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Cost-Effectiveness of Rivaroxaban Compared with Enoxaparin plus Warfarin for the Treatment of Hospitalized Acute Deep Vein Thrombosis in China

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Abstract

Objective: Limited economic evaluation data for rivaroxaban compared with standard of care (SOC) exists in China. The objective of this analysis was to evaluate the cost-effectiveness of rivaroxaban compared with current SOC (enoxaparin overlapped with warfarin) for the treatment of acute deep vein thrombosis (DVT) in China.

Methods: A Markov model was adapted from a payer's perspective to evaluate the costs and quality-adjusted life years (QALYs) of DVT patients treated with rivaroxaban or enoxaparin/warfarin. Clinical data from the EINSTEIN DVT trial were obtained to estimate the transition probabilities. Data on Chinese health resource use, unit costs and utility parameters were collected from previously published literature and used to estimate the total costs and QALYs. The time horizon was set at 5 years and a 3-month cycle length was used in the model. A 5% discount rate was applied to the projected costs. One-way sensitivity analyses and probabilistic sensitivity analyses (PSA) were undertaken to assess the impact of uncertainty on results.

Results: Rivaroxaban therapy resulted in an increase of 0.008 QALYs and was associated with lower total costs compared with enoxaparin/warfarin (USD 4,744.4 vs USD 5,572.4, respectively), demonstrating it to be a cost-saving treatment strategy. The results were mainly sensitive to length of hospitalization due to DVT on enoxaparin/warfarin, cost per day of hospitalization and the difference in LoS of rivaroxaban and enoxaparin/warfarin treated patients.

Conclusion: Rivaroxaban therapy resulted in a cost saving compared with enoxaparin/warfarin for the anticoagulation treatment of patients with hospitalized acute DVT in China.

Keywords: China, cost-effectiveness, deep vein thrombosis, rivaroxaban, Enoxaparin/warfarin

Article summary

Strengths and limitations of this study:

1. This study evaluated the cost effectiveness of rivaroxaban for acute deep vein thrombosis treatment in China with a well-acknowledged and transparent method.

2. This study could support the decision making of stakeholders in China, including hospitals, payers and physicians.

3. In this analysis, we set a lot of assumptions, in terms of patients' characteristics, inpatient setting and the treatment duration, which may limit the results being extrapolated to whole population.

4. The utility data in the model were derived from literature and not specific to the Chinese population, which may impact the estimation of QALY.

Introduction

Deep vein thrombosis (DVT) and pulmonary embolism (PE) together constitute venous thromboembolism (VTE) – a common disorder causing substantial disease burden and mortality globally [1]. In China, the incidence of VTE (DVT and PE) is high among hospitalized patients [2,3], with incidence rate of 30.0, 8.7 and 3.0 per 100,000 reported for DVT, PE and PE with DVT in a large epidemiological study in Chinese population. In addition, mortality rates of DVT, PE and PE with DVT were 9.0%, 17.4%, and 13.3%, respectively [4]. Consistent with this, VTE is among the major causes of death in hospitals [5]. Clinical guidelines recommend the use of anticoagulant therapy to minimize the risk of mortality and VTE recurrence, with low molecular weight heparins (LMWH) overlapped with vitamin-K-antagonists (VKAs; mostly warfarin) being one of the current standard of care (SoC) [6]. However, there are several limitations to the SoC, e.g. patients requiring injection, frequent international normalization ratio (INR) monitoring and dose titrations [7], which result in unsatisfactory compliance and therapeutic outcomes in clinical practice [7].

Rivaroxaban, an orally-administered anticoagulant which does not require frequent monitoring or dose adjustments [8-10], when compared with enoxaparin plus warfarin (enoxaparin/warfarin), displayed similar efficacy and safety in preventing recurrent DVT and reducing the risk of bleeding events, as reported in the EINSTEIN DVT trial [11]. Evidence from several studies also suggests that rivaroxaban treatment results in a significant decrease in the number of hospitalizations and outpatient visits, as well as a reduction in total hospitalization costs [12, 13].

Although rivaroxaban has been approved for DVT treatment in China, its higher price [14] compared with warfarin might be a barrier for some patients and payers. To address the concern of limited cost-effectiveness evidence for rivaroxaban and enoxaparin/warfarin in DVT, this study

aimed to evaluate the cost-effectiveness of rivaroxaban vs enoxaparin/warfarin from a Chinese healthcare perspective based on findings of the EINSTEIN DVT trial [15].

Methods

A Markov model was developed to estimate the cost effectiveness of rivaroxaban compared with enoxaparin/warfarin in the treatment of patients with acute DVT in hospitals, from the Chinese healthcare payer perspective, for a duration of 5 years. The results of our study were reported using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) [17].

The patients evaluated in our model met the description of participants from the acute DVT arm of the EINSTEIN DVT trial [15]. All patients age was set to 56 years at baseline as per the EINSTEIN study. The patients entered the model in the "On Treatment" state and received oral rivaroxaban (15 mg twice daily for 21 days followed by 20 mg once daily) or enoxaparin (1.0 mg/kg subcutaneously for 8 days) plus warfarin (target INR of 2.0–3.0). Based on the perception that, in Chinese clinical practice, the actual anticoagulant treatment duration for DVT patients is <3 months, the model assumed that all patients had received 3 months of anticoagulation treatment. The model also assumed that all patients received inpatient treatment in the acute phase, because the main risk factors of acute DVT events in China were prolonged immobilization and malignant tumors [16] and those patients were most likely to get treatment in inpatient setting when DVT was provoked.

The outcomes of the model included assessment of quality-adjusted life years (QALYs) and cost of treatment with rivaroxaban or enoxaparin/warfarin. Factors affecting the cost-effectiveness model were also determined. The model allowed tracking of DVT patients through a standard treatment pathway and captured the common complications associated with DVT and its anticoagulant treatment. Probabilities of treatment discontinuation due to bleeding or non-compliance were also considered in the model. A 3-month cycle length with a 5-year time horizon

was used. Total medical costs were considered from a Chinese healthcare perspective and expressed as the 2017 USD exchange rate (1 USD = 6.67 Chinese Yuan), with future costs discounted at 5% per year.

Model framework

The Markov model was developed with 12 health states (Figure 1) and presents progression between health states according to transition probabilities. The model also shows the estimates of life expectancy, health outcomes, resource use and cost of treatment. As per the model, patients were assumed to be on-treatment upon initiation of either rivaroxaban or enoxaparin treatment after an index DVT event. Post-therapy, the patients may undergo several transition states, including acute bleeding events such as major intracranial (IC) bleeding, extracranial (EC) or clinically relevant non-major (CRNM) bleeding, as well as recurrent VTE events (DVT or PE). The common long-term complications were considered in the model, including post-IC bleed state following IC bleed events, chronic thromboembolic pulmonary hypertension (CTEPH) after PE events and post-thrombotic syndrome (PTS) after DVT events. Recurrent DVT, risk of CTEPH and death were also considered in patients not receiving therapy. Each state was assigned a cost and utility weighting to calculate the total costs and QALYs of patients simulated in the model [18].

Model inputs

Core clinical data

The clinical inputs used in the model, regarding the cost, safety and probability of events for both rivaroxaban and SoC, were obtained from the EINSTEIN DVT study [15]. The trial is a multicenter, randomized, open-label, event-driven trial powered to show non-inferiority against warfarin. Total 3449 patients were included in the study: 1731 given rivaroxaban and 1718 given enoxaparin plus a vitamin K antagonist. The primary efficacy outcome was recurrent venous

thromboembolism and the principal safety outcome was major bleeding or clinically relevant nonmajor bleeding.

For the time-period of 0–3 months (cycle 1), event data for recurrent VTE, major bleeding (both IC and EC bleeding), and CRNM bleeding were considered as the baseline (Table 1) [15]. The probability of events with rivaroxaban in cycle 1 was inputted from the hazard ratio (HR) of rivaroxaban compared with enoxaparin/warfarin. Transition probabilities per cycle were calculated based on event risk. This was mainly derived from the EINSTEIN DVT trial and other published literature [19-22].

Risk of post-treatment events, including recurrent VTE, bleeding, PTS, CTEPH and event-specific mortality rates in subsequent cycles were obtained from the published literature (Table 1).

Table 1. Model inputs

	Base case (lower–upper)	Distribution	Source
Baseline events risk (0-3 months) – Enoxaparin/warfarin			
rVTE	2.6% (1.8%–3.3%)	Beta	EINSTEIN-DVT [15]
Probability that rVTE is DVT	48.3% (37.8%–58.8%)	Beta	EINSTEIN-DVT [15]
Major bleeding	0.9% (0.4%–1.3%)	Beta	EINSTEIN-DVT [15]
Probability major bleeding is intracranial bleeding	12.5% (1%–24%)	Beta	EINSTEIN-DVT [15]
CRNM bleeding	4.9% (3.9%–5.9%)	Beta	EINSTEIN-DVT [15]
HR – rivaroxaban vs enoxaparin/warfarin			
rVTE	0.68 (0.44–1.04)	Log-normal	EINSTEIN-DVT [15]
Major bleeding	0.65 (0.33–1.30)	Log-normal	EINSTEIN-DVT [15]
CRNM bleeding	1.055 (0.828–1.342)	Log-normal	EINSTEIN-DVT [15]
Events risk – long-term complications			
rVTE (10-year risk)	39.9% (35.4%–44.4%)	Beta	Prandoni 2007 [39]

Bleeding (subsequent cycles)	0	-	Assumption
Post intracranial bleeding	56.4%	-	Linkins 2010 [20]
CTEPH (2-year risk)	1.25% (1.14%–1.63%)	Beta	Miniati 2006 [21]
PTS (1-year risk)	18% (14.7%–21.3%)	Beta	Prandoni 1997 [22]
Mortality			
PE	25.0% (17%–33%)	Beta	EINSTEIN-DVT [15]
DVT	0.0%	-	Assumption
Intracranial bleeding	43.6% (36.5%–50.7%)	Beta	Linkins 2010 [20]
Major extracranial bleeding	3.9% (2.7%–5.4%)	Beta	Linkins 2010 [20]
CTEPH (3-year mortality)	26.0% (22%–30%)	Beta	Condliffe 2008 [22]
Utility scores			
Population norm	0.929 (0.917–0.941)	Beta	Guan 2015 [23]
DVT	0.884 (0.674–1.000)	Beta	Locadia 2004 [24]
PE	0.663 (0.379–0.905)	Beta	Locadia 2004 [24]
Intracranial bleeding	0.347 (0.147–0.558)	Beta	Locadia 2004 [24]
Major extracranial bleeding	0.684 (0.516–0.905)	Beta	Locadia 2004 [24]
CRNM bleeding	1.000	Beta	Assumption
Post intracranial bleeding	0.713 (0.702–0.724)	Beta	Rivero-Aries 2010 [27]
CTEPH	0.560 (0.528–0.592)	Beta	Meads 2008 [28]
Mild PTS	1.000 (0.91–1.00)	Beta	Lenert 1997 [26]
Severe PTS	0.93 (0.76–1.00)	Beta	Lenert 1997 [26]
Warfarin (disutility)	0.988 (0.95–1.00)	Beta	Marchetti 2001 [29]
Enoxaparin (disutility)	0.988 (0.95-1.00)	-	Assumption
Rivaroxaban (disutility)	1.000	-	Assumption

Drug costs (USD)			Integrated
Rivaroxaban (price/15 mg tablet)	4.17 (2.92–5.42)	-	Management Platform of Beijing Medicine
Rivaroxaban (price/20 mg tablet)	5.19 (3.63–6.75)	-	Sunshine Purchase [31]
Warfarin (price/3 mg tablet/day)	0.08 (0.06–0.10)	-	
Enoxaparin (6000 units: 0.6 ml)	8.71 (6.10–11.32)	-	
Monitoring cost (USD)			
Warfarin monitoring (per time)	10.98 (7.69–14.27)	Gamma	Local charge
Rivaroxaban monitoring (per time)	10.98 (7.69–14.27)	Gamma	Assumption
Costs of events (USD)			
Recurrent VTE-DVT	3853 (2697–5009)	Gamma	Li et al [32]
Recurrent VTE-PE	4083(2858–5308)	Gamma	Li et al [32]
CRNM bleeding	8.25 (5.77–10.72)	Gamma	Wu et al [33]
Major bleeding (extracranial)	2999 (2099–3898)	Gamma	Wu et al [33]
Major bleeding (intracranial)	3834 (2684–4984)	Gamma	Wu et al [33]
Post intracranial bleeding	339.6 (237.7–441.5)	Gamma	Wu et al [33]
Mild/moderate PTS	59.97 (41.98–77.96)	Gamma	Chen et al [34]
Severe PTS	487.3(341.1–633.4)	Gamma	Chen et al [34]
CTEPH	4873 (3411–6334)	Gamma	Chen et al [34]
Resource utilization for acute DVT treatment			
Days of enoxaparin injection	8 (6–11)	Normal	EINSTEIN-DVT [15]
Frequency of monitoring – Enoxaparin/Warfarin	8 (5.6–10.4)	Gamma	Assumption
Frequency of monitoring – rivaroxaban	3 (2.1–3.9)	Gamma	Assumption
Length of stay of patients – Enoxaparin/Warfarin	14.6 (10.22–18.98)	Gamma	Wu [7]
Difference in length of stay of patients – rivaroxaban vs Enoxaparin/Warfarin	3 (2.1–3.9)	Gamma	van Bellen [30]

CRNM, clinically relevant non-major; CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; HR, hazard ratio; PE, pulmonary embolism; PTS, post-thrombotic syndrome; VTE, venous thromboembolism; rVTE, recurrent venous thromboembolism

Discontinuation rates

Based on findings from the EINSTEIN DVT study, the model assumed that all patients with IC bleeding, 40% of patients with major EC bleeding and 11.3% of those with CRNM bleeding would discontinue treatment. Complete discontinuation was assumed for patients with major bleeding events. However, for CRNM bleeding events it was assumed that patients would discontinue therapy for 1 month only and treatment costs would be incurred for the remainder of the cycle.

Utility inputs

Utility values define health state associated quality of life with a range of 0–1 (0= death and 1= best estimated health state). Evidence from published literature was used to determine the various utility values [18,23-25]. The Chinese population norm value was taken as 0.929 (95% CI 0.917–0.941), which was established in the landmark national EQ-5D survey [23]. This value was used as the basis for calculating the utilities of every health state. The utility value used for DVT was 0.884 (95% CI 0.674–1.000), as demonstrated in the report by Locadia et al (2004) [24]. Previous studies [25] have reported increased treatment satisfaction with rivaroxaban compared with enoxaparin/warfarin; therefore, a disutility weight of 1.00 was assumed for rivaroxaban and a disutility value of 0.988 was assumed for enoxaparin/warfarin. Utilities for other states was based on values in previously published literature [26-29] (Table1).

Resource utilization and cost inputs

On entry into the model, resource utilization related to the index event (DVT) was used to analyze the difference between rivaroxaban and enoxaparin/warfarin, especially in terms of drug utilization, monitoring frequency and hospitalization. We assumed that patients received standard dosage and 3 months treatment in the absence of contraindications. It was also conservatively assumed that, in the first 3 months, patients receiving rivaroxaban would require 3 drug monitoring visits and patients receiving enoxaparin/warfarin therapy would require 8 visits. The length of stay for

hospitalized patients with DVT was set as 14.6 days (range 10.22–18.98 days) with enoxaparin/warfarin treatment [7] and was assumed to be three days shorter with rivaroxaban therapy [30]. Unit costs of rivaroxaban, enoxaparin and warfarin were based on local drug tariffs in China (Table 1). The daily cost of hospitalization was based on published literature (USD 363.65, range USD 254.55–USD 472.74) [31,32], with an average length of stay (LoS) of 14.60 days (range 10.22–18.98 days) for patients receiving enoxaparin/warfarin [7]. The costs of managing the event were also based on published literature [7, 15, 31,32,33,34] and assumed to be equal across all treatment arms (Table 1).

Data analysis

Data from published studies and assumptions from Tables 1- were used to calculate mean estimates of 5-year costs and QALYs for rivaroxaban and enoxaparin/warfarin. Base case analysis – total costs and QALYs – were calculated for patients receiving rivaroxaban or SoC. Furthermore, the incremental cost effectiveness ratio (ICER) was also calculated. Besides, we assumed a willingness-to-pay threshold (WTP) of USD 14,992.5 per QALY (i.e. CNY 100,000 originally in the model), which was less than three times the gross domestic product (GDP) per capita in China in 2016 (USD 24351.8 [35]). An ICER of less than USD 14,992.5 per QALY is then an indication that rivaroxaban is cost-effectiveness [36].

To explore the effect of parameter uncertainty, we conducted one-way and probabilistic sensitivity analyses (PSA). In the one-way sensitivity analysis, the minimum and maximum estimates of clinical data, utility and costs were used in the model. For PSA, the variables were specified as distributions: the clinical input followed beta or normal distribution; costs inputs followed gamma distribution and utility data followed beta distribution . Then we run 1,000 simulations in PSA to get 1000 estimates of incremental costs and QALYs. All analyses were carried out using Microsoft Excel.

Patient and Public Involvement

Patients were not involved.

Results

Base case analysis

The results of the base case cost-effectiveness analysis are presented in Table 2. Treatment with rivaroxaban and enoxaparin/warfarin over a 3-month period, estimated for a time duration of 5 years, showed that rivaroxaban therapy was associated with a gain of 0.008 QALYs, (4.111 QALYs with rivaroxaban compared with 4.103 QALYs with enoxaparin/warfarin).. Although the drug acquisition cost of rivaroxaban was higher compared with enoxaparin/warfarin (USD 504.9 vs USD 145.8; difference of USD 359.0), the monitoring cost (USD 24.3 vs USD 64.3; difference of USD –40.0) and treatment cost for VTE events (USD vs USD 4,770.8; difference of USD –1,145.5) with rivaroxaban were lower compared with those for enoxaparin/warfarin. This resulted in an overall lower total cost of treatment with rivaroxaban than with enoxaparin/warfarin (USD 4,744.4 vs USD 5,572.4, respectively; incremental costs USD –828.0). The cost of treating bleeding events, PTS and CTEPH were similar with both treatments and did not impact the overall cost of treatment (Table 2).

Table 2. Total costs and QALYs for rivaroxaban and enoxaparin/warfarin

Outcomes	Rivaroxaban	Enoxaparin/warfarin	Incremental
Total cost (USD)	**4744.4**	**5572.4**	**-828.0**
Drug acquisition cost	504.9	145.8	359.0
Monitoring cost	24.3	64.3	–40.0
VTE event treatment cost	3625.2	4770.8	–1145.5

Bleeding treatment cost	33.8	33.7	0.1
PTS/CTEPH	556.1	557.8	–1.6
QALY	**4.111**	**4.103**	**0.008**
Incremental QALY	-	-	Dominant

CTEPH, chronic thromboembolic pulmonary hypertension; PTS, post-thrombotic syndrome; VTE, venous thromboembolism; QALY, quality-adjusted life year

One-way sensitivity analysis

Since rivaroxaban was dominant in the base-case analysis, a net monetary benefit (NMB) OWSA was conducted to examine economic value. The top 10 most sensitive parameters affecting the rivaroxaban and enoxaparin/warfarin cost-effectiveness model are presented in Figure 2. According to the OWSA, the cost effectiveness of rivaroxaban compared with enoxaparin/warfarin was most sensitive to the length of hospital stay (LoS) of patients on enoxaparin/warfarin, cost per day of hospitalization and the difference in LoS between patients receiving rivaroxaban and enoxaparin/warfarin; these parameters acted as the main drivers of the cost differences. Overall, rivaroxaban showed a positive NMB irrespective of the parameters or the values used.

Probabilistic sensitivity analysis

The PSA confirmed the cost effectiveness of rivaroxaban over enoxaparin/warfarin (Figure3). The majority of simulations showed that 3 months of treatment with rivaroxaban was more cost-effective than the equivalent duration of enoxaparin/warfarin treatment, which resulted in a 99.6% likelihood of rivaroxaban being cost-effective at a WTP threshold of USD 14,992.5 per QALY.

Discussion

This study was an economic evaluation of rivaroxaban anticoagulation therapy compared with SoC for DVT treatment from a Chinese healthcare payer perspective. From the base case analysis,

it was observed that, over a 5-year period, rivaroxaban appeared to be more cost-effective than SoC for the treatment of hospitalized acute DVT in China despite having a higher price per unit than warfarin. These results were mainly driven by the lower hospitalization cost of patients receiving rivaroxaban. The sensitivity analyses also showed the robustness of the model used.

Our findings show that hospitalization costs for monitoring and VTE-related events were lower with rivaroxaban compared with SoC treatment. Although only 0.008 additional QALYs were achieved with rivaroxaban treatment, the PSA suggested that the probability of rivaroxaban being more cost-effective than SoC treatment would be 99.6% per 1000 iterations, indicating that rivaroxaban has greater cost-saving potential than enoxaparin/warfarin, at a WTP threshold of USD 14,992.5 per QALY.

The results of our study are in line with those presented in previous studies. Studies in the Western population have demonstrated the cost-effectiveness of rivaroxaban over LMWH/VKA, placebo, LMWH alone and VKA alone for VTE recurrence and other transition events [18, 37–39]. In a cost-effectiveness analysis, rivaroxaban showed per-patient cost savings at 3-, 6- and 12-months compared with enoxaparin/warfarin in the EINTEIN DVT trial; the HR of VTE, discount rate and mean age were the driving factors affecting this model [18]. Coleman et al. showed greater QALYs gained with rivaroxaban treatment compared with placebo (16.167 vs 16.134) despite a higher treatment cost (USD 22,645 vs USD 22,083), suggesting the higher cost-effectiveness of rivaroxaban over placebo, assuming a willingness-to-pay threshold of USD 50,000 per QALYs gained [37]. An economic comparison of rivaroxaban and warfarin in the US showed a lower cost of treatment with rivaroxaban (USD 3195 vs USD 6188), as well as more QALYs gained (9.29 QALYs vs 9.14 QALYs). However, rivaroxaban was not more cost-effective than warfarin when major bleeding risk with rivaroxaban exceeded 3.8% [38]. Gourzoulidis G et al reported the cost-effectiveness analysis of rivaroxaban for VTE treatment in Greece from a third-party payer perspective, which also showed rivaroxaban was cost effectiveness compared SoC[39].The

findings from all these studies suggest that treatment with rivaroxaban results in greater cost benefits and clinical outcomes from both payer and societal perspectives.

The findings of our study imply that, despite the cost of rivaroxaban being higher than that of warfarin, it has the potential to reduce the overall economic burden of DVT treatment by reducing hospitalization costs. This is particularly meaningful for the Chinese healthcare system and its hospitals and payers, who are struggling to reduce patient LoS and healthcare expenses [40]. With rivaroxaban, patients may have higher utility and satisfaction, as well as lower economic burden due to early discharge and convenient disease management methods. However, the duration of anti-coagulation and patients' age must be important consideration, as in previous study, recurrence of VTE was associated with shorter duration of anti-coagulation, older age and primary DVT [41].

Although methodological standards were followed for the conduct of this analysis, it has several limitations. Firstly, we set a lot of assumptions in the model which may not reflect real-world clinical practice, e.g. all patients were receiving inpatient treatment and the anticoagulant duration was only 3 months with frequent monitoring visits. We then extrapolated the results to wider populations, focusing on the high impact of hospitalizations. Secondly, clinical and utility data were derived from many sources, some of which were not specific to the Chinese population. For example, the clinical inputs on efficacy and safety were taken from the EINSTEIN DVT trial, and some of the utilities data came from international literature because of a lack of Chinese-specific sources; therefore, further validation is warranted before applying these findings in real-world treatment settings. However, including the limited economic data available from China was the best possible measure taken to address the concern. Thirdly, our model lacked analyses based on patient/societal perspectives, which may also be beneficial in evaluating the indirect cost of

rivaroxaban treatment. Real-world studies would also be useful to evaluate the actual cost-effectiveness of rivaroxaban and further justify its clinical and economic value.

Conclusion

In conclusion, our study showed rivaroxaban to be a cost-saving treatment option when compared with enoxaparin/warfarin therapy for hospitalized acute DVT treatment in Chinese patients. The sensitivity of the cost-effectiveness model was mainly driven by the LoS of patients on enoxaparin/warfarin treatment, cost per day of hospitalization and the difference in LoS of rivaroxaban and enoxaparin/warfarin treated patients.

Abbreviations

CE	Cost-effectiveness
CRNM	Clinically relevant non-major
CTEPH	Chronic thromboembolic pulmonary hypertension
DVT	Deep vein thrombosis
HR	Hazard ratio
ICER	Incremental CE ratios
INR	International normalization ratio
ITT	Intention-to-treat
LMWH	Low molecular weight heparins
LoS	Length of stay
OWSA	One-way sensitivity analysis
PE	Pulmonary embolism
PSA	Probabilistic sensitivity analyses
PTS	Post-thrombotic syndrome
QALY	Quality-adjusted life year
RR	Relative risk
SoC	Standard of care
VKA	Vitamin-K-antagonist

Declarations

Ethics approval and consent to participate:

All procedures performed in studies involving human participants were in accordance with the ethical standards of the ethical committee of Peking University Health Science Center (IRB00001052-17006) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent for publication

Not applicable.

Availability of data and material

No additional data available.

Competing interests

Li Yang has nothing to disclose. Jingjing Wu is an employee of Bayer Healthcare Company Ltd.

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Authors' contributions

YL contributed to the design, interpretation of the data and revisions and WJ contributed to the modelling and drafting the manuscript.

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acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients. *Haematologica.* 2007;92:199–205.

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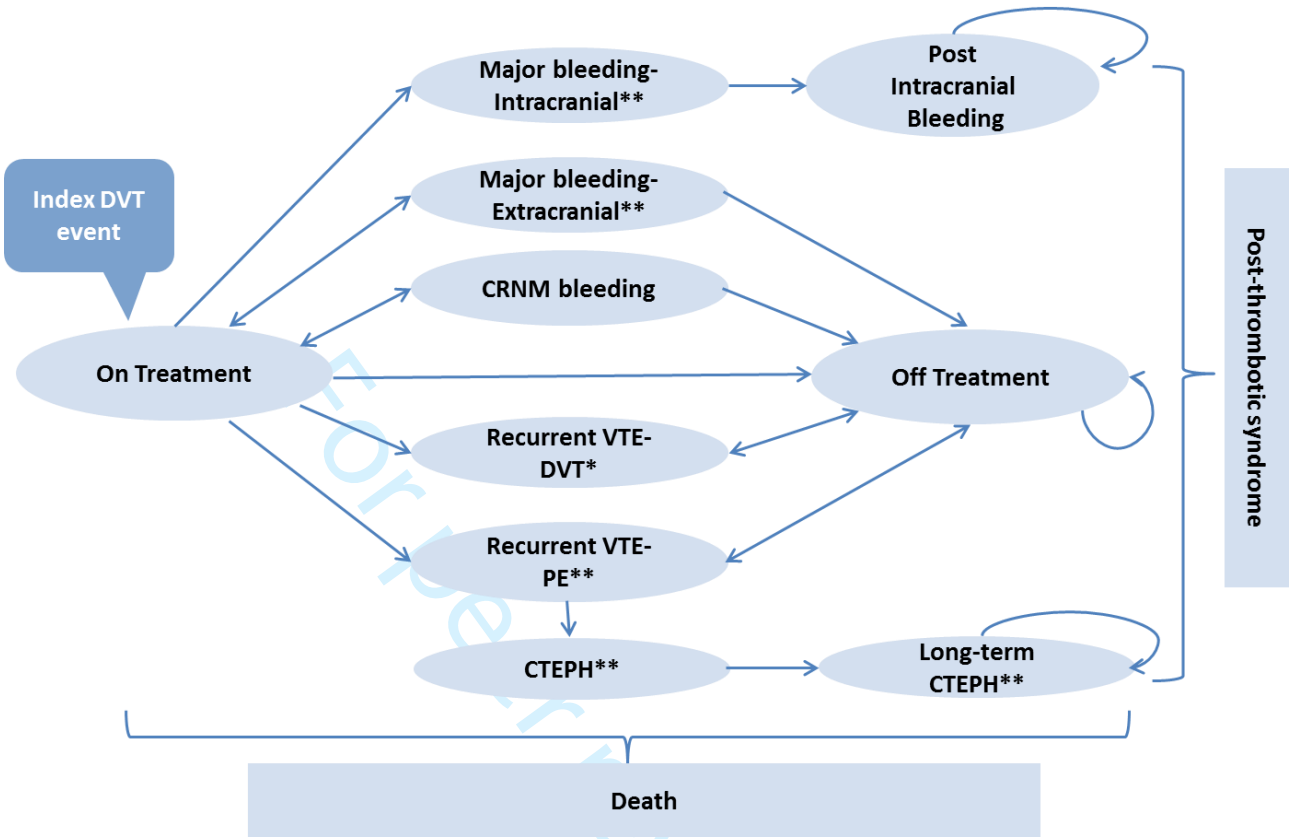
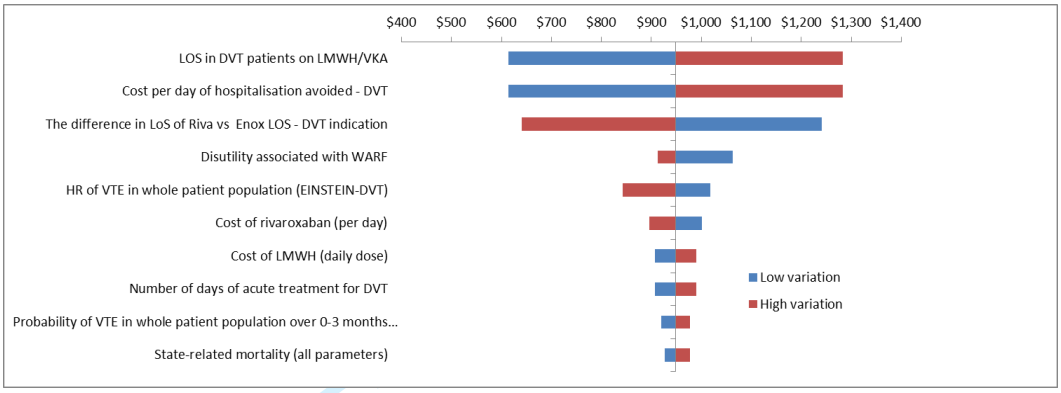
Figure 1. Model schematic [21]



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

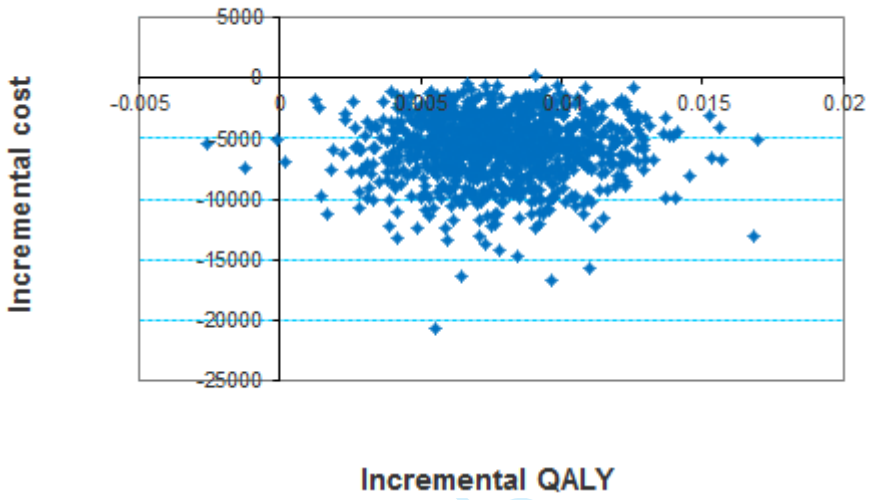
CRNM, clinically relevant non-major; VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism; CTEPH, chronic thromboembolic pulmonary hypertension; PTS, post-thrombotic syndrome

Figure 2. One-way sensitivity analysis tornado diagram for rivaroxaban compared with Standard of care (Net monetary benefit, Quality-adjusted life year based)



LOS, length of stay; DVT, deep vein thrombosis; LMWH, low molecular weight heparin; VKA, vitamin-K-antagonists; Riva, rivaroxaban; Enox, enoxaparin; VTE, venous thromboembolism; WARF, warfarin

Figure 3. Cost-effectiveness plane for rivaroxaban vs enoxaparin/warfarin, based on whole study Hazard ratios (5-year , Quality-adjusted life year outcome)



HR, hazard ratio, QALY, quality-adjusted life year

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
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 2
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	Page 4
		Present the study question and its relevance for health policy or practice decisions.	Page 4
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Page 5
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Page 5
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Page 6
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Page 5
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Page 5
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Page 6
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 5
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	Page 6
	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	NA
Measurement and	12	If applicable, describe the population and methods	NA

CHEERS Checklist

Items to include when reporting economic evaluations of health interventions

valuation of preference based outcomes		used to elicit preferences for outcomes.	
Estimating resources and costs	13a	*Single study-based economic evaluation:* 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.	NA
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate 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.	Page 10
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 6
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 6
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Page 11
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 11
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 7-9
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	Page 12-13

		cost-effectiveness ratios.	
Characterising uncertainty	20a	*Single study-based economic evaluation:* 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).	NA
	20b	*Model-based economic evaluation:* 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
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.	NA
Discussion			
Study findings, limitations, generalizability, and current knowledge	22	Summaries key study findings and describe how they support the conclusions reached. Discuss limitations and the generalizability of the findings and how the findings fit with current knowledge.	Page 13-16
Other			
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 18
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 18

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Cost-Effectiveness of Rivaroxaban Compared with Enoxaparin plus Warfarin for the Treatment of Hospitalized Acute Deep Vein Thrombosis in China

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Abstract

Objective: Limited economic evaluation data for rivaroxaban compared with standard of care (SOC) exists in China. The objective of this analysis was to evaluate the cost-effectiveness of rivaroxaban compared with current SOC (enoxaparin overlapped with warfarin) for the treatment of acute deep vein thrombosis (DVT) in China.

Methods: A Markov model was adapted from a payer's perspective to evaluate the costs and quality-adjusted life years (QALYs) of DVT patients treated with rivaroxaban or enoxaparin/warfarin. Clinical data from the EINSTEIN DVT trial were obtained to estimate the transition probabilities. Data on Chinese health resource use, unit costs and utility parameters were collected from previously published literature and used to estimate the total costs and QALYs. The time horizon was set at 5 years and a 3-month cycle length was used in the model. A 5% discount rate was applied to the projected costs. One-way sensitivity analyses and probabilistic sensitivity analyses (PSA) were undertaken to assess the impact of uncertainty on results.

Results: Rivaroxaban therapy resulted in an increase of 0.008 QALYs and was associated with lower total costs compared with enoxaparin/warfarin (USD 4,744.4 vs USD 5,572.4, respectively), demonstrating it to be a cost-saving treatment strategy. The results were mainly sensitive to length of hospitalization due to DVT on enoxaparin/warfarin, cost per day of hospitalization and the difference in LoS of rivaroxaban and enoxaparin/warfarin treated patients.

Conclusion: Rivaroxaban therapy resulted in a cost saving compared with enoxaparin/warfarin for the anticoagulation treatment of patients with hospitalized acute DVT in China.

Keywords: China, cost-effectiveness, deep vein thrombosis, rivaroxaban, Enoxaparin/warfarin

Article summary

Strengths and limitations of this study:

1. This study evaluated the cost effectiveness of rivaroxaban for acute deep vein thrombosis treatment in China with a well-acknowledged and transparent method.

2. This study could support the decision making of stakeholders in China, including hospitals, payers and physicians.

3. In this analysis, we set a lot of assumptions, in terms of patients' characteristics, inpatient setting and the treatment duration, which may limit the results being extrapolated to whole population.

4. The utility data in the model were derived from literature and not specific to the Chinese population, which may impact the estimation of QALY.

Introduction

Deep vein thrombosis (DVT) and pulmonary embolism (PE) together constitute venous thromboembolism (VTE) – a common disorder causing substantial disease burden and mortality globally [1]. In China, the incidence of VTE (DVT and PE) is high among hospitalized patients [2,3], with incidence rate of 30.0, 8.7 and 3.0 per 100,000 reported for DVT, PE and PE with DVT in a large epidemiological study in Chinese population. In addition, mortality rates of DVT, PE and PE with DVT were 9.0%, 17.4%, and 13.3%, respectively [4]. Consistent with this, VTE is among the major causes of death in hospitals [5]. Clinical guidelines recommend the use of anticoagulant therapy to minimize the risk of mortality and VTE recurrence, with low molecular weight heparins (LMWH) overlapped with vitamin-K-antagonists (VKAs; mostly warfarin) being one of the current standard of care (SoC) [6]. However, there are several limitations to the SoC, e.g. patients requiring injection, frequent international normalization ratio (INR) monitoring and dose titrations [7], which result in unsatisfactory compliance and therapeutic outcomes in clinical practice [7].

Rivaroxaban, an orally-administered anticoagulant which does not require frequent monitoring or dose adjustments [8-10], when compared with enoxaparin plus warfarin (enoxaparin/warfarin), displayed similar efficacy and safety in preventing recurrent DVT and reducing the risk of bleeding events, as reported in the EINSTEIN DVT trial [11]. Evidence from several studies also suggests that rivaroxaban treatment results in a significant decrease in the number of hospitalizations and outpatient visits, as well as a reduction in total hospitalization costs [12, 13].

Although rivaroxaban has been approved for DVT treatment in China, its higher price [14] compared with warfarin might be a barrier for some patients and payers. To address the concern of limited cost-effectiveness evidence for rivaroxaban and enoxaparin/warfarin in DVT, this study

aimed to evaluate the cost-effectiveness of rivaroxaban vs enoxaparin/warfarin from a Chinese healthcare perspective based on findings of the EINSTEIN DVT trial [15].

Methods

A Markov model was developed to estimate the cost effectiveness of rivaroxaban compared with enoxaparin/warfarin in the treatment of patients with acute DVT in hospitals, from the Chinese healthcare payer perspective, for a duration of 5 years. The duration was set based on previous publication [16] and clinical practice in China. The results of our study were reported using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) [17].

The patients evaluated in our model met the description of participants from the acute DVT arm of the EINSTEIN DVT trial [15]. All patients age was set to 56 years at baseline as per the EINSTEIN study. The patients entered the model in the "On Treatment" state and received oral rivaroxaban (15 mg twice daily for 21 days followed by 20 mg once daily) or enoxaparin (1.0 mg/kg subcutaneously for 8 days) plus warfarin (target INR of 2.0–3.0). Based on the perception that, in Chinese clinical practice, the actual anticoagulant treatment duration for DVT patients is <3 months, the model assumed that all patients had received 3 months of anticoagulation treatment. The model also assumed that all patients received inpatient treatment in the acute phase, because the main risk factors of acute DVT events in China were prolonged immobilization and malignant tumors [18] and those patients were most likely to get treatment in inpatient setting when DVT was provoked.

The outcomes of the model included assessment of quality-adjusted life years (QALYs) and cost of treatment with rivaroxaban or enoxaparin/warfarin. Factors affecting the cost-effectiveness model were also determined. The model allowed tracking of DVT patients through a standard treatment pathway and captured the common complications associated with DVT and its anticoagulant treatment. Probabilities of treatment discontinuation due to bleeding or non-

compliance were also considered in the model. A 3-month cycle length with a 5-year time horizon was used. Total medical costs were considered from a Chinese healthcare perspective and expressed as the 2017 USD exchange rate (1 USD = 6.67 Chinese Yuan), with future costs discounted at 5% per year.

Model framework

The Markov model was developed with 12 health states (Figure 1) and presents progression between health states according to transition probabilities. The model also shows the estimates of life expectancy, health outcomes, resource use and cost of treatment. As per the model, patients were assumed to be on-treatment upon initiation of either rivaroxaban or enoxaparin treatment after an index DVT event. Post-therapy, the patients may undergo several transition states, including acute bleeding events such as major intracranial (IC) bleeding, extracranial (EC) or clinically relevant non-major (CRNM) bleeding, as well as recurrent VTE events (DVT or PE). The common long-term complications were considered in the model, including post-IC bleed state following IC bleed events, chronic thromboembolic pulmonary hypertension (CTEPH) after PE events and post-thrombotic syndrome (PTS) after DVT events. Recurrent DVT, risk of CTEPH and death were also considered in patients not receiving therapy. Each state was assigned a cost and utility weighting to calculate the total costs and QALYs of patients simulated in the model [19].

Model inputs

Core clinical data

The clinical inputs used in the model, regarding the cost, safety and probability of events for both rivaroxaban and SoC, were obtained from the EINSTEIN DVT study [15]. The trial is a multicenter, randomized, open-label, event-driven trial powered to show non-inferiority against warfarin. Total 3449 patients were included in the study: 1731 given rivaroxaban and 1718 given

enoxaparin plus a vitamin K antagonist. The primary efficacy outcome was recurrent venous thromboembolism and the principal safety outcome was major bleeding or clinically relevant nonmajor bleeding.

For the time-period of 0–3 months (cycle 1), event data for recurrent VTE, major bleeding (both IC and EC bleeding), and CRNM bleeding were considered as the baseline (Table 1) [15]. The probability of events with rivaroxaban in cycle 1 was inputted from the hazard ratio (HR) of rivaroxaban compared with enoxaparin/warfarin. Transition probabilities per cycle were calculated based on event risk. This was mainly derived from the EINSTEIN DVT trial and other published literature [20-24].

Risk of post-treatment events, including recurrent VTE, bleeding, PTS, CTEPH and event-specific mortality rates in subsequent cycles were obtained from the published literature (Table 1).

Table 1. Model inputs

	Base case (lower–upper)	Distribution	Source
Baseline events risk (0-3 months) – Enoxaparin/warfarin			
rVTE	2.6% (1.8%–3.3%)	Beta	EINSTEIN-DVT [15]
Probability that rVTE is DVT	48.3% (37.8%–58.8%)	Beta	EINSTEIN-DVT [15]
Major bleeding	0.9% (0.4%–1.3%)	Beta	EINSTEIN-DVT [15]
Probability major bleeding is intracranial bleeding	12.5% (1%–24%)	Beta	EINSTEIN-DVT [15]
CRNM bleeding	4.9% (3.9%–5.9%)	Beta	EINSTEIN-DVT [15]
HR – rivaroxaban vs enoxaparin/warfarin			
rVTE	0.68 (0.44–1.04)	Log-normal	EINSTEIN-DVT [15]
Major bleeding	0.65 (0.33–1.30)	Log-normal	EINSTEIN-DVT [15]
CRNM bleeding	1.055 (0.828–1.342)	Log-normal	EINSTEIN-DVT [15]

Events risk – long-term complications			
rVTE (10-year risk)	39.9% (35.4%–44.4%)	Beta	Prandoni 2007 [20]
Bleeding (subsequent cycles)	0	-	Assumption
Post intracranial bleeding	56.4%	-	Linkins 2010 [21]
CTEPH (2-year risk)	1.25% (1.14%–1.63%)	Beta	Miniati 2006 [22]
PTS (1-year risk)	18% (14.7%–21.3%)	Beta	Prandoni 1997 [23]
Mortality			
PE	25.0% (17%–33%)	Beta	EINSTEIN-DVT [15]
DVT	0.0%	-	Assumption
Intracranial bleeding	43.6% (36.5%–50.7%)	Beta	Linkins 2010 [21]
Major extracranial bleeding	3.9% (2.7%–5.4%)	Beta	Linkins 2010 [21]
CTEPH (3-year mortality)	26.0% (22%–30%)	Beta	Condliffe 2008 [24]
Utility scores			
Population norm	0.929 (0.917–0.941)	Beta	Guan 2015 [25]
DVT	0.884 (0.674–1.000)	Beta	Locadia 2004 [26]
PE	0.663 (0.379–0.905)	Beta	Locadia 2004 [26]
Intracranial bleeding	0.347 (0.147–0.558)	Beta	Locadia 2004 [26]
Major extracranial bleeding	0.684 (0.516–0.905)	Beta	Locadia 2004 [26]
CRNM bleeding	1.000	Beta	Assumption
Post intracranial bleeding	0.713 (0.702–0.724)	Beta	Rivero-Aries 2010 [27]
CTEPH	0.560 (0.528–0.592)	Beta	Meads 2008 [28]
Mild PTS	1.000 (0.91–1.00)	Beta	Lenert 1997 [29]
Severe PTS	0.93 (0.76–1.00)	Beta	Lenert 1997 [29]
Warfarin (disutility)	0.988 (0.95–1.00)	Beta	Marchetti 2001 [30]

Enoxaparin (disutility)	0.988 (0.95-1.00)	-	Assumption
Rivaroxaban (disutility)	1.000	-	Assumption
Drug costs (USD)			Integrated
Rivaroxaban (price/15 mg tablet)	4.17 (2.92–5.42)	-	Management Platform of Beijing Medicine
Rivaroxaban (price/20 mg tablet)	5.19 (3.63–6.75)	-	Sunshine Purchase [14]
Warfarin (price/3 mg tablet/day)	0.08 (0.06–0.10)	-	
Enoxaparin (6000 units: 0.6 ml)	8.71 (6.10–11.32)	-	
Monitoring cost (USD)			
Warfarin monitoring (per time)	10.98 (7.69–14.27)	Gamma	Local charge
Rivaroxaban monitoring (per time)	10.98 (7.69–14.27)	Gamma	Assumption
Costs of events (USD)			
Recurrent VTE-DVT	3853 (2697–5009)	Gamma	Li et al [31]
Recurrent VTE-PE	4083(2858–5308)	Gamma	Li et al [31]
CRNM bleeding	8.25 (5.77–10.72)	Gamma	Wu et al [32]
Major bleeding (extracranial)	2999 (2099–3898)	Gamma	Wu et al [32]
Major bleeding (intracranial)	3834 (2684–4984)	Gamma	Wu et al [32]
Post intracranial bleeding	339.6 (237.7–441.5)	Gamma	Wu et al [32]
Mild/moderate PTS	59.97 (41.98–77.96)	Gamma	Chen et al [33]
Severe PTS	487.3(341.1–633.4)	Gamma	Chen et al [33]
CTEPH	4873 (3411–6334)	Gamma	Chen et al [33]
Resource utilization for acute DVT treatment			
Days of enoxaparin injection	8 (6–11)	Normal	EINSTEIN-DVT [15]
Frequency of monitoring – Enoxaparin/Warfarin	8 (5.6–10.4)	Gamma	Assumption
Frequency of monitoring – rivaroxaban	3 (2.1–3.9)	Gamma	Assumption
Length of stay of patients – Enoxaparin/Warfarin	14.6 (10.22–18.98)	Gamma	Wu [7]
Difference in length of stay of patients – rivaroxaban vs Enoxaparin/Warfarin	3 (2.1–3.9)	Gamma	van Bellen [34]

CRNM, clinically relevant non-major; CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; HR, hazard ratio; PE, pulmonary embolism; PTS, post-thrombotic syndrome; VTE, venous thromboembolism; rVTE, recurrent venous thromboembolism

Discontinuation rates

Based on findings from the EINSTEIN DVT study, the model assumed that all patients with IC bleeding, 40% of patients with major EC bleeding and 11.3% of those with CRNM bleeding would discontinue treatment. Complete discontinuation was assumed for patients with major bleeding events. However, for CRNM bleeding events it was assumed that patients would discontinue therapy for 1 month only and treatment costs would be incurred for the remainder of the cycle.

Utility inputs

Utility values define health state associated quality of life with a range of 0–1 (0= death and 1= best estimated health state). Evidence from published literature was used to determine the various utility values. The Chinese population norm value was taken as 0.929 (95% CI 0.917–0.941), which was established in the landmark national EQ-5D survey [25]. This value was used as the basis for calculating the utilities of every health state. The utility value used for DVT was 0.884 (95% CI 0.674–1.000), as demonstrated in the report by Locadia et al (2004) [26]. Previous studies [35] have reported increased treatment satisfaction with rivaroxaban compared with enoxaparin/warfarin; therefore, a disutility weight of 1.00 was assumed for rivaroxaban and a disutility value of 0.988 was assumed for enoxaparin/warfarin. Utilities for other states was based on values in previously published literature [26-30] (Table1).

Resource utilization and cost inputs

On entry into the model, resource utilization related to the index event (DVT) was used to analyze the difference between rivaroxaban and enoxaparin/warfarin, especially in terms of drug utilization, monitoring frequency and hospitalization. We assumed that patients received standard dosage and 3 months treatment in the absence of contraindications. It was also conservatively assumed that, in the first 3 months, patients receiving rivaroxaban would require 3 drug monitoring visits and patients receiving enoxaparin/warfarin therapy would require 8 visits. The length of stay for

hospitalized patients with DVT was set as 14.6 days (range 10.22–18.98 days) with enoxaparin/warfarin treatment [7] and was assumed to be three days shorter with rivaroxaban therapy [34]. Unit costs of rivaroxaban, enoxaparin and warfarin were based on local drug tariffs in China (Table 1). The daily cost of hospitalization was based on published literature (USD 363.65, range USD 254.55–USD 472.74) [31], with an average length of stay (LoS) of 14.6 days (range 10.22–18.98 days) for patients receiving enoxaparin/warfarin [7]. The costs of managing the event were also based on published literature [31-33] and assumed to be equal across all treatment arms (Table 1).

Data analysis

Data from published studies and assumptions from Tables 1- were used to calculate mean estimates of 5-year costs and QALYs for rivaroxaban and enoxaparin/warfarin. Base case analysis – total costs and QALYs – were calculated for patients receiving rivaroxaban or SoC. Furthermore, the incremental cost effectiveness ratio (ICER) was also calculated. Besides, we assumed a willingness-to-pay threshold (WTP) of USD 14,992.5 per QALY (i.e. CNY 100,000 originally in the model), which was less than three times the gross domestic product (GDP) per capita in China in 2016 (USD 24351.8 [36]). An ICER of less than USD 14,992.5 per QALY is then an indication that rivaroxaban is cost-effectiveness [37].

To explore the effect of parameter uncertainty, we conducted one-way and probabilistic sensitivity analyses (PSA). In the one-way sensitivity analysis, the minimum and maximum estimates of clinical data, utility and costs were used in the model. For PSA, the variables were specified as distributions: the clinical input followed beta or normal distribution; costs inputs followed gamma distribution and utility data followed beta distribution. Then we run 1,000 simulations in PSA to get 1000 estimates of incremental costs and QALYs. All analyses were carried out using Microsoft Excel.

Patient and Public Involvement

Patients were not involved.

Results

Base case analysis

The results of the base case cost-effectiveness analysis are presented in Table 2. Treatment with rivaroxaban and enoxaparin/warfarin over a 3-month period, estimated for a time duration of 5 years, showed that rivaroxaban therapy was associated with a gain of 0.008 QALYs, (4.111 QALYs with rivaroxaban compared with 4.103 QALYs with enoxaparin/warfarin). Although the drug acquisition cost of rivaroxaban was higher compared with enoxaparin/warfarin (USD 504.9 vs USD 145.8; difference of USD 359.0), the monitoring cost (USD 24.3 vs USD 64.3; difference of USD –40.0) and treatment cost for VTE events (USD vs USD 4,770.8; difference of USD –1,145.5) with rivaroxaban were lower compared with those for enoxaparin/warfarin. This resulted in an overall lower total cost of treatment with rivaroxaban than with enoxaparin/warfarin (USD 4,744.4 vs USD 5,572.4, respectively; incremental costs USD –828.0). The cost of treating bleeding events, PTS and CTEPH were similar with both treatments and did not impact the overall cost of treatment (Table 2).

Table 2. Total costs and QALYs for rivaroxaban and enoxaparin/warfarin

Outcomes	Rivaroxaban	Enoxaparin/warfarin	Incremental
Total cost (USD)	**4744.4**	**5572.4**	**-828.0**
Drug acquisition cost	504.9	145.8	359.0
Monitoring cost	24.3	64.3	–40.0
VTE event treatment cost	3625.2	4770.8	–1145.5

Bleeding treatment cost	33.8	33.7	0.1
PTS/CTEPH	556.1	557.8	–1.6
QALY	**4.111**	**4.103**	**0.008**
Incremental QALY	-	-	Dominant

CTEPH, chronic thromboembolic pulmonary hypertension; PTS, post-thrombotic syndrome; VTE, venous thromboembolism; QALY, quality-adjusted life year

One-way sensitivity analysis

Since rivaroxaban was dominant in the base-case analysis, a net monetary benefit (NMB) OWSA was conducted to examine economic value. The top 10 most sensitive parameters affecting the rivaroxaban and enoxaparin/warfarin cost-effectiveness model are presented in Figure 2. According to the OWSA, the cost effectiveness of rivaroxaban compared with enoxaparin/warfarin was most sensitive to the length of hospital stay (LoS) of patients on enoxaparin/warfarin, cost per day of hospitalization and the difference in LoS between patients receiving rivaroxaban and enoxaparin/warfarin; these parameters acted as the main drivers of the cost differences. Overall, rivaroxaban showed a positive NMB irrespective of the parameters or the values used.

Probabilistic sensitivity analysis

The PSA confirmed the cost effectiveness of rivaroxaban over enoxaparin/warfarin (Figure3). The majority of simulations showed that 3 months of treatment with rivaroxaban was more cost-effective than the equivalent duration of enoxaparin/warfarin treatment, which resulted in a 99.6% likelihood of rivaroxaban being cost-effective at a WTP threshold of USD 14,992.5 per QALY.

Discussion

This study was an economic evaluation of rivaroxaban anticoagulation therapy compared with SoC for DVT treatment from a Chinese healthcare payer perspective. From the base case analysis,

it was observed that, over a 5-year period, rivaroxaban appeared to be more cost-effective than SoC for the treatment of hospitalized acute DVT in China despite having a higher price per unit than warfarin. These results were mainly driven by the lower hospitalization cost of patients receiving rivaroxaban. The sensitivity analyses also showed the robustness of the model used.

Our findings show that hospitalization costs for monitoring and VTE-related events were lower with rivaroxaban compared with SoC treatment. Although only 0.008 additional QALYs were achieved with rivaroxaban treatment, the PSA suggested that the probability of rivaroxaban being more cost-effective than SoC treatment would be 99.6% per 1000 iterations, indicating that rivaroxaban has greater cost-saving potential than enoxaparin/warfarin, at a WTP threshold of USD 14,992.5 per QALY.

The results of our study are in line with those presented in previous studies. Studies in the Western population have demonstrated the cost-effectiveness of rivaroxaban over LMWH/VKA, placebo, LMWH alone and VKA alone for VTE recurrence and other transition events [19, 38–40]. In a cost-effectiveness analysis, rivaroxaban showed per-patient cost savings at 3-, 6- and 12-months compared with enoxaparin/warfarin in the EINTEIN DVT trial; the HR of VTE, discount rate and mean age were the driving factors affecting this model [19]. Coleman et al. showed greater QALYs gained with rivaroxaban treatment compared with placebo (16.167 vs 16.134) despite a higher treatment cost (USD 22,645 vs USD 22,083), suggesting the higher cost-effectiveness of rivaroxaban over placebo, assuming a willingness-to-pay threshold of USD 50,000 per QALYs gained [38]. An economic comparison of rivaroxaban and warfarin in the US showed a lower cost of treatment with rivaroxaban (USD 3195 vs USD 6188), as well as more QALYs gained (9.29 QALYs vs 9.14 QALYs). However, rivaroxaban was not more cost-effective than warfarin when major bleeding risk with rivaroxaban exceeded 3.8% [39]. Gourzoulidis G et al reported the cost-effectiveness analysis of rivaroxaban for VTE treatment in Greece from a third-party payer perspective, which also showed rivaroxaban was cost effectiveness compared SoC[40].The

findings from all these studies suggest that treatment with rivaroxaban results in greater cost benefits and clinical outcomes from both payer and societal perspectives.

The findings of our study imply that, despite the cost of rivaroxaban being higher than that of warfarin, it has the potential to reduce the overall economic burden of DVT treatment by reducing hospitalization costs. This is particularly meaningful for the Chinese healthcare system and its hospitals and payers, who are struggling to reduce patient LoS and healthcare expenses [41]. With rivaroxaban, patients may have higher utility and satisfaction, as well as lower economic burden due to early discharge and convenient disease management methods. However, the duration of anti-coagulation and patients' age must be important consideration, as in previous study, recurrence of VTE was associated with shorter duration of anti-coagulation, older age and primary DVT [20].

Although methodological standards were followed for the conduct of this analysis, it has several limitations. Firstly, we set a lot of assumptions in the model which may not reflect real-world clinical practice, e.g. all patients were receiving inpatient treatment and the anticoagulant duration was only 3 months with frequent monitoring visits. We then extrapolated the results to wider populations, focusing on the high impact of hospitalizations. Secondly, clinical and utility data were derived from many sources, some of which were not specific to the Chinese population. For example, the clinical inputs on efficacy and safety were taken from the EINSTEIN DVT trial, and some of the utilities data came from international literature because of a lack of Chinese-specific sources; therefore, further validation is warranted before applying these findings in real-world treatment settings. However, including the limited economic data available from China was the best possible measure taken to address the concern. Thirdly, our model lacked analyses based on patient/societal perspectives, which may also be beneficial in evaluating the indirect cost of

rivaroxaban treatment. Real-world studies would also be useful to evaluate the actual cost-effectiveness of rivaroxaban and further justify its clinical and economic value.

Conclusion

In conclusion, our study showed rivaroxaban to be a cost-saving treatment option when compared with enoxaparin/warfarin therapy for hospitalized acute DVT treatment in Chinese patients. The sensitivity of the cost-effectiveness model was mainly driven by the LoS of patients on enoxaparin/warfarin treatment, cost per day of hospitalization and the difference in LoS of rivaroxaban and enoxaparin/warfarin treated patients.

Abbreviations

CE	Cost-effectiveness
CRNM	Clinically relevant non-major
CTEPH	Chronic thromboembolic pulmonary hypertension
DVT	Deep vein thrombosis
HR	Hazard ratio
ICER	Incremental CE ratios
INR	International normalization ratio
ITT	Intention-to-treat
LMWH	Low molecular weight heparins
LoS	Length of stay
OWSA	One-way sensitivity analysis
PE	Pulmonary embolism
PSA	Probabilistic sensitivity analyses
PTS	Post-thrombotic syndrome
QALY	Quality-adjusted life year
RR	Relative risk
SoC	Standard of care
VKA	Vitamin-K-antagonist

Declarations

Ethics approval and consent to participate:

All procedures performed in studies involving human participants were in accordance with the ethical standards of the ethical committee of Peking University Health Science Center (IRB00001052-17006) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent for publication

Not applicable.

Availability of data and material

No additional data available.

Competing interests

Li Yang has nothing to disclose. Jingjing Wu is an employee of Bayer Healthcare Company Ltd.

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Authors' contributions

YL contributed to the design, interpretation of the data and revisions and WJ contributed to the modelling and drafting the manuscript.

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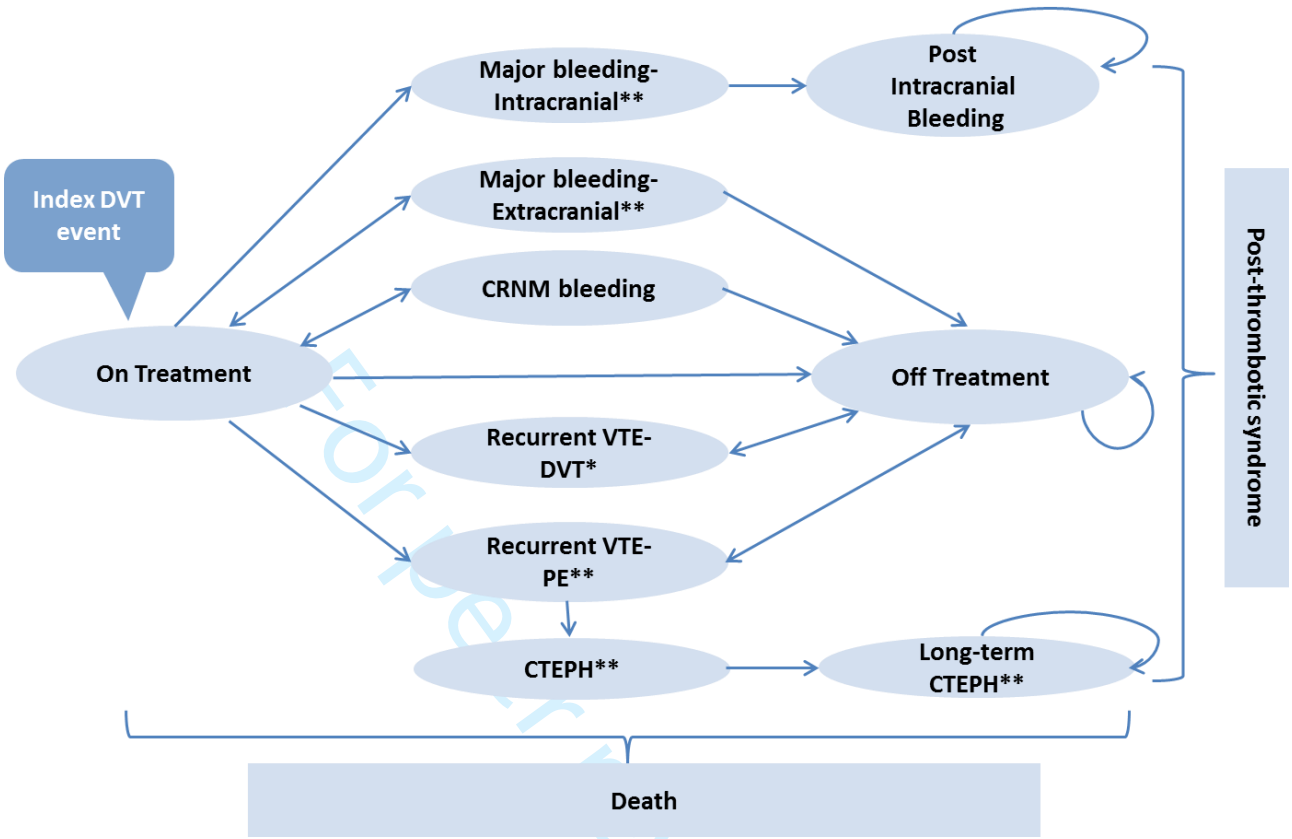
List of tables

Figures

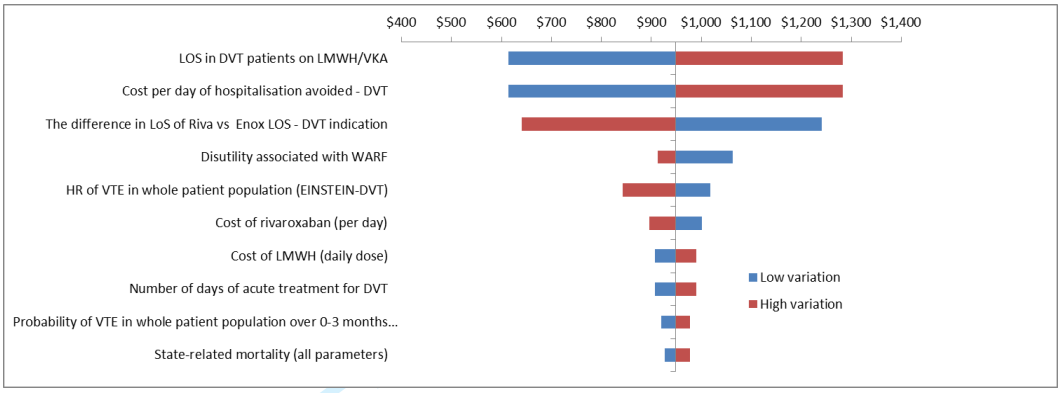
Figure 1. Model schematic [21]



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

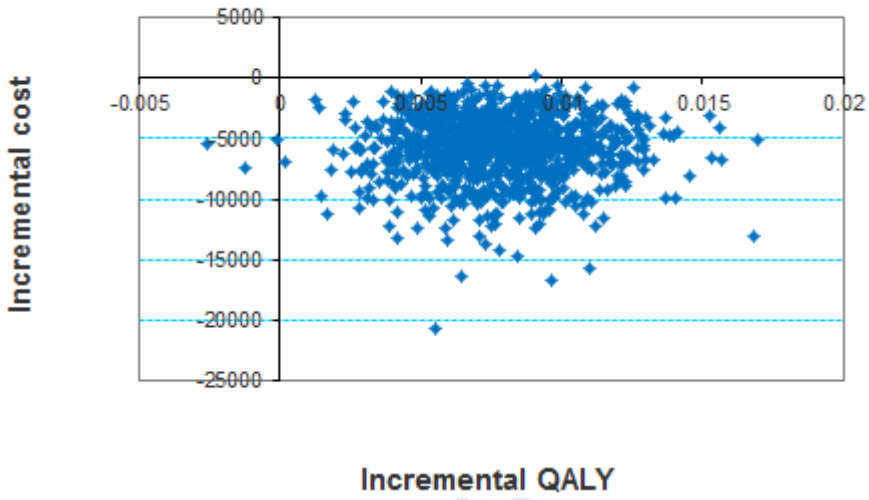
CRNM, clinically relevant non-major; VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism; CTEPH, chronic thromboembolic pulmonary hypertension; PTS, post-thrombotic syndrome

Figure 2. One-way sensitivity analysis tornado diagram for rivaroxaban compared with Standard of care (Net monetary benefit, Quality-adjusted life year based)



LOS, length of stay; DVT, deep vein thrombosis; LMWH, low molecular weight heparin; VKA, vitamin-K-antagonists; Riva, rivaroxaban; Enox, enoxaparin; VTE, venous thromboembolism; WARF, warfarin

Figure 3. Cost-effectiveness plane for rivaroxaban vs enoxaparin/warfarin, based on whole study Hazard ratios (5-year , Quality-adjusted life year outcome)



HR, hazard ratio, QALY, quality-adjusted life year

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
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 2
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	Page 4
		Present the study question and its relevance for health policy or practice decisions.	Page 4-5
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Page 5
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Page 5
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Page 5
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Page 5
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Page 5
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Page 6
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 5
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	Page 6-7
	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	NA

Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	NA
Estimating resources and costs	13a	*Single study-based economic evaluation:* 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.	NA
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate 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.	Page 10-11
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 6
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 6
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Page 11
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 11
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 7-9
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	Page 12-13

		comparator groups. If applicable, report incremental cost-effectiveness ratios.	
Characterising uncertainty	20a	*Single study-based economic evaluation:* 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).	NA
	20b	*Model-based economic evaluation:* 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
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.	NA
Discussion			
Study findings, limitations, generalizability, and current knowledge	22	Summaries key study findings and describe how they support the conclusions reached. Discuss limitations and the generalizability of the findings and how the findings fit with current knowledge.	Page 14-16
Other			
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 18
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 18