The analyses were conducted based on publicly available
26 648 information which is presented and referenced in the article and Supporting Information files, and did
27 649 therefore not require any patient consent forms or approval from an ethical review board.

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29 650

30 651 **Patient and public involvement statement:** It was not appropriate to involve patients or the public in
31 652 the design, or conduct, or reporting, or dissemination plans of our research, because this health
32 653 economic analysis was based on publicly available data and solely concentrated on the analysis of the
33 654 economics consequence of treating cancer patients with rivaroxaban instead of the current standard
34 655 of care.

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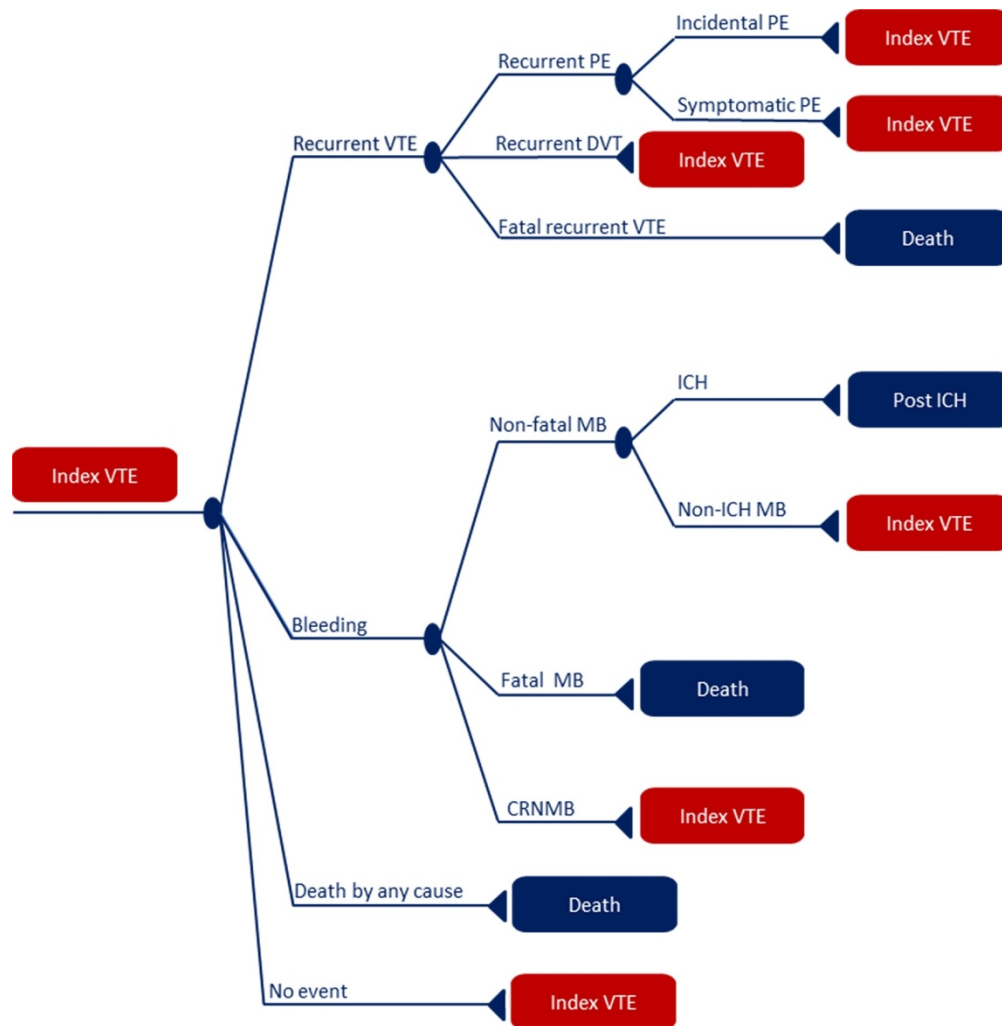
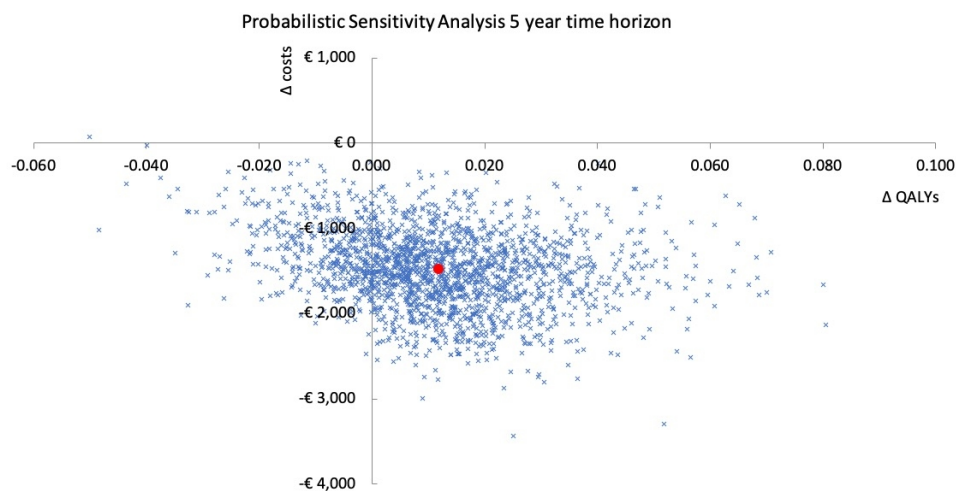


Figure 1. Model outline. All patients enter the model in the 'Index VTE' state and move to other states upon the occurrence of one of the following events: recurrent incidental PE, recurrent symptomatic PE, fatal recurrent VTE, recurrent DVT, ICH, non-ICH MB, fatal MB, CRNMB, or death by any cause. The triangles represent the health state a patient will enter after an event. The blue squares are permanent states, in which a patient will remain until death while not being at risk for other events. The red squares represent a transient state: the patient will re-enter the model in the 'Index VTE' state. Abbreviations: CRNMB, clinically relevant non-major bleeding; DVT, deep vein thrombosis; ICH, intracranial haemorrhage; MB, major bleeding; PE, pulmonary embolism; VTE, venous thromboembolism

74x75mm (600 x 600 DPI)



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Figure 2. Probabilistic sensitivity analysis of the base case with five-year time horizon (base case analysis). The red mark represents the deterministic incremental cost-effectiveness ratio. Abbreviation: QALY, quality adjusted life-year

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206x112mm (144 x 144 DPI)

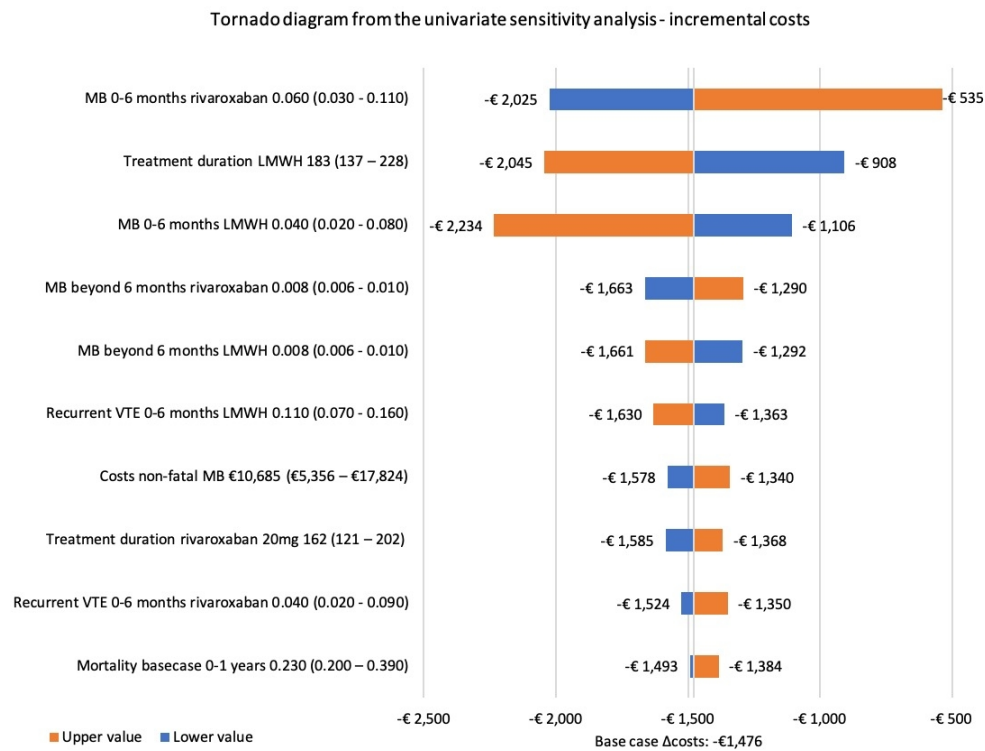


Figure 3. Tornado diagram from the univariate sensitivity analysis for the base case analysis showing the impact of parameters on the incremental costs. Abbreviations: ICH, intracranial haemorrhage; MB, major bleeding; PE, pulmonary embolism; VTE, venous thromboembolism

195x149mm (144 x 144 DPI)

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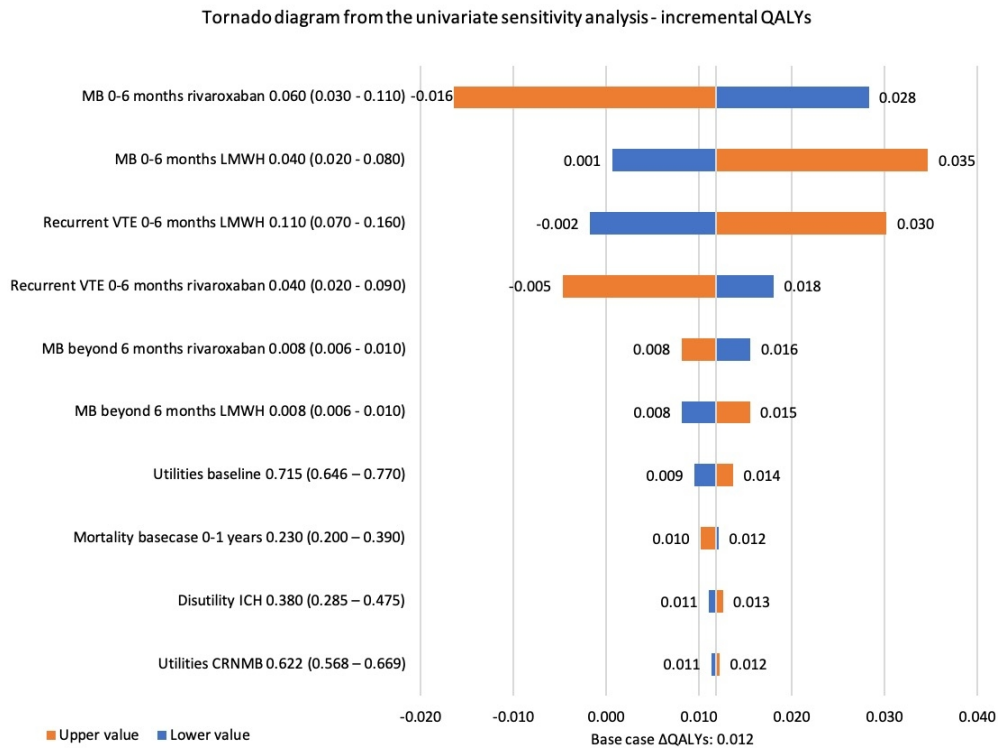


Figure 4. Tornado diagram from the univariate sensitivity analysis for the base case analysis showing the impact of parameters on the incremental QALYs. Abbreviations: CRNMB, clinically relevant non-major bleeding; ICH, intracranial haemorrhage; MB, major bleeding; VTE, venous thromboembolism

195x149mm (144 x 144 DPI)

Supplementary data file – Table S1

Manuscript title: Cost-effectiveness analysis and budget impact of rivaroxaban in cancer patients at risk of recurrent venous thromboembolism

Table S1. Transition probabilities used in the cost-effectiveness model

	Rivaroxaban (95% CI)	LMWH (95% CI)	Distribution	Reference
Recurrent VTE				
0–6 months	0.040 (0.020 – 0.090)	0.110 (0.070 – 0.160)	Beta	[1]
6–12 months	0.040 (0.031 – 0.050)		Beta	[2]
1–2 years	0.034 (0.027 – 0.042)		Beta	[2]
2–3 years	0.021 (0.014 – 0.029)		Beta	[2]
3–4 years	0.016 (0.009 – 0.026)		Beta	[2]
4–5 months	0.013 (0.006 – 0.024)		Beta	[2]
Type of recurrent VTE				
Symptomatic PE	17.4% ($\alpha = 4, \beta = 19$)		Dirichlet	[1]
Incidental PE	30.4% ($\alpha = 7, \beta = 16$)		Dirichlet	[1]
DVT	43.5% ($\alpha = 10, \beta = 13$)		Dirichlet	[1]
Fatal PE	8.7% ($\alpha = 2, \beta = 21$)		Dirichlet	[1]
MB				
0–6 months	0.060 (0.030 – 0.110)	0.040 (0.020 – 0.080)	Beta	[1]
Beyond 6 months treatment	0.008 (0.006 – 0.010)		Beta	[3]
Type of MB				
ICH	10% ($\alpha = 5, \beta = 45$)		Dirichlet	[3]
Non-ICH MB	86% ($\alpha = 43, \beta = 7$)		Dirichlet	[3]
Fatal MB	4% ($\alpha = 2, \beta = 48$)		Dirichlet	[3]
CRNMB				
0–6 months	0.130 (0.090 – 0.190)	0.040 (0.020 – 0.090)	Beta	[1]
Beyond 6 months treatment	0.008 (0.006 – 0.010)		Beta	[3]
PTS				
0–6 months	0.015 (0.011 – 0.019)		Beta	[4]
6–12 months	0.012 (0.009 – 0.015)		Beta	[4]
12–18 months	0.008 (0.006 – 0.010)		Beta	[4]
18–24 months	0.025 (0.023 – 0.019)		Beta	[4]
24–30 months	0.011 (0.008 – 0.014)		Beta	[4]
30–36 months	0.006 (0.005 – 0.008)		Beta	[4]
3–4 years	0.001 (0.0008 – 0.0013)		Beta	[4]
4–5 years	0.001 (0.0008 – 0.0013)		Beta	[4]
CTEPH (annual risk)	0.0057 (0.0002 – 0.012)		Beta	[5]
Mortality (annual risk)				
0–1 years	0.230 (0.200 – 0.390)		Beta	[6]
1–2 years	0.104 (0.088 – 0.180)		Beta	[6]
2–3 years	0.058 (0.055 – 0.120)		Beta	[6]
3–4 years	0.046 (0.043 – 0.068)		Beta	[6]
4–5 years	0.032 (0.030 – 0.073)		Beta	[6]
Relative risk of recurrent VTE, MB, and CRNMB for LMWH versus placebo, used in scenario 5				
Recurrent VTE (any)	5.170		Fixed	[7]
MB	0.242		Fixed	[7]
CRNMB	1.000		Fixed	[7]

Drug-specific distribution of the type of VTE, used in scenario 6				
<i>Symptomatic PE</i>	28.6% ($\alpha = 2, \beta = 5$)	12.5% ($\alpha = 2, \beta = 14$)	Dirichlet	[1]
<i>Incidental PE</i>	14.3% ($\alpha = 1, \beta = 6$)	37.5% ($\alpha = 6, \beta = 10$)	Dirichlet	[1]
<i>DVT</i>	42.9% ($\alpha = 3, \beta = 4$)	43.8% ($\alpha = 7, \beta = 9$)	Dirichlet	[1]
<i>Fatal PE</i>	14.3% ($\alpha = 1, \beta = 6$)	6.3% ($\alpha = 1, \beta = 15$)	Dirichlet	[1]
Drug-specific distribution of the type of MB, used in scenario 6				
<i>ICH</i>	6.1% ($\alpha = 2, \beta = 31$)	17.6% ($\alpha = 3, \beta = 14$)	Dirichlet	[3]
<i>Non-ICH MB</i>	93.9% ($\alpha = 31, \beta = 2$)	70.6% ($\alpha = 12, \beta = 5$)	Dirichlet	[3]
<i>Fatal MB</i>	0% ($\alpha = 0, \beta = 33$)	11.8% ($\alpha = 2, \beta = 15$)	Dirichlet	[3]

Abbreviations: CI, confidence interval; CRNMB, clinically relevant non-major bleeding; CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; ICH, intracranial haemorrhage; LMWH, low-molecular weight heparin; MB, major bleeding; PE, pulmonary embolism; PTS, post-thrombotic syndrome; SE, standard error; VTE, venous thromboembolism

References

1. Young AM, Marshall A, Thirlwall J, Chapman O, Lokare A, Hill C, et al. Comparison of an Oral Factor Xa Inhibitor With Low Molecular Weight Heparin in Patients With Cancer With Venous Thromboembolism: Results of a Randomized Trial (SELECT-D). *J Clin Oncol*. 2018;36(20):2017–23.
2. Cohen AT, Katholing A, Rietbrock S, Bamber L, Martinez C. Epidemiology of first and recurrent venous thromboembolism in patients with active cancer. *Thromb Haemost*. 2017;117(01):57–65.
3. Raskob GE, van Es N, Verhamme P, Carrier M, Di Nisio M, Garcia D, et al. Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism. *N Engl J Med*. 2018;378(7):615–24.
4. 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(4):423–8.
5. Klok FA, van Kralingen KW, van Dijk APJ, Heyning FH, Vliegen HW, Huisman M V. Prospective cardiopulmonary screening program to detect chronic thromboembolic pulmonary hypertension in patients after acute pulmonary embolism. *Haematologica*. 2010;95(6):970–5.
6. The Netherlands Cancer Registry. Survival statistics - all tumours 1961-2015 [Internet].
7. Napolitano M, Saccullo G, Malato A, Sprini D, Ageno W, Imberti D, et al. Optimal duration of low molecular weight heparin for the treatment of cancer-related deep vein thrombosis: the Cancer-DACUS Study. *J Clin Oncol*. 2014;32(32):3607–12.

Supplementary data file – Table S2

Manuscript title: Cost-effectiveness analysis and budget impact of rivaroxaban in cancer patients at risk of recurrent venous thromboembolism

Table S2. Costs included in the cost-effectiveness model (Euros, 2019)

	Value (95% CI)	Distribution	Reference
Event costs			
Recurrent VTE			
Symptomatic PE	€4,717 (€2,364 – €7,868)	Gamma	[1]
Incidental PE	€0	Fixed	Assumption
DVT	€663 (€464 – €862)	Gamma	[1]
Fatal recurrent VTE ^a	€4,717 (€2,364 – €7,868)	Gamma	[1]
ICH acute care costs	€22,769 (€11,644 – €31,175)	Gamma	[2]
ICH long-term costs (monthly)	€637 (€319 – €1,063)	Gamma	[1]
Non-ICH MB	€10,685 (€5,356 – €17,824)	Gamma	[1]
Fatal MB	€10,685 (€5,356 – €17,824)	Gamma	[1]
CRNMB	€274 (€137 – €457)	Gamma	[1]
PTS	€1,431 (€717 – €2,387)	Gamma	[1]
CTEPH acute care costs	€7,843 (€3,931 – €16,433)	Gamma	[1]
CTEPH long-term costs (monthly)	€89 (€45 – €149)	Gamma	[1]
Treatment costs			
Drug cost (daily)			
LMWH ^b	€9.93	Fixed	[3]
Rivaroxaban 15 mg	€4.58	Fixed	[3]
Rivaroxaban 20 mg	€2.29	Fixed	[3]
Treatment duration (days)			
LMWH	183 (137 – 228)	Gamma	[4]
Rivaroxaban 15 mg	21 (16 – 26)	Gamma	[4]
Rivaroxaban 20 mg	162 (121 – 202)	Gamma	[4]
LMWH administration costs			
Costs for home caregiver (per hour)	€59.34 (€44.51 – €74.18)	Gamma	[5]
Duration of at home administration (hour)	0.25 (0.19 – 0.31)	Gamma	Assumption
Hospitalisation duration PE (days) ^c	6.6 (5.0 – 8.3)	Gamma	[6]
Renal monitoring ^c	€1.64 (€1.23 – €2.05)	Gamma	[7]
Indirect costs			
Travel costs			
Cost per km	€0.20 (€0.15 – €0.25)	Gamma	[8]
Distance to hospital (km)	7	Fixed	[8]
Distance to GP (km)	1.1	Fixed	[8]
Informal care costs			
PE	€1,515 (€1,136 – €1,894)	Gamma	[5,9]
DVT	€233 (€175 – €291)	Gamma	[5,9]
ICH (acute informal care costs)	€1,515 (€1,136 – €1,894)	Gamma	[5,9]
ICH (long-term informal care costs, monthly)	€626 (€470 – €783)	Gamma	[10]
Non-ICH MB	€758 (€568 – €947)	Gamma	[5,9]
CRNMB	€117 (€87 – €146)	Gamma	[5,9]

Abbreviations: CI, confidence interval; CRNMB, clinically relevant non-major bleeding; CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; GP, general practitioner; ICH, intracranial haemorrhage; LMWH, low-molecular weight heparin; MB, major bleeding; PE, pulmonary embolism; PTS, post-thrombotic syndrome; VTE, venous thromboembolism

^aAssumed to be equal to the costs of non-fatal PE

^bBased on an average weight between 69 and 82 kg.

^cBased on DRG code 070419 and only taken into account for rivaroxaban treated patients

References

1. Heisen M, Treur MJ, Heemstra HE, Giesen EBW, Postma MJ. Cost-effectiveness analysis of rivaroxaban for treatment and secondary prevention of venous thromboembolism in the Netherlands. *J Med Econ*. 2017 Aug 3;20(8):813–24.
2. Baeten S a, van Exel NJ a, Dirks M, Koopmanschap M a, Dippel DW, Niessen LW. Lifetime health effects and medical costs of integrated stroke services - a non-randomized controlled cluster-trial based life table approach. *Cost Eff Resour Alloc*. 2010;8(1):21.
3. Medicijnkosten.nl. The National Health Care Institute (ZIN) [Internet].
4. Young AM, Marshall A, Thirlwall J, Chapman O, Lokare A, Hill C, et al. Comparison of an Oral Factor Xa Inhibitor With Low Molecular Weight Heparin in Patients With Cancer With Venous Thromboembolism: Results of a Randomized Trial (SELECT-D). *J Clin Oncol*. 2018;36(20):2017–23.
5. Hakkaart-van Roijen L, van der Linden N, Bouwmans C, Kanters T, Swan Tan S. *Kostenhandleiding: Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg*. Zorginstituut Ned. 2016;1–120.
6. van Bellen B, Bamber L, Correa de Carvalho F, Prins M, Wang M, Lensing AWA. Reduction in the length of stay with rivaroxaban as a single-drug regimen for the treatment of deep vein thrombosis and pulmonary embolism. *Curr Med Res Opin*. 2014;30(5):829–37.
7. Dutch Health Authorities. NZa zorgproductapplicatie. Declaration code: 070419. [Internet]. 2018.
8. Roijen LH, Linden N van der, Bouwmans C, Kanters T, Tan SS. *Dutch manual for costing studies in health care*. Diemen; 2015.
9. de Klerk M, de Boer A, Plaisier I, Schyns P, Kooiker S. *Informeel hulp: wie doet er wat? - Rapport - SCP* [Internet]. 2015-35. 2015.
10. van den Berg B, Brouwer W, van Exel J, Koopmanschap M, van den Bos GAM, Rutten F. Economic valuation of informal care: lessons from the application of the opportunity costs and proxy good methods. *Soc Sci Med*. 2006;62(4):835–45.

Supplementary data file – Table S3

Manuscript title: Cost-effectiveness analysis and budget impact of rivaroxaban in cancer patients at risk of recurrent venous thromboembolism

Table S3. Utility values included in the cost-effectiveness model

	Value (95% CI)	Distribution	Reference
Utilities			
Index VTE			
0–1 month	0.565 (0.501 – 0.620)	Beta	[1]
1–2 months	0.655 (0.585 – 0.713)	Beta	[1]
2–3 months	0.674 (0.606 – 0.729)	Beta	[1]
3–4 months	0.698 (0.635 – 0.750)	Beta	[1]
4–5 months	0.707 (0.645 – 0.758)	Beta	[1]
Baseline utility 6 months after index VTE	0.715 (0.646 – 0.770)	Beta	[1]
Recurrent VTE			
DVT	0.605 (0.514 – 0.678)	Beta	[1]
Non-fatal symptomatic PE	0.621 (0.477 – 0.725)	Beta	[1]
Non-fatal incidental PE	0.664 (0.615 – 0.707)	Beta	[1]
Non-ICH MB	0.593 (0.461 – 0.693)	Beta	[1]
CRNMB	0.622 (0.568 – 0.669)	Beta	[1]
Utility decrements			
Recurrent VTE within first six months after index VTE			
DVT	0.040 (0.000 – 0.158)	Beta	[1]
Symptomatic PE	0.024 (0.000 – 0.195)	Beta	[1]
Incidental PE	0.189 (0.021 – 0.404)	Beta	[1]
ICH			
Severe PTS (<6 months after diagnosis)	0.186 (0.090 – 0.280)	Beta	[1]
Severe PTS (>6 months after diagnosis)	0.070 (0.053 – 0.088)	Beta	[2]
CTEPH			
0-1 year	0.194 (0.071 – 0.303)	Beta	[3]
1–4 years	0.109 (0.000 – 0.244)	Beta	[3]
4–5 years	0.079 (0.000 – 0.277)	Beta	[3]

Abbreviations: CI, confidence interval; CRNMB, clinically relevant non-major bleeding; CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; ICH, intracranial haemorrhage; MB, major bleeding; PE, pulmonary embolism; PTS, post-thrombotic syndrome; VTE, venous thromboembolism

References

- Lloyd AJ, Dewilde S, Noble S, Reimer E, Lee AYY. What Impact Does Venous Thromboembolism and Bleeding Have on Cancer Patients' Quality of Life? *Value Heal*. 2018;21(4):449–55.
- Stevanović J, de Jong LA, Kappelhoff BS, Dvortsin EP, Voorhaar M, Postma MJ. Dabigatran for the Treatment and Secondary Prevention of Venous Thromboembolism; A Cost-Effectiveness Analysis for the Netherlands. *PLoS One*. 2016;11(10):e0163550.
- Roman A, Barbera JA, Castillo MJ, Muñoz R, Escribano P. Health-related quality of life in a national cohort of patients with pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension. *Arch Bronconeumol*. 2013;49(5):181–8.

Supplementary data file – Figure S1

Manuscript title: Cost-effectiveness analysis and budget impact of rivaroxaban in cancer patients at risk of recurrent venous thromboembolism

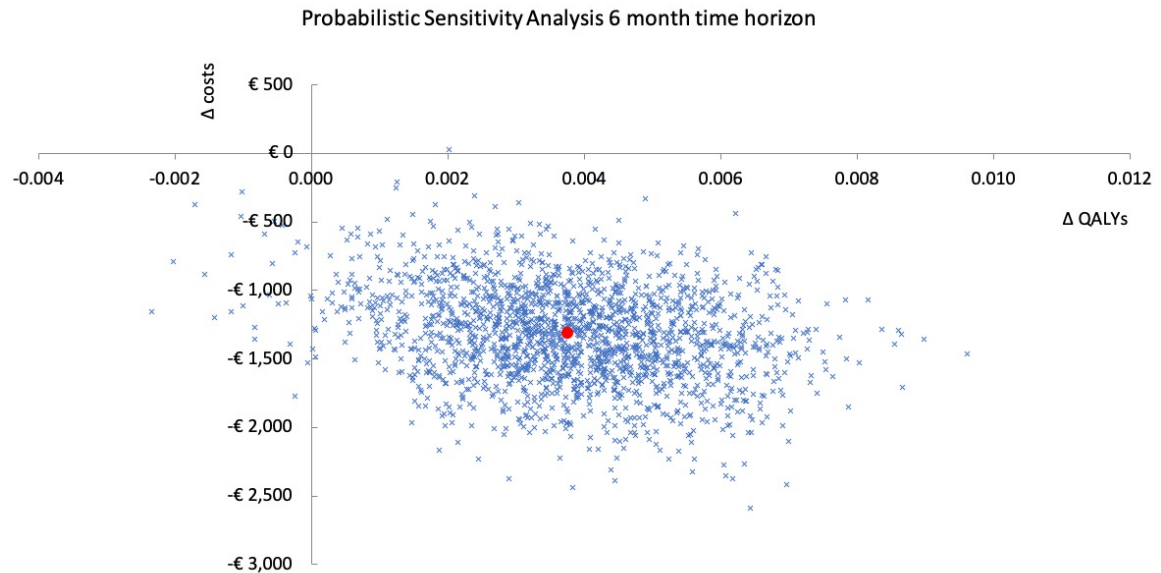


Figure S1. Probabilistic sensitivity analysis with six-month time horizon (scenario 1). The red mark represents the deterministic incremental cost-effectiveness ratio. Abbreviation: QALY, quality adjusted life-year

Supplementary data file – Figure S2

Manuscript title: Cost-effectiveness analysis and budget impact of rivaroxaban in cancer patients at risk of recurrent venous thromboembolism

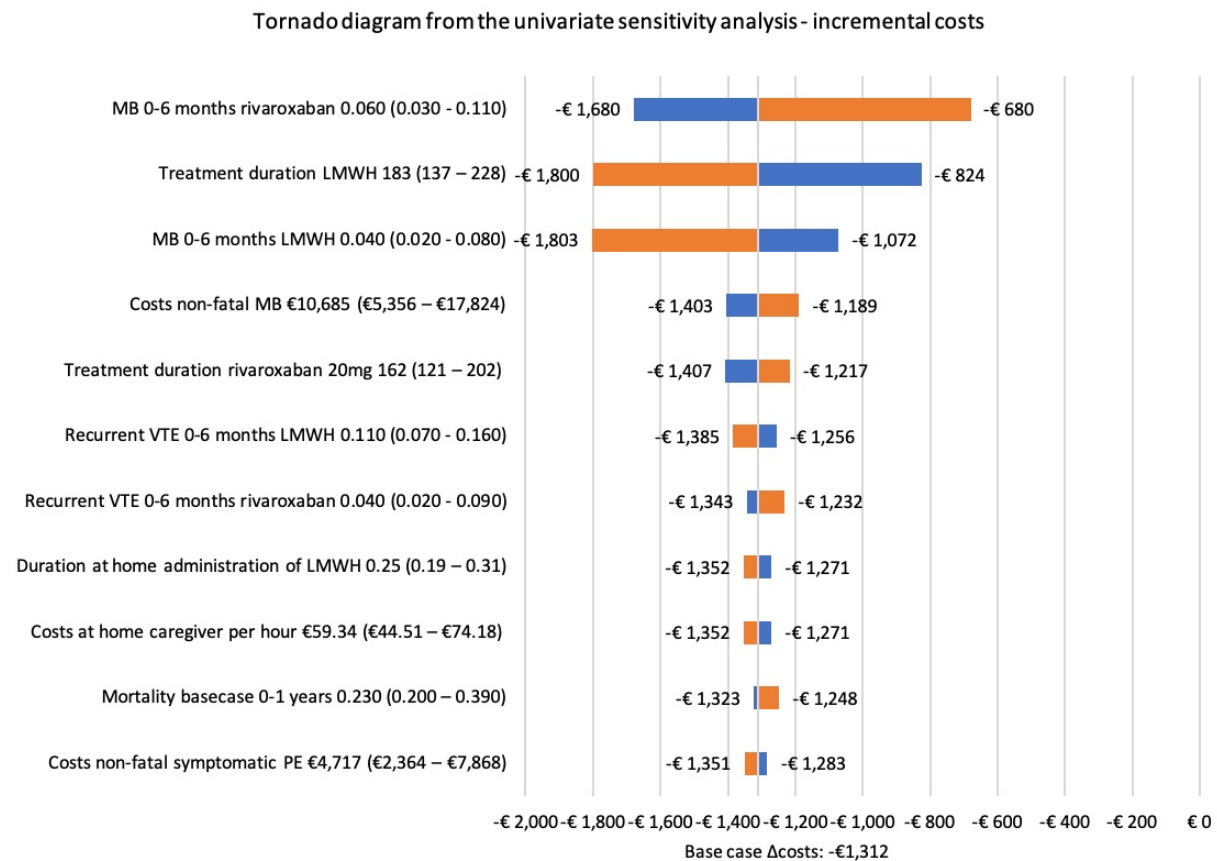


Figure S2. Tornado diagram from the univariate sensitivity analysis for scenario 1 showing the impact of parameters on the incremental costs. Abbreviations: MB, major bleeding; PE, pulmonary embolism; VTE, venous thromboembolism

Supplementary data file – Figure S3

Manuscript title: Cost-effectiveness analysis and budget impact of rivaroxaban in cancer patients at risk of recurrent venous thromboembolism

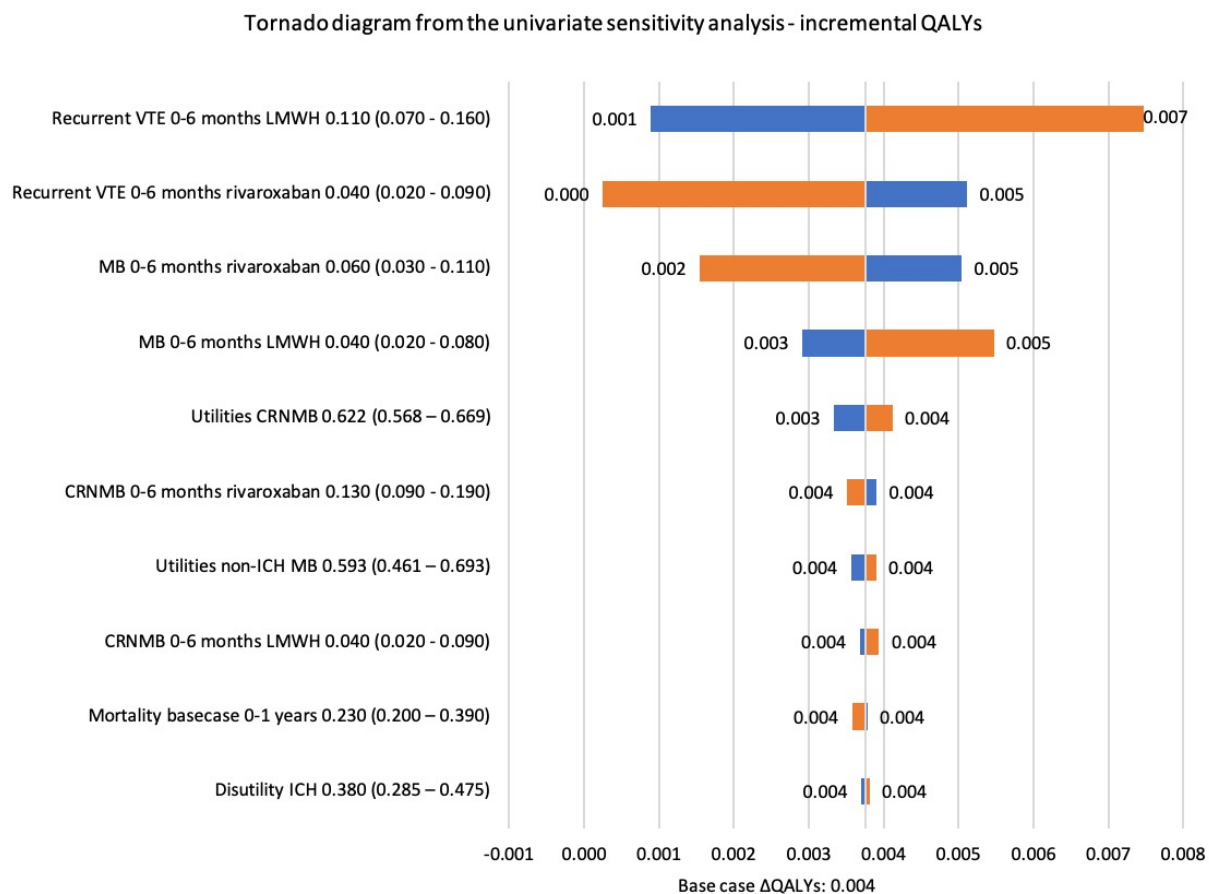


Figure S3. Tornado diagram from the univariate sensitivity analysis for scenario 1 showing the impact of parameters on the incremental QALYs. Abbreviations: CRNMB, clinically relevant non-major bleeding; ICH, intracranial haemorrhage; MB, major bleeding; PE, pulmonary embolism; VTE, venous thromboembolism

CHEERS checklist—Items to include when reporting economic evaluations of health interventions

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as “cost-effectiveness analysis”, and describe the interventions compared.	Page 1, line 9-10
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Page 1, line 34-64
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	Page 4, line 91-120
		Present the study question and its relevance for health policy or practice decisions.	Page 4, line 121-126
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Page 5, line 149-151 Page 5, line 179
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Page 4, line 130-140
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Page 5, line 135-137
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Page 4, line 130-132
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Page 5, line 152-154
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Page 8, line 241 Page 9, line 264
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Page 4, line 133-140
Measurement of effectiveness	11a	<i>Single study-based estimates:</i> Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	
	11b	<i>Synthesis-based estimates:</i> Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	Page 6, line 184-210
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	
Estimating resources and costs	13a	<i>Single study-based economic evaluation:</i> Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
	13b	<i>Model-based economic evaluation:</i> Describe approaches and data sources used to estimate	Page 8, line 213-253

Section/item	Item No	Recommendation	Reported on page No/ line No
		resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Page 8, line 246
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Page 5, line 143-176
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Page 5, line 162-166 Page 8, line 230-240
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Page 7, line 190-201 Page 10, line 284-301
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Page 6, line 201-210 Page 8, line 241-253 Page 9, line 264-271 Page 10, line 276-278
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Page 11, line 320-323 Page 14, line 393-398
Characterising uncertainty	20a	<i>Single study-based economic evaluation:</i> Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	
	20b	<i>Model-based economic evaluation:</i> Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Page 13, line 354-389
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	Page 12, line 311-333
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Page 11, line 323-351
Other			

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Section/item	Item No	Recommendation	Reported on page No/ line No
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Page 3, line 79
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Page 3, line 81-84

For consistency, the CHEERS statement checklist format is based on the format of the CONSORT statement checklist

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