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ORIGINAL RESEARCH

A Cost Effectiveness Analysis of Rivaroxaban Compared to Warfarin for Deep Vein Thrombosis (DVT) Treatment in Ethiopia

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Background: Deep vein thrombosis and pulmonary embolism are known by the collective name venous thromboembolism. Deep vein thrombosis is the third most common cardiovascular disorder in the world. The disease is also prevalent in Africa including Ethiopia, besides lack of studies that show epidemiology of the disease.

Objective: To assess cost effectiveness of rivaroxaban compared to warfarin-based therapy for deep vein thrombosis patients in Ethiopia.

Methods: A Markov model was built to compare cost and effectiveness of rivaroxaban 15mg bid for three weeks and 20mg per day for the rest to adjusted dose of warfarin for one year using a restricted societal perspective. The population in this analysis was a hypothetical cohort of deep vein thrombosis patients 40 years old with no contraindication, comorbidity and concomitant therapy. The patients were followed yearly for 24 years up to their average life expectancy.

Results: Rivaroxaban therapy resulted in higher quality adjusted life years with a value of 16.78, while warfarin-based treatment resulted in 16.34 quality adjusted life years. Total lifetime costs were $988.58 for rivaroxaban and $932.92 for unfractionated heparin/warfarin. Therefore, rivaroxaban resulted in a gain of 0.443 quality adjusted life years at an additional cost of $55.661. The incremental cost effectiveness ratios for rivaroxaban compared with warfarin was $125.683 per quality adjusted life year saved which is less than willingness to pay threshold of $783 per quality adjusted life year saved. Warfarin resulted in a net monetary benefit of $11,859.72, while that of rivaroxaban is $12,150.82, meaning rivaroxaban is cost-effective. Sensitivity analyses found that the model was sensitive to utility of no deep vein thrombosis, effectiveness of rivaroxaban and cost of rivaroxaban respectively.

Conclusion: This study showed that rivaroxaban is a cost effective alternative and substituting rivaroxaban for warfarin is acceptable to willingness to pay threshold.

Keywords: cost effectiveness, DVT, rivaroxaban, warfarin, Ethiopia

Introduction

Background

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are known by the collective name venous thromboembolism.[1] DVT is the third most common cardiovascular disorder in the world, which affects 2 million people every year in the United States. Its overall prevalence rate is generally 1–2 cases per 1000 population in the western world, and from these 0.5 cases per 1000 population develop PE.[1,2] The disease is also prevalent in Africa including Ethiopia, besides limited studies that showed its epidemiology.[3]

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If left untreated, DVT is a life-threatening disorder, and will became a major problem when the clot formed in the invisible deep veins reaches the lung artery. In one study, previous history of DVT/PE (25%), surgery (20%), trauma (12%), cancer (4–6%) and immobility (8%) were the main risk factors while 25–50% of cases were idiopathic.[3,4] Bleeding and PE due to medications are the major complications of DVT.[4]

Alleviating the clot, promoting cure and preventing complications are the main objectives of DVT treatment. Unfractionated heparin (UFH) with warfarin is still the standard first line treatment in Ethiopia. Rivaroxaban provides a simple, fixed-dose regimen for treating DVT and for continued treatment, without the need for laboratory monitoring.[5] Warfarin based therapy is less costly, less effective, with slower effect, had many food and drug interactions, require regular monitoring, and had severe bleeding, but the reverse is true for rivaroxaban[6,7] and there are no previous cost effectiveness (CE) studies in the Ethiopian setting comparing the two strategies. These differences gave us initiation to do a CE analysis in order to compare the economic and clinical outcomes of rivaroxaban with the current standard (UFH with warfarin) by constructing a Markov model in a cohort of individuals following an initial DVT diagnosis. This study aimed to assess the CE of rivaroxaban compared to UFH/Enoxaparin with Warfarin for treatment of DVT in patients aged 40 from the restricted societal perspective in Ethiopia.

Methods
Study population
The target population was hypothetical adult DVT patients with no contraindication, comorbid disease or concomitant therapy at age of 40 Years (the age of high prevalence and sex distribution in Ethiopia).[3]

Perspective and audience
The analysis was conducted from the restricted societal perspective. Direct medical cost, patient cost, and costs covered by government were included. The reason behind conducting such analysis was to assist decision makers (MOH and Health institutions) to choose the best anticoagulant strategy for DVT patients.

Comparators
Two possible alternatives, either rivaroxaban (newly introduced) 15 mg PO bid for three weeks and then 20 mg PO per day for 1 year or a standard strategy (first line), UFH/Enoxaparin for 5–7 days plus Warfarin 5 mg PO per day for one year was considered.

The international normalized ratio monitoring for warfarin is assumed to be done every other day for one week, every week for three weeks, and every two weeks for one month, then every month for 1 year was considered.

Time horizon
The clinical outcomes and economic costs of DVT are difficult to determine early. So, the time horizon of analysis was used with 1-year cycle length for 24 years (until life expectancy of a healthy Ethiopian).

Discount rate
Discounting was necessary since the study had time horizon of lifetime, both costs and benefits were discounted with global discount rate, 3%.

Choice of outcomes measures
Since DVT affects QOL and mortality of patients, health outcomes in terms of effectiveness, cost, QALY and incremental cost effectiveness ratio (ICER), was done.

Measurement of effectiveness
The primary measure of treatment effectiveness was QALYs gained. Clinical trials, pooled analysis and other articles from PubMed were used as a source of data to measure QALY. QALY is common measure of effectiveness that takes into account the quantity of years lived adjusted to its quality.[8]

Resources and costs
Currency, price date and conversion
The cost data were collected in Ethiopian Birr and converted to United States Dollar (US$) with the exchange rate of 1US$/39.2652v Ethiopian birr on January 5, 2021 from National Bank of Ethiopia.

Cost
Since our perspective is restricted societal, all direct medical costs associated with each treatment like cost of medications, hospitalization, laboratory (monitoring, and diagnostic if complication), professional service, one-time treatment of cost of complication and side effects were included.

The sites of data collection were Tikur anbessa specialized hospital (TASH). The prices of the medicines (UFH/warfarin and Rivaroxaban) were obtained from TASH database and Ethiopian Pharmaceutical supply agency (EPSA) price list. The cost of hospitalization, laboratory, complications and side effects were derived from TASH which is the main

cardiology center in Ethiopia. Professional service cost was estimated based on daily salary of each professional per the number of patients served per day. The average hospital stay was obtained based on expert's opinion and the laboratory cost for regular monitoring and diagnostic (complications) were collected from TASH laboratory department. Cost of blood was estimated from Ethiopian Red Cross Association.

To estimate the total costs for treating DVT per cycle length, the costs of the drug after hospitalization and regular laboratory monitoring costs were added to cost of professional service, and complications. The total cost of treating DVT in warfarin and rivaroxaban arm per patient per year were estimated before discounting. The detailed calculation of each component of cost was explained according to the practice at TASH.

The cost of follow up is the cost incurred during the follow up for 1 year. It includes drug cost, monitoring laboratory cost, and service cost. The cost of bleeding is also high which includes the cost of blood and other supplementary therapies during bleeding management.

Model overview

A Markov model was designed to follow the two identical cohorts of hypothetical DVT patients. Each patient was presented with DVT diagnosis without any complication or comorbidity. The patients were followed for 24 years

starting from treatment initiation. In each cycle of the treatment/follow-up, different health states of the disease including the treatments will occur according to the known history of disease and drugs. From these, recurrent DVT with or without PE and bleeding is one.

Each treatment option might result in one of the health states, No DVT, DVT, death or intermediate states (PE and Bleeding). Patients may transit to death from any health state. Bleeding and other complications increase the risk of death in the model. These health states were chosen in this model, as they were the most common complications reported in the clinical trials and are highly expensive to treat. Model creation and analysis were performed by using Tree-Age – 2018 software and the Markov model structure is depicted in Figure 1.

Key assumptions

Several assumptions were made in the design of the model:

1. The two hypothetical cohorts had uniform case distribution and condition with ENSTIEN-DVT /PE clinical trials. Each group received either rivaroxaban or Standard therapy only. No patients in the sample population were contraindicated to the treatments, have comorbid diseases or not take concomitant medication that
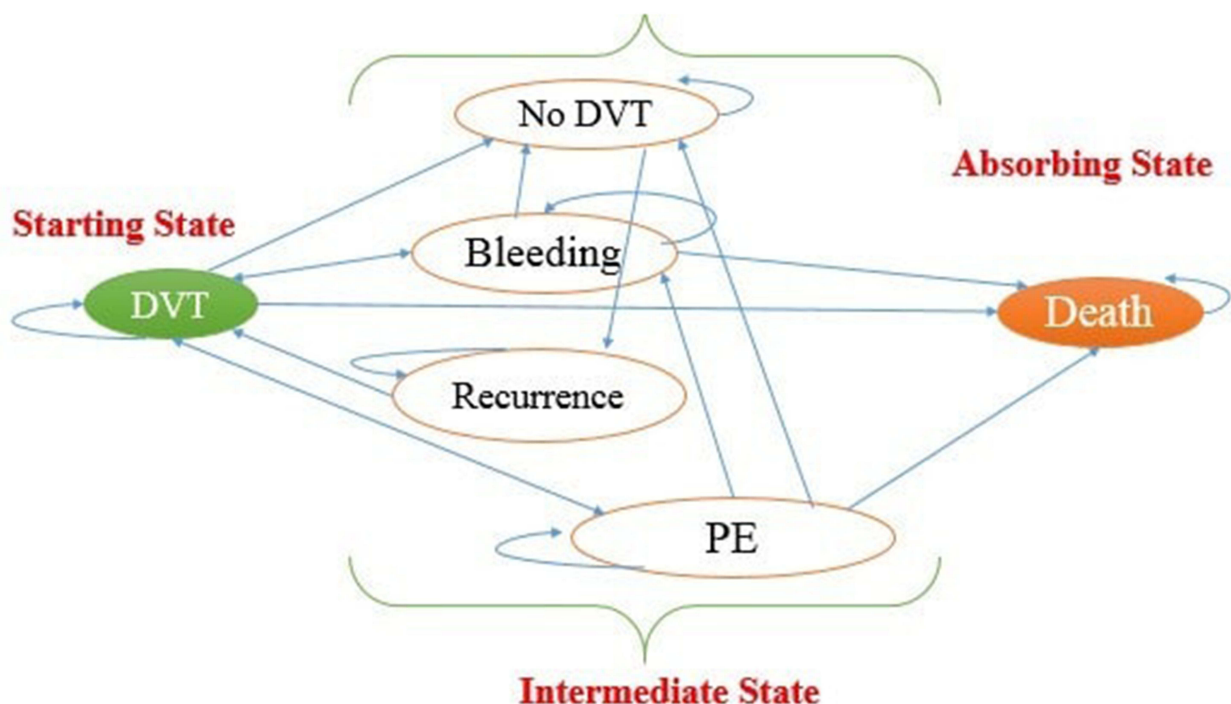

Figure 1 State diagram for the economic model.

will affect the efficacy of the two strategies because these conditions create dilemma in the outcome of the model.

2. Costs of minor side effects and complications was similar across both treatments and for major complications and adverse events (bleeding and PE), average costs of one-time total treatment/hospitalization cost for that event were considered.

3. All patients at first and during complications were considered as admitted because the disease is severe, acute and asymptomatic at first.

4. We assumed there will be no lost from treatment. Adherence rates for both treatment alternatives were assumed similar. If this is not true, the difference in the outcome may be due to adherence or left from treatment.

5. Generic drug was used for the treatment and costing, since the cost of brand drugs is very expensive.

6. Patients develop the adverse event or complication once through one cycle period.

7. Willingness to pay (WTP) was set to be US$783 in Ethiopia.

Base case values

The inputs of this analysis were mainly obtained from the ENSTIEN-DVT/PE clinical trial and other supplementary reviews and literatures.[5,9]

Probabilities

The probabilities of adverse events and complications were based on data from the ENSTIEN-DVT/PE clinical trial.[5,9] Mortality rates of DVT, PE and bleeding were estimated from previous literature (Table 1). Probability of No DVT is similar between patients that develop bleeding and non-bleeding and PE does not affect the probability of bleeding.[10]

Utility

The type of anticoagulation therapy may affect patient's quality of life or utility. Rivaroxaban has advantages over

Table 1 Base-Case Probability Values and Ranges, Base-Case Utility Values and Ranges, and Cost of Treatment Ranges Used in Sensitivity Analysis (95% CI or ± 20%)

Variable	Base Case	Probability Ranges		Reference
		Minimum	Maximum	
Rivaroxaban				
Probability of Bleeding	0.0096	0.0048	0.0143	[10]
Probability of Recurrence	0.0210	0.0168	0.0252	[5,9]
Probability of death from PE	0.1300	0.1040	0.1560	[5,9]
Probability of death in bleeding	0.0600	0.0480	0.0720	[5,9]
Probability of recurrent PE	0.0100	0.0080	0.0120	[1]
Probability of PE after DVT	0.0020	0.0016	0.0024	[2]
Common variable				
Probability of PE end with DVT	0.6050	0.4840	0.7260	[5]
Warfarin				
Probability of Bleeding	0.0166	0.0083	0.0249	[4]
Probability of Recurrence	0.0230	0.0184	0.0276	[5,9]
Probability of death from PE	0.1500	0.1200	0.1800	[5,9]
Probability of death in bleeding	0.0900	0.072	0.1080	[5,9]
Probability of recurrent PE	0.0200	0.0160	0.0240	[1]
Probability of PE after DVT	0.0043	0.0034	0.0052	[2]
Utility of DVT	0.8400	0.6400	0.9800	[12,13]
Utility of No DVT	1.0000	0.8000	1.0000	
Cost of Rivaroxaban	1767.14	1413.712	2120.568	TASH and EPSA
Cost of Warfarin	1491.83	1193.464	1790.196	TASH and EPSA

warfarin as the patients do not require continuous monitoring or food restriction and had fewer drug-drug interactions.

In our study, the mean utility of patients on warfarin therapy was used in the model. The utility of patients on rivaroxaban was greater than warfarin, because rivaroxaban does not require routine monitoring. By definition, utility of dead patients is zero. Utilities of patients experiencing each health state were obtained from literature (Table 1).

Efficacy/Effectiveness
The effectiveness of the two treatment strategies/drugs were obtained from a medical literature.[11] (Table 2).

Hospitalization stay
Data on hospitalization and length of stay was reported from EINSTEIN-DVT/PE[5,9] but due to variations between settings, local experts at TASH were consulted (Table 2).

Sensitivity analysis
Several sensitivity analyses were performed to test the uncertainty of the estimate values, model assumptions, and how it affects the result of the outcome.

One-way sensitivity analysis was performed on highly influential variables which include utility of No DVT, effectiveness and cost of rivaroxaban over plausible ranges presented in the above tables. The values of ranges were obtained from previous literatures by using 95% CI if available, or by calculating a range of 20% in each direction.

In addition, two-way sensitivity analysis was performed between cost of warfarin and cost of rivaroxaban. Two-way sensitivity analysis allows us to demonstrate impact of the two variables when changing their values simultaneously within given ranges.

Scenario analysis
A scenario analyses was also conducted, focusing on cost of warfarin monitoring laboratory. This variable was selected because international normalized ratio monitoring is done for warfarin therapy only and we want to know what will happen if cost of monitoring was not included, ie the influence of this cost on the overall CE.

Calibration/Validation
Before analyzing the results of this model, it was ensured that the results were logically believable and could be explained accurately (face validity). This was done by consulting experts and TASH cardiology residents. The model was also assessed for logical inconsistencies by evaluating it under hypothetical conditions. The mathematical calculations were confirmed to be accurate and consistent with the specifications of the model (internal validity).

Operational definitions
Cost: direct medical cost of treatment, monitoring, hospitalization, and service.

Table 2 Base-Case LOS and Effectiveness (95% CI) Values and Ranges for Analysis

Variable	Base Case	Distribution Ranges		Reference
		Minimum	Maximum	
Rivaroxaban				
Effectiveness	0.9940	0.9750	1.0000	[11]
LOS at Hospital (days) in rivaroxaban for cost only				
DVT PE	5 6			[12]
Bleeding	6			Expert opinion
Warfarin				
Effectiveness	0.9870	0.9400	1.0000	[11]
LOS at Hospital (days) in Warfarin for cost only				
DVT PE	8 7			[12]
Bleeding	10			Expert opinion

Table 3 Base Case Cost Effectiveness Table

Strategy	Cost ($)	Incr. Cost ($)	Effectiveness (QALY)	Incr. Effe. (QALY)	C/E	ICER ($/QALY)	NMB ($)
Warfarin	932.92	–	16.34	–	57.10		11,859.72
Rivaroxaban	988.58	55.66	16.78	0.443	58.91	125.68	12,150.82

Abbreviations: Incr.cost, incremental cost; Incr. Effe., incremental effectiveness.

Effectiveness: the capacity of producing the desired outcome/result at the end of treatment.

Length of stay: duration of time in which a certain health state remains.

No DVT: when patients become free from DVT.

Standard therapy: represents UFH/Warfarin treatment.

Warfarin: in the document, warfarin represents standard therapy.

Results

Base case analysis

In the base case analysis, rivaroxaban therapy resulted in higher QALYs with a value of 16.78, while warfarin-based treatment resulted in 16.34 QALYs (Table 3). Total lifetime costs were $988.58 for rivaroxaban and $932.92 for UFH/warfarin. Therefore, rivaroxaban resulted in a gain of 0.443 QALYS at an additional cost of $55.661. Rivaroxaban resulted in $58.91 per QALY while warfarin resulted $57.10 only, which is acceptable cost increase per QALY. The ICERs for rivaroxaban compared with warfarin was $125.68 per QALY saved which is less than willingness to pay threshold of $783 per QALY saved. Warfarin resulted in a NMB of $11,859.72 while that of rivaroxaban is $12,150.82 meaning rivaroxaban is cost-effective. Therefore, for DVT treatment in the Ethiopian setting, rivaroxaban is considered the more cost-effective choice (Figure 2).
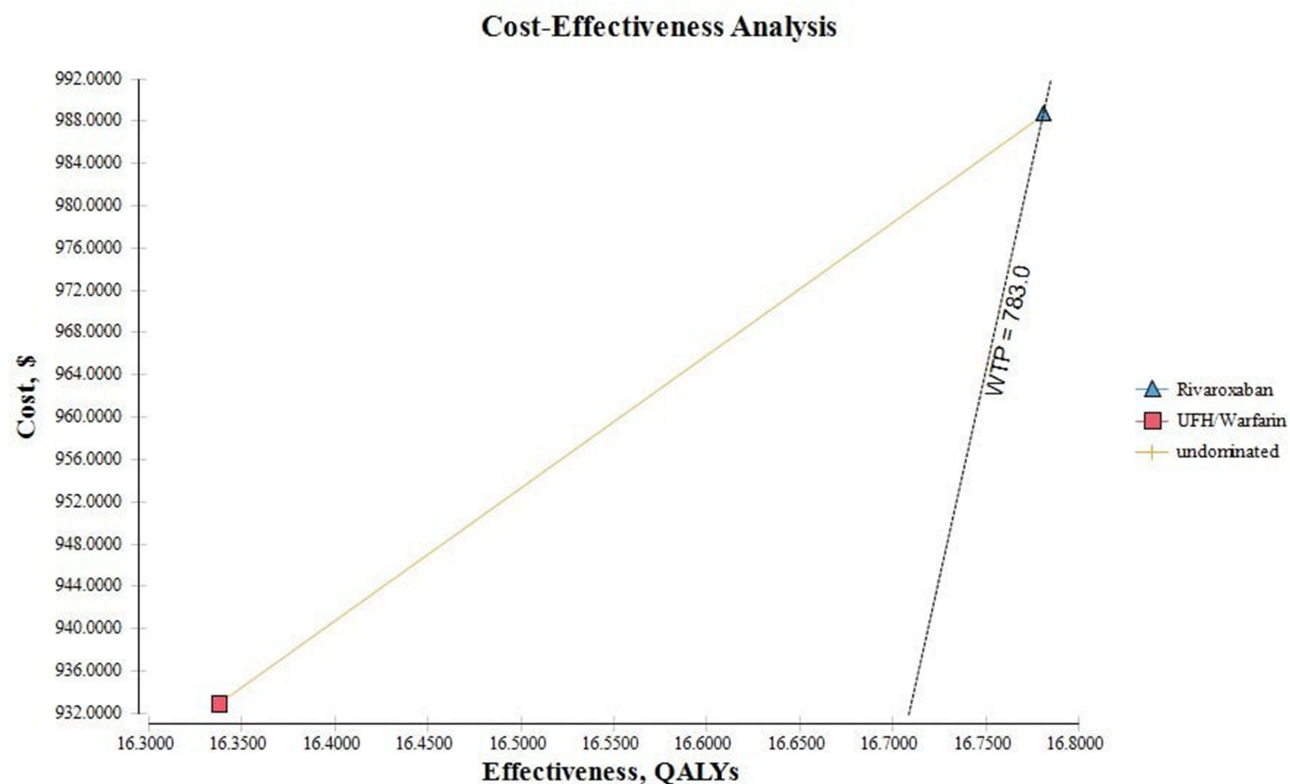
One-way sensitivity analyses

From the tornado diagram (Figure 3) with the results of a series of one-way sensitivity analyses, the variables with the most influential impact were, Utility of No DVT, Effectiveness of rivaroxaban and Cost of rivaroxaban,

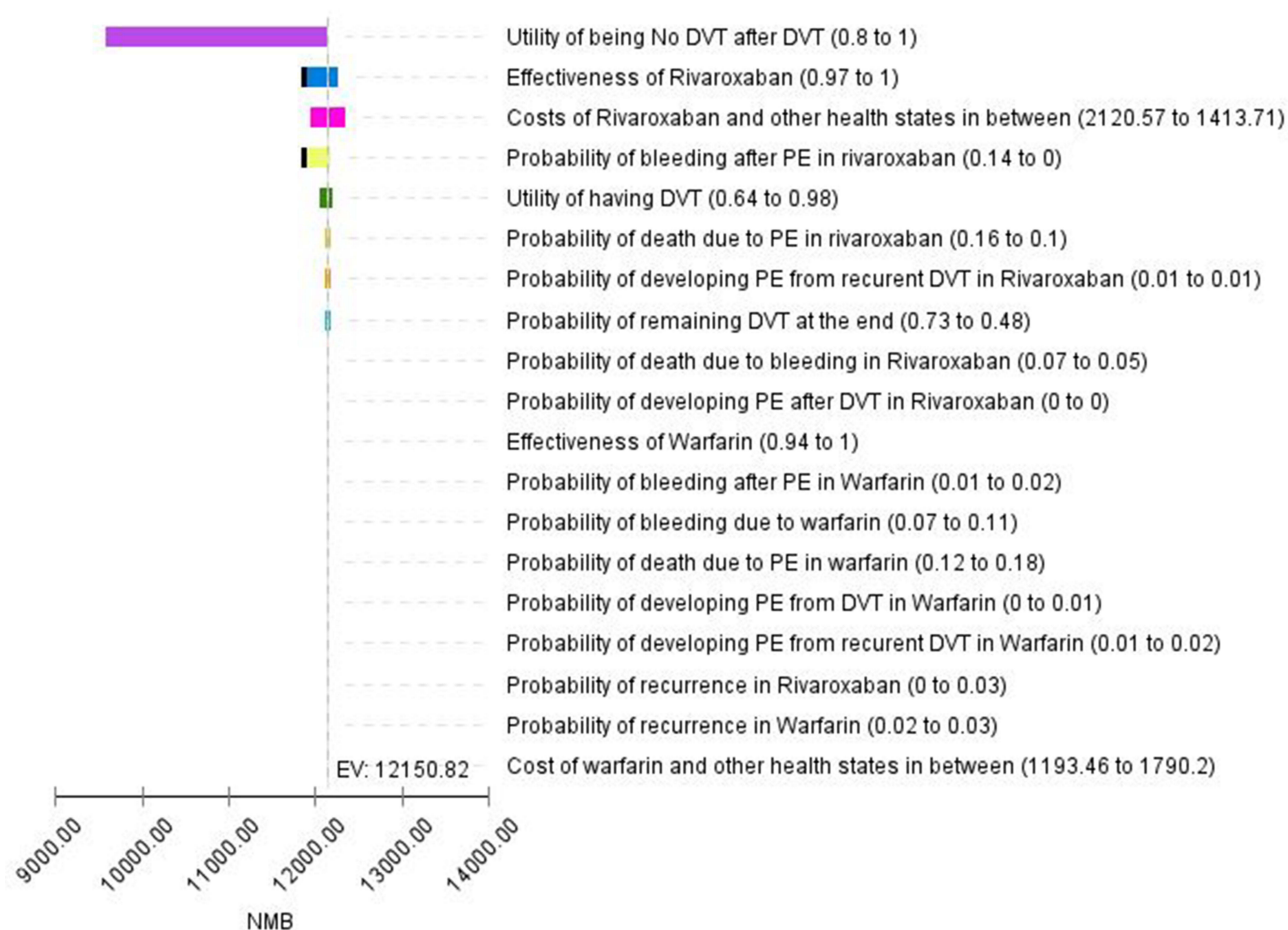**Figure 2** Base case cost effectiveness graph.

Figure 3 Tornado diagram that demonstrates influence of each variable on the base case results.

respectively. Based on the tornado diagram, one-way sensitivity analyses were done for these influential variables with the higher impact on the model over plausible ranges.

Varying the utilities of No DVT had an impact on NMB value of both strategies. If the value for utility of No DVT changed from 0.8 through one, NMB value for warfarin and rivaroxaban increases simultaneously but the increase in rivaroxaban is greater throughout as it is the cost-effective strategy (Table 4). NMB graph enables us to identify exactly the threshold in which below/above it the result will change. The analysis values showed that at all values of the utility of No DVT in the plausible range, rivaroxaban is a cost-effective strategy (Figure 4).

A one-way sensitivity analysis was also conducted on cost of rivaroxaban. Varying values of cost of rivaroxaban on plausible ranges influence the ICER values compared to warfarin therapy from the base case analysis. Below the base

case value, warfarin was dominated but becomes undominated when cost of rivaroxaban increases from the base case. NMB graph for one-way sensitivity analysis of cost of rivaroxaban showed that if the cost of rivaroxaban increased, NMB of rivaroxaban decreased and that of warfarin was unaffected (Figure 5). At all points in the plausible range under WTP, rivaroxaban resulted in greater NMB, which confirms it is the cost-effective choice (Table 4).

Another one-way sensitivity analysis was performed for the effectiveness of rivaroxaban and the result indicates that it had an impact on ICER value. As effectiveness increases, the ICER value decreases and at maximum effectiveness, warfarin becomes dominated. When the effectiveness of rivaroxaban reaches 0.9784, the NMB of the two strategies is equal and for higher effectiveness values from the threshold (Table 5), warfarin is more cost effective (Figure 6). The NMB table also shows that

Table 4 Net Monetary Benefit Table for Sensitivity Analysis of Utility of No DVT, Cost of Rivaroxaban and Effectiveness of Rivaroxaban

Cost of Rivaroxaban	Rivaroxaban	UFH/Warfarin
1413.712	12,348.538	11,859.715
1590.426	12,249.680	11,859.715
1767.140	12,150.822	11,859.715
1943.854	12,051.964	11,859.715
2120.568	11,953.106	11,859.715
Utility of No DVT		
0.800	9596.530	9383.449
0.850	10,235.103	10,002.516
0.900	10,873.676	10,621.582
0.950	11,512.249	11,240.648
1.000	12,150.822	11,859.715
Effectiveness of Rivaroxaban	Rivaroxaban	UFH/Warfarin
0.975	11,796.164	11,859.715
0.981	11,912.837	11,859.715
0.988	12,029.501	11,859.715
0.994	12,146.156	11,859.715
1.000	12,262.802	11,859.715

the NMB of rivaroxaban increases through the range and after threshold effectiveness, its value becomes greater than warfarin (Table 6).

Two-way sensitivity analysis

The two-way sensitivity analysis for the cost of warfarin and cost of rivaroxaban indicated that warfarin treatment would have a chance of being cost effective when cost of warfarin is less than $1342.647 and cost of rivaroxaban is greater than $1943.854 otherwise, rivaroxaban is the cost-effective choice. These two points are the approximate thresholds taken from the graph of the two cost values that determine cost effective choice (Figure 7).

Scenario analysis

Scenario 1: If cost of monitoring for warfarin was not considered

In this scenario, we go through to check what will happen if cost of monitoring for warfarin was missed and the results are presented in Table 6. The yearly monitoring cost of warfarin is $32.39. So, this scenario assesses whether this cost affects the CE plane. According to the results, rivaroxaban is still the cost-effective alternative with $988.58 per 16.78 QALYs while warfarin has $912.67 per 16.34 QALYs. Rivaroxaban has $12,150.82 NMB which is greater than warfarin (only 11,879.97) under WTP threshold. Since the ICER is less than WTP threshold, rivaroxaban with high NMB and effectiveness becomes cost effective.

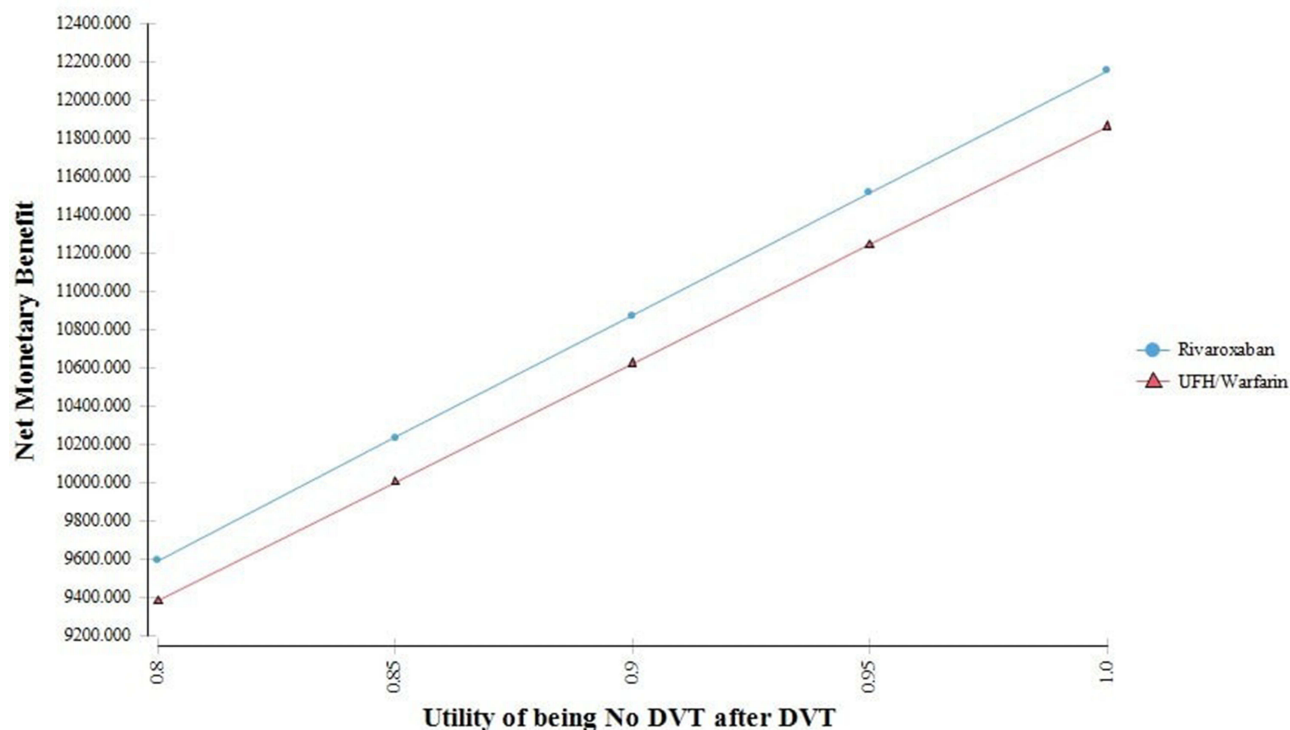**Figure 4** Net benefit graph for one-way sensitivity analysis of utility of No DVT.
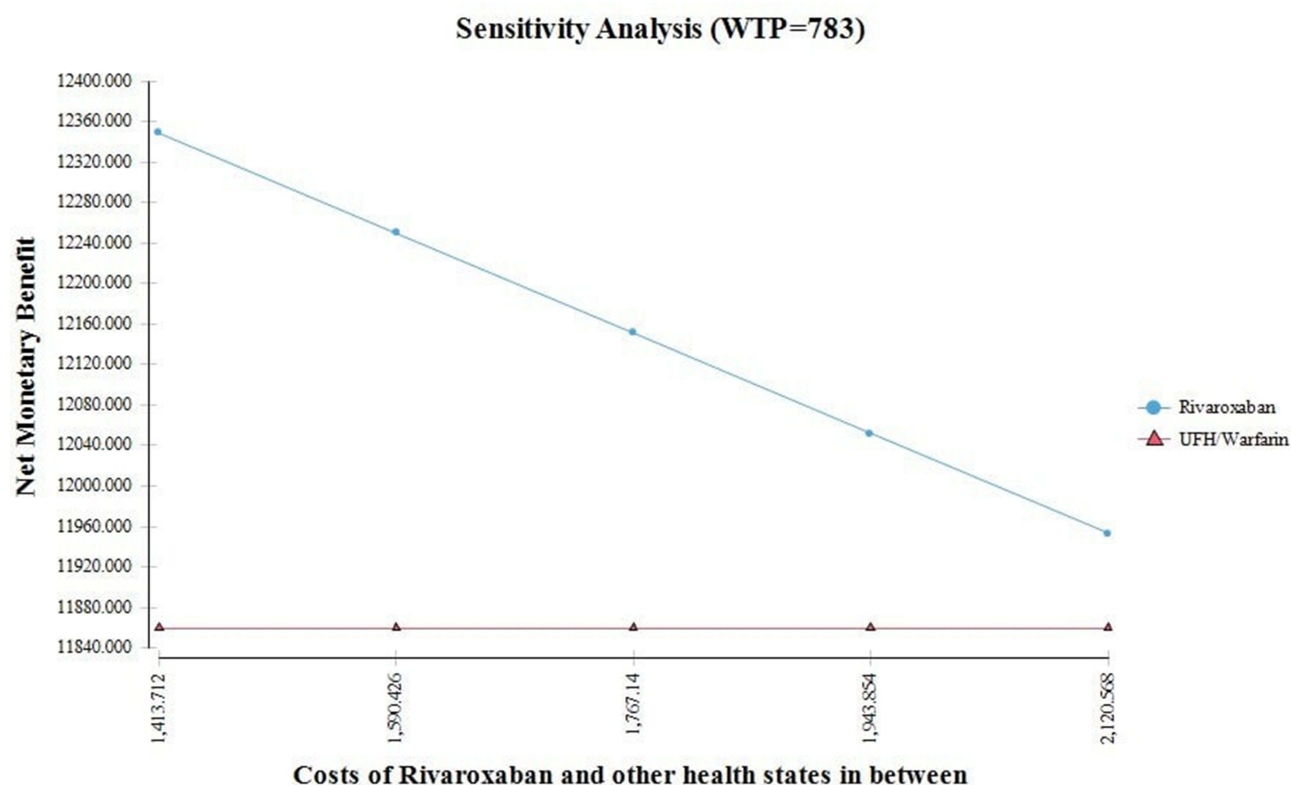
Sensitivity Analysis (WTP=783)

Figure 5 Net benefit graph for one-way sensitivity analysis on cost of rivaroxaban.

Acceptability curve

Rivaroxaban was the preferred (cost effective) strategy at all willingness-to-pay thresholds according to the acceptability curve result (Figure 8). Therefore, rivaroxaban is an acceptable strategy in WTP threshold.

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis is used to determine uncertainties in the model. The result shows that warfarin is cost effective until a WTP threshold of 156.6 while rivaroxaban is the acceptable strategy in the long term above a threshold of 156.6 (Figure 9).

Discussions

In this study, we assessed CE of rivaroxaban compared to UFH/warfarin for DVT treatment. For DVT patients, it is more cost effective to treat them with rivaroxaban than warfarin in Ethiopian setting under WTP threshold of $783. Rivaroxaban therapy resulted in higher QALYs with a value of 16.78, while warfarin-based treatment resulted in 16.34 QALYs. The analysis also showed that rivaroxaban was cost effective which resulted in $12,150.82 NMB while that of warfarin is $11,859.72 only. The ICERs for rivaroxaban compared with warfarin was $125.683 per QALY saved which is acceptable based on WTP threshold of $783 per QALY saved.

Previous CE studies have concluded that rivaroxaban is more cost effective compared to warfarin.[6] concluded rivaroxaban strategy costs less ($3195 vs $6188) and was more effective than warfarin (9.29 QALYs vs 9.14 QALYs). Our result is also coherent with this study.[12] In this study, Rivaroxaban was dominant (cheaper and more effective) and, therefore, cost-effective, in both patients with DVT and PE in three-treatment durations (3, 6 or

Table 5 Threshold Analysis for Sensitivity Analysis of Effectiveness of Rivaroxaban

Attribute Name	Variable Name	Threshold	Comparator	Baseline	Exp. Value	WTP
NMB	eRiva	0.9784	Warfarin	Rivaroxaban	11,859.71	783
Cost	eRiva	0.9972	Warfarin	Rivaroxaban	932.9198	783

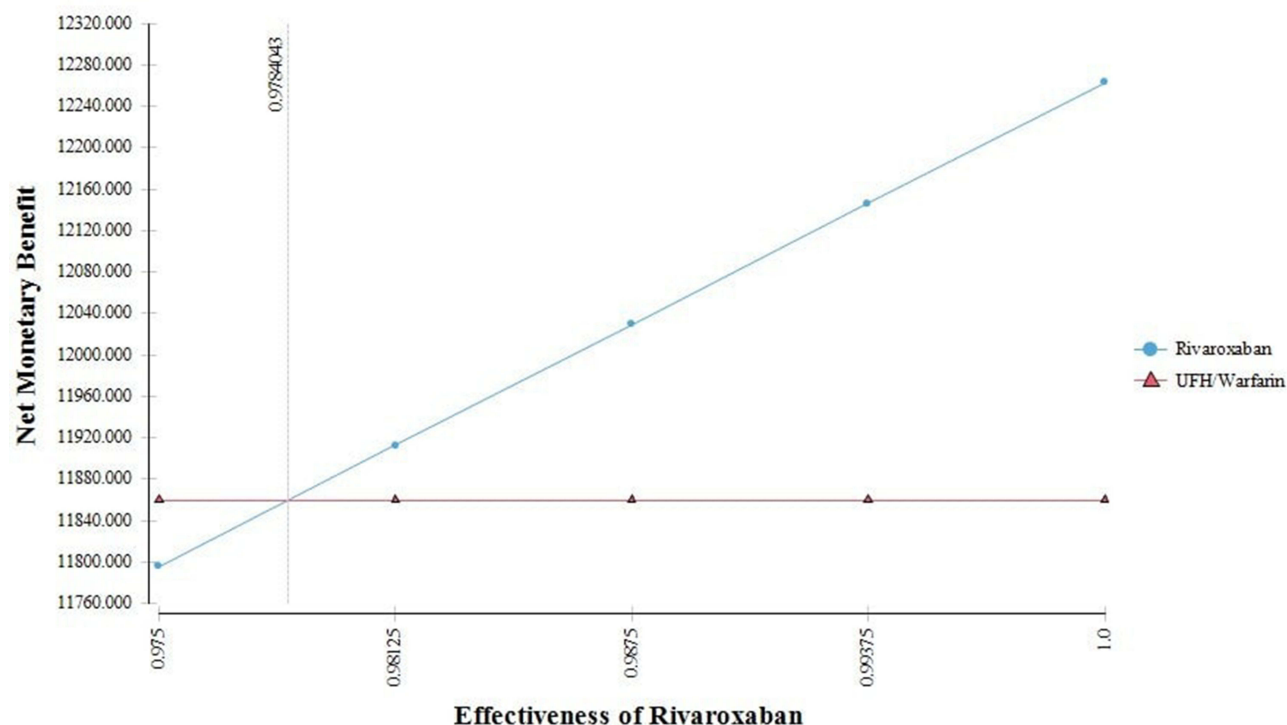**Abbreviation**: eRiva, effectiveness of rivaroxaban.

Figure 6 Net benefit graph for one-way sensitivity analysis on effectiveness of rivaroxaban.

12 months), and was cost-effective in patients requiring lifelong anticoagulation (ICERs: $8677 per QALY and $7072 per QALY in patients with DVT and PE, respectively). Our study is supported by different studies in other countries and settings. In addition, a cross sectional study done in Brazil, considering thromboprophylaxis showed both rivaroxaban and enoxaparin showed equivalence in effectiveness and safety but enoxaparin was highly expensive resulting in rivaroxaban being a cost-effective strategy.[14]

Similar study done in China also showed a supportive result to this study. Rivaroxaban therapy resulted in an increase of 0.008 QALYs and was related with lower total costs compared with warfarin (US$4744.4 vs US$5572.4, respectively). There rivaroxaban was the most cost saving strategy.[15] Similar pattern was observed in Greece for DVT and PE patients, there rivaroxaban was

a dominant (less costly, more effective) and cost-effective (ICER: €177 per QALY gained).[16] Another study done in Japan among non-valvular atrial fibrillation patients for the treatment of stroke prevention identified that Rivaroxaban was cost-effective compared to warfarin (ICER= €24,446.42/QALY).[17] Even in different disease in US citizens, Warfarin is less cost effective compared with Apixaban for treatment of atrial fibrillation. Apixaban compared with Warfarin resulted in ICER of $53,925/QALY.[18]

In contrast to this, studies showed that rivaroxaban is associated with greater costs but fewer QALYs than LMWH/VKA,[19] and Rivaroxaban was a dominated less cost-effective option compared with oral anticoagulants in Colombia for atrial fibrillation therapy.[20] This difference may be due to duration of therapy (<6 month), patient age groups used (65) and from assumptions about the patient

Table 6 Cost Effectiveness Table for Scenario Analysis

Strategy	Cost	Incr. Cost	Effectiveness	Incr. Effe	ICER	NMB	C/E	Dominance
Warfarin	912.67		16.34			11,879.97	55.86	Undominated
Rivaroxaban	988.58	75.92	16.78	0.44	171.42	12,150.82	58.91	Undominated

Abbreviations: Incr.cost, incremental cost; Incr.Effe, incremental effectiveness.
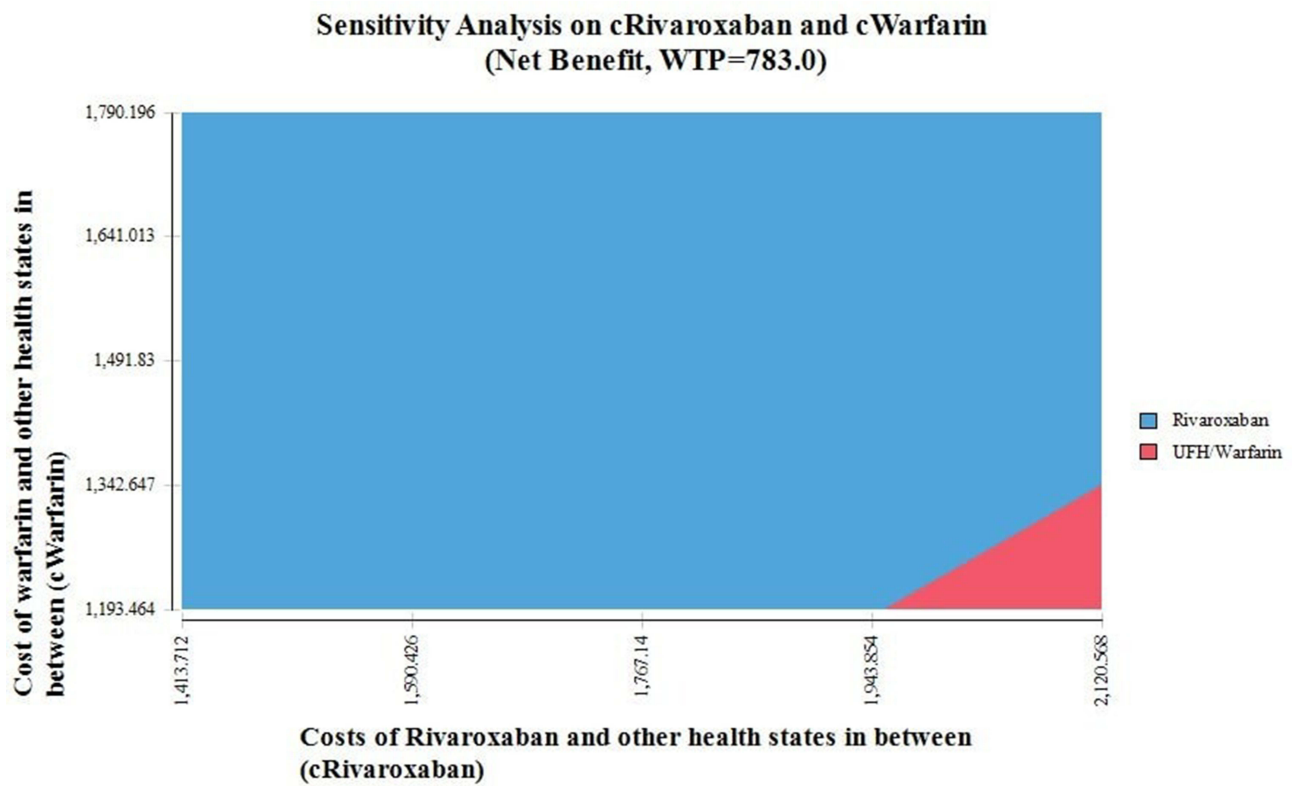
Figure 7 Net benefit graph for two-way sensitivity analysis on cost of warfarin and rivaroxaban.
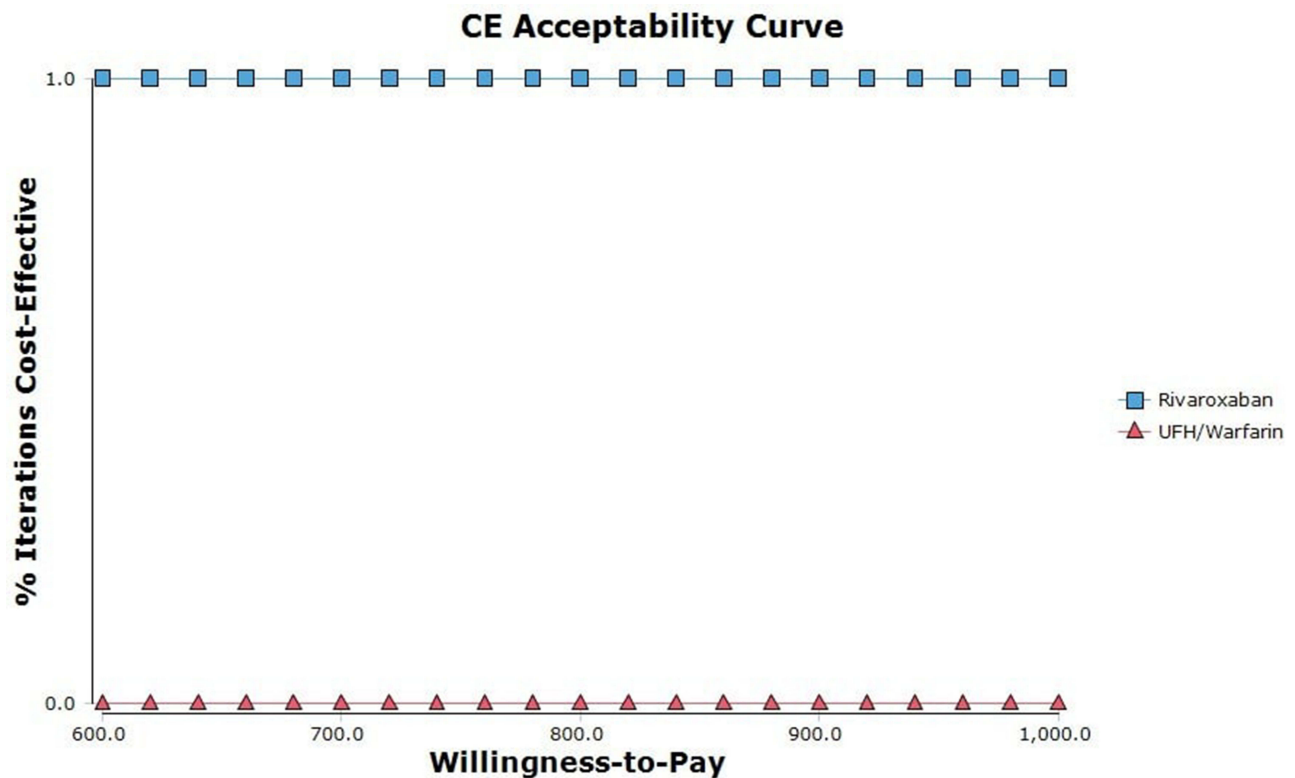

Figure 8 Monte Carlo Simulation cost effectiveness Acceptability curve at WTP.
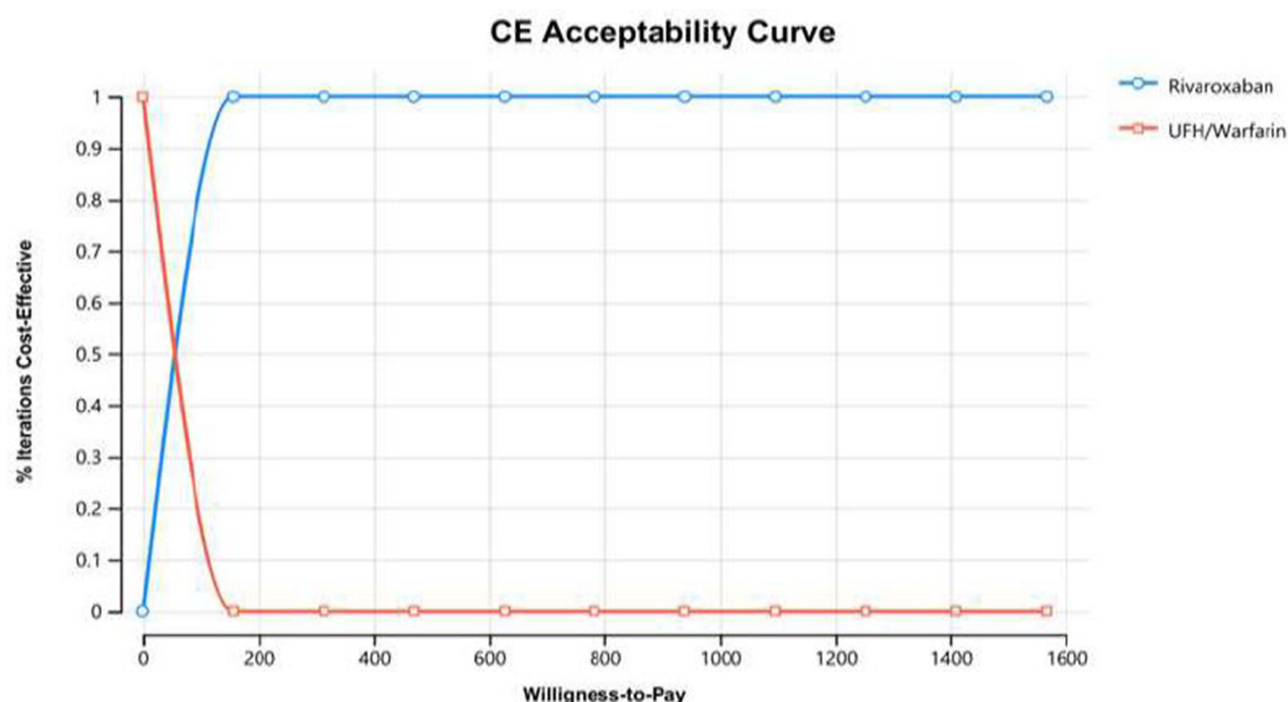
CE Acceptability Curve

Figure 9 Probabilistic sensitivity analysis acceptability curve.

population being treated and the setting of treatment in different countries.

In addition to the findings of this study, there are other reasons to limit its use in replacing warfarin in real world practice. One is that most evidences for its use comes from specific populations of DVT patients aged 40 years old with no contraindications, complication and concomitant medication, which is not true in the real world that elderly patients have complications and comorbidities. The second limitation is that the data was collected from studies done in other country settings which results in unreliability. Third, we assumed that all patients in both treatment options had the same medication adherence rates. This might differ from the real world, because each option differed in dosage regimen, safety profile, and monitoring. Although this study was done from restricted societal perspective, we only captured direct medical costs associated with each treatment option and some governmental costs only, and the long-term effect of both treatments was not addressed due to the lack of data regarding long-term effect of rivaroxaban and government covered cost.

Despite the limitations, this study also has a number of strengths. The study modeled the decision problem by communicating clinical experts and most of the data were obtained from reliable stage three clinical trials and systematic reviews. So, it can be used as a starting topic

for further research. The study can also be used for policy decision making.

Conclusion

In conclusion, treatment of DVT with rivaroxaban is an economical and effective strategy for patients aged 40 years old with higher risk of PE in Ethiopia. This result is highly affected by utility of No DVT, effectiveness and cost of rivaroxaban. Because this model was built upon clinical trial data, future studies may be needed to assess effectiveness, safety and long-term effects of rivaroxaban compared to warfarin in real world settings.

Our finding showed that rivaroxaban is a more cost-effective alternative than warfarin-based therapy. Therefore, we recommend that MOH should facilitate scholars to research the safety profile of rivaroxaban for long-term use, and in collaboration with EPSA, the drug should be availed at each health facility and should replace warfarin therapy for DVT patients.

Abbreviations

CE, cost effectiveness; DVT, Deep Vein Thrombosis; EPSA, Ethiopian Pharmaceutical Supply Agency; ICER, Incremental Cost Effectiveness Ratio; MOH, Ministry of Health; NMB, Net Monetary Benefit; PE, pulmonary embolism; QALY, quality adjusted life years; QOL,

Quality of life; TASH, Tikur Anbessa Specialized Hospital; UFH, Unfractionated Heparin; US$, United States Dollar; WTP, Willingness to Pay.

Ethical Approval and Consent to Participate

Ethical approval was gained from Addis Ababa University School of Pharmacy.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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References

1. Prins MH, Lensing AWA, Bauersachs R, et al. Oral Rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies. *Thromb J*. 2013;11:21. doi:10.1186/1477-9560-11-21
2. Gader AA, Haggaz AED, Adam I. Epidemiology of deep venous thrombosis during pregnancy and puerperium in Sudanese women. *Vasc Health Risk Manag*. 2009;5(1):85–87.
3. Haile L, Hawaz Y, Assefa G. Risk factors of deep venous thrombosis in duplex and colour Doppler ultrasound at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia. *East Cent Afr J Surg*. 2013;18 (2):2073–9990.
4. Buller HR, Prins MH, Lensing AW, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *New Eng J Med*. 2012;366(14):1287–1297.
5. The EINSTEIN-DVT Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. *New Eng J Med*. 2010;363:2499–2510. doi:10.1056/NEJMoa1007903
6. Seaman CD, Smith KJ, Ragni MV. Rivaroxaban versus warfarin anticoagulation for the prevention of recurrent venous thromboembolism: AUS perspective. *Thromb Res*. 2013;132:647–651. doi:10.1016/j.thromres.2013.09.015
7. Smock KJ. Update on anticoagulants monitoring practice. University of Utah Department of Pathology: ARUP Laboratories; 2017.
8. Venturini F, Johnson KA. Introduction to pharmacoeconomic principles and application in pharmacy practice. *CJHP*. 2002;14:6–15.
9. The EINSTEIN–PE Investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *New Eng J Med*. 2012;366:1287–1297. doi:10.1056/NEJMoa1113572
10. National Institute for Health and Clinical Excellence. Rivaroxaban for the treatment of deep vein thrombosis and prevention of deep vein thrombosis and pulmonary embolism: final appraisal determination. 2012.
11. Lee S, Anglade MW, Pham D, Pisacane R, Kluger J, Coleman,CI. Cost-effectiveness of rivaroxaban compared to warfarin for stroke prevention in atrial fibrillation. *Am J Cardiol*. 2012;110(6):845–851. doi:10.1016/j.amjcard.2012.05.011
12. Bamber L, Muston D, McLeod E, Guillermin A, Lowin J, Patel R. Cost-effectiveness analysis of treatment of venous thromboembolism with rivaroxaban compared with combined low molecular weight heparin/ vitamin K antagonist. *Thromb J*. 2015;13:20. doi:10.1186/s12959-015-0051-3
13. Santos IF, Pereira S, Mcleod E, Guillermin AL, Chatzitheofilou I. Economic analysis of rivaroxaban for the treatment and long-term prevention of venous thromboembolism in Portugal. *Acta Med Port*. 2014;27(5):615–624. doi:10.20344/amp.5257
14. Marques GL, DeFranca AC, Saito AC, et al. Clinical outcomes and costs of rivaroxaban for thromboprophylaxis in acutely ill medical inpatients: a cross-sectional study. *Cureus*. 2021;13(6). doi:10.7759/cureus.15497
15. Yang L, Wu J. Cost-effectiveness of rivaroxaban compared with enoxaparin plus warfarin for the treatment of hospitalized acute deep vein thrombosis in China. *BMJ Open*. 2020;10(7):e038433. doi:10.1136/bmjopen-2020-038433
16. Gourzoulidis G, Kourlaba G, Kakisis J, et al. Cost-effectiveness analysis of rivaroxaban for treatment of deep vein thrombosis and pulmonary embolism in Greece. *Clin Drug Investig*. 2017;37 (9):833–844. doi:10.1007/s40261-017-0540-1
17. Hori M, Tanahashi N, Akiyama S, Kiyabu G, Goto R. Cost-effectiveness of rivaroxaban versus warfarin for stroke prevention in non-valvular atrial fibrillation in the Japanese healthcare setting. *J Med Econ*. 2020;23:252–261. doi:10.1080/13696998.2019.1688821
18. Cowper PA, Sheng S, Lopes RD, et al. Economic analysis of apixaban therapy for patients with atrial fibrillation from a US perspective results from the ARISTOTLE randomized clinical trial. *JAMA Cardiol*. 2017;2:525–534. doi:10.1001/jamacardio.2017.0065
19. Klarenbach LK, Boucher M, So H, Manns B, Tonelli M. Direct oral anticoagulants for the treatment of venous thromboembolic events: economic evaluation. Ottawa: CADTH technology review; 2016.
20. Mendoza JA, Silva FA, Rangel LM. Cost-effectiveness of new oral anticoagulants and warfarin in atrial fibrillation from adverse events perspective. *Rev Colomb Cardiol*. 2019;26(2):70–77. doi:10.1016/j.rccar.2018.10.011