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ORIGINAL ARTICLE

# Health Economic Analysis of Rivaroxaban and Warfarin for Venous Thromboembolism Management in Chinese Patients

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## Abstract

**Purpose** Rivaroxaban, a direct oral anticoagulant, has demonstrated non-inferiority to warfarin for venous thromboembolism (VTE) treatment in clinical trials. This study aimed to analyze the direct medical costs for VTE management with rivaroxaban versus warfarin in Hong Kong Chinese patients.

**Methods** In this retrospective observational study, VTE patients admitted to the Princess Margaret Hospital from March 2012 to February 2017 who were initiated and discharged with either rivaroxaban or warfarin were included. Patient demographic and clinical data, and healthcare resource utilization for VTE management were collected for the VTE index admission and 1-year post-discharge period.

**Results** A total of 181 patients (90 in the rivaroxaban group; 91 in the warfarin group) were included. The mean (± SD) length of stay (LOS) was 4.8 ± 2.7 days and 8.0 ± 3.0 days in the rivaroxaban and warfarin groups, respectively ($p > 0.001$). The total cost for VTE index admission in the rivaroxaban group was significantly lower than that of the warfarin group (USD 5473 ± 1914 versus USD 3457 ± 1796; $p < 0.001$) (USD 1 = HKD 7.8). Recurrent VTE and bleeding rates in 1-year post-discharge period were not significantly different between the two groups. The direct total cost of the rivaroxaban group (USD 1271 ± 767) was significantly lower than that of the warfarin group (USD 1739 ± 1045) in 1-year post-discharge period ($p < 0.001$).

**Conclusions** Total direct cost and LOS for VTE admission and total cost in 1-year post-discharge period were significantly lower in patients initiated and discharged with rivaroxaban than those of warfarin.

**Keywords** Venous thromboembolism · Rivaroxaban · Warfarin · Cost analysis · Direct oral anticoagulants

## Introduction

Venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE), constitutes a major burden of disease. In Hong Kong, VTE is estimated to occur in about 42 persons per 100,000 annually, with high 30-day mortality rates associated with DVT (7.4%) and PE (13.3%) [1, 2].

Oral anticoagulation therapy is the mainstay for prevention of recurrent thrombotic events and VTE-associated death. The conventional therapy consisted of low molecular weight heparin (LMWH) bridging to warfarin for at least 3 months. Four direct oral anticoagulants (DOACs) (rivaroxaban, dabigatran, apixaban, and edoxaban) were reported to be non-inferior to warfarin with lower risk of bleeding in multi-centered randomized control trials [3–7] and have been recommended over warfarin for the treatment of VTE in non-cancer patients since 2016 [8].

Rivaroxaban is the first DOAC to receive regulatory approval for acute and continuous treatment of VTE in Hong Kong, and it is used as monotherapy without parenteral anticoagulant bridging [3, 4, 9]. Unlike warfarin therapy, rivaroxaban does not require international normalization ratio (INR) monitoring [10]. The use of rivaroxaban for VTE treatment may allow early discharge, shorten the hospital length of stay (LOS), and potentially decrease hospitalization cost [11]. Healthcare cost studies of rivaroxaban have found reduction

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in hospital LOS and lower cost for outpatient visits and laboratory monitoring when compared to warfarin in countries such as the USA and the UK. Nevertheless, the economic benefits of rivaroxaban varied in different countries, subject to drug cost, and healthcare resource variation [11–15]. This study aimed to evaluate the health economic outcomes of rivaroxaban and warfarin for management of VTE in Hong Kong.

## Methods

### Study Design

The study was a retrospective cohort study of patients admitted to the Princess Margaret Hospital with a diagnosis of VTE between 1 March 2012 and 28 February 2017. Patient inclusion criteria (identified from electronic medical records) were ethnic Chinese men or women aged ≥ 18 years with a primary diagnosis of VTE (defined as DVT [ICD-10 diagnosis code, I80, I82.1, I82.2, I82.3, I82.8, I82.9] or PE [ICD-10 diagnosis code, I26]) and were initiated and later discharged with either rivaroxaban or warfarin. Exclusion criteria included oral or parenteral anticoagulant treatment prior to admission; concurrent diagnosis that required acute inpatient care; indication for anticoagulation in addition to VTE treatment; documented history of coagulopathy or thrombophilia; contraindication to anticoagulation; malignant diseases; pregnant or lactating women; thrombectomy; vena cava filter placement or fibrinolytic agent administered during index hospitalization stay; estimated glomerular filtration rate < 30 mL/min/1.73 $m^2$ at the time of admission. Princess Margaret Hospital is a 1700-bed major acute general hospital in Hong Kong. The study protocol was approved by the Clinical Research Ethics Committee for Kowloon West Cluster.

### Outcome Measurements

Demographic data (age, gender, smoking status) and comorbidities were collected. All VTE cases were categorized into DVT and PE, provoked or unprovoked VTE. Provoked VTE was defined as VTE occurring in the presence of the following risk factors less than 90 days before VTE diagnosis: surgery with general anesthesia, immobilization for at least 3 days, estrogen therapy, and hospital admission for acute illness [16]. If the patient had more than one hospitalization for VTE during the study period, the first episode was considered as the index admission.

The primary outcome measurement was hospitalization cost for the index VTE admission. The secondary outcomes included direct medical cost for VTE management and clinical outcomes in the 1-year post-discharge period.

The cost analysis was conducted from the perspective of the Hong Kong public healthcare provider. Direct medical costs were determined for inpatient care of the VTE index admission by the utilization of major healthcare resources and the unit cost of each major resource item, including hospital stay, anticoagulants (rivaroxaban, warfarin, and LMWH), VTE-related laboratory tests (renal function test, liver function test, APTT/PT, D-dimer, and complete blood count), and radiology services (chest X-ray, Doppler ultrasound, and contrast CT scan). The utilization of major resources was retrieved from the patient medical records. The unit cost of each item was approximated from the fees and charges of the Hospital Authority applied to non-residents of Hong Kong. The study hospital belongs to the Hospital Authority, the only public healthcare provider of Hong Kong. Hospital Authority is non-profit making and is subsidized by the Government of Hong Kong SAR, and the charges applicable to non-residents of Hong Kong were therefore assumed to solely represent the costs of healthcare resource (including labor costs). The unit costs of medication were drug acquisition costs. The total direct medical cost in the 1-year post-discharge period was estimated by the unit cost and utilization of follow-up outpatient visits, coagulation tests, anticoagulants, emergency department visits, and inpatient care of recurrent VTE or bleeding complications. Similarly, the resource utilization was collected from patient medical records.

The clinical outcomes comprised recurrent VTE, death contributed to VTE, major and minor bleeding complications [17], and INR control of warfarin cohort. INR 2.0–3.0 was the target range for VTE and time-in-therapeutic range (TTR) was calculated for patients in the warfarin cohort. INR records after day 15 of warfarin initiation and excluding periods of planned warfarin interruption were retrieved. INR values between two INR assessments are estimated using linear interpolation described by Rosendaal et al. [18], and TTR was defined as proportion patient days in follow-up period with in-range INRs.

### Statistical Analysis

All statistical analysis was computed using IBM Statistical Package for the Social Science (SPSS) version 20. Categorical variables were expressed in numbers and percentages while continuous variables were expressed in mean and standard deviation (SD). Patient characteristics and treatment outcomes in the rivaroxaban and warfarin groups were presented by descriptive statistics.

Univariate analysis was first performed on demographic and clinical variables to screen for the potential predictors with association to high cost (> 75th percentile) for VTE admission. Variables with a frequency of ≥ 5% were included in the univariate analysis. Factors found to have potential associations ($p \leq 0.1$) were further analyzed by backward stepwise

logistic models. The effect estimates for significant predictors were reported as odds ratio (OR) with 95% CI. A $p$ value < 0.05 was considered statistically significant.

## Results

### Patient Enrolment

A total of 300 subjects were found to fulfil the inclusion inclusion criteria, and 119 subjects were excluded for malignant cancer ($n = 46$), concurrent diagnosis requiring acute inpatient care ($n = 26$), renal insufficiency ($n = 22$), prior use of anticoagulant ($n = 12$), received thrombolytics or surgical embolectomy ($n = 6$), indication for anticoagulation in addition to VTE treatment ($n = 4$), and coagulopathy/thrombophilia ($n = 3$). The cost analysis of index VTE admission included 181 patients (90 in the rivaroxaban group; 91 in the warfarin group).

### Patient Demographics

Patient demographics and clinical characteristics are shown in Table 1. The mean ages were 63.3 ± 18.2 years and 61.8 ± 17.9 years in the rivaroxaban and warfarin groups, respectively ($p = 0.585$). Hypertension, hyperlipidemia, and diabetes mellitus were the most frequently reported comorbidities in both groups. DVT was the common VTE (rivaroxaban group 72.2%; warfarin group 76.9%). There was no statistically significant difference in the demographics and underlying clinical characteristics between the two groups.

### Total Medical Cost and LOS for VTE Index Admission

VTE-associated costs and LOS for VTE index admission are shown in Table 2. The patients in the rivaroxaban group had significantly shorter LOS than those in the warfarin group for both DVT and PE. Of the same study group, LOS for PE was significantly longer than that for DVT (rivaroxaban group, $p < 0.001$; warfarin group, $p = 0.028$). There was no admission to intensive care unit in both study groups.

The total direct cost for VTE index admission of the warfarin group was significantly higher than that of the rivaroxaban group (USD 5473 ± 1914 versus USD 3457 ± 1796; $p < 0.001$) (USD 1 = HKD 7.8). Hospital stay was the most costly item, followed by radiology, laboratory tests, and anticoagulants in both study groups. Costs of hospital stay, laboratory services, and anticoagulants were significantly higher in the warfarin group ($p < 0.001$).

Factors associated with high cost for VTE admission are shown in Table 3. High cost was defined as > 75 percentile (> USD 6263) of total cost for VTE index admission. Rivaroxaban and PE were two factors retained in the final logistic mode. Rivaroxaban (OR = 0.284; 95% CI 0.122, 0.658) was the negative predictor of high-cost hospitalizations while PE (OR 3.814; 95% CI 1.681–8.654) was the positive predictor of high-cost hospitalizations.

### Clinical Outcomes and Direct Medical Cost in 1-Year Post-discharge

In the outcome analysis of 1-year post-discharge, 6 of 90 patients in the rivaroxaban group were excluded (4 default follow-up; 2 switched to oral anticoagulant) and 9 of 91 patients in the warfarin group were excluded (2 default follow-up; 7 switched to oral anticoagulant). A total of 166 patients (84 in the rivaroxaban group; 82 in the warfarin group) were included in the 1-year post-discharge analysis. The TTR was 45.9% in the warfarin group, and 48.1% and 6% of the follow-up time were spent with INR < 2 and INR > 3, respectively.

Recurrent VTE occurred in 2 patients (2.4%) receiving rivaroxaban and 6 patients (7.3%) receiving warfarin (Table 4) and all recurrent cases manifested as DVT (RR 0.32; 95% CI 0.06–1.62; $p = 0.277$). All recurrent DVT cases in the warfarin group had TTR less than 65%. Major bleeding occurred in 2 patients (2.4%) and 1 patient (1.2%) in the rivaroxaban and warfarin groups, respectively (RR 1.98; 95% CI 0.18–22.22; $p = 0.509$). Clinically relevant non-major bleeding occurred in 4 patients (6%) receiving rivaroxaban and 10 patients (12.3%) receiving warfarin (RR 0.36; 95% CI 0.11–1.20; $p = 0.100$).

The total direct cost of the rivaroxaban group (USD 1271 ± 767) was significantly lower than that of the warfarin group (USD 1739 ± 1045) in 1-year post-discharge ($p < 0.001$) (Table 4). The cost of emergency department visit and hospitalization for VTE-related complications was also lower in the rivaroxaban group, however the difference did not achieve statistical significance. The cost of oral anticoagulant in the rivaroxaban group was higher than that of the warfarin group ($p < 0.001$), whereas the costs for outpatient visits and coagulation tests were lower in the rivaroxaban group ($p < 0.001$). The direct medical cost was significantly higher for patients with TTR < 65% ($n = 56$) than that with TTR ≥ 60% ($n = 26$) (USD 1878 ± 1187 versus USD 1440 ± 549; $p = 0.025$) in the warfarin group.

## Discussion

The drug cost of DOACs is one of the considerations in the selection of oral anticoagulant therapy for patients admitted for VTE. Warfarin is available as a generic item and the drug cost is significantly lower than DOACs, yet the economic advantage in drug cost difference is possibly offset by the resources used on anticoagulation control optimization. In the present study, the total cost for VTE admission was significantly higher in patients initiated and later discharged with warfarin than that with

**Table 1** Patient demographics and clinical characteristics

| Characteristics | Rivaroxaban ($n = 90$) | Warfarin ($n = 91$) | $p$ value |
|---|---|---|---|
| Age (years) (mean ± SD) | 63.3 ± 18.2 | 61.8 ± 17.9 | 0.585 |
| Male (%) | 37 (41.1%) | 43 (47.3%) | 0.248 |
| Smoking status (%) | | | |
| Non-smoker | 74 (82.2%) | 72 (79.1%) | 0.837 |
| Smoker | 14 (15.6%) | 16 (17.6%) | |
| Ex-smoker | 2 (2.2%) | 3 (3.3%) | |
| Type of venous thromboembolism (VTE) | | | 0.498 |
| Deep venous thrombosis | 65 (72.2%) | 70 (76.9%) | |
| Pulmonary embolism | 25 (27.8%) | 21 (23.1%) | |
| Cause of VTE | | | |
| Unprovoked | 62 (68.9%) | 73 (80.2%) | 0.090 |
| Provoked | 28 (31.1%) | 18 (19.8%) | |
| Immobilization | 19 (21.1%) | 5 (5.5%) | |
| Recent surgery or trauma | 7 (7.8%) | 8 (8.8%) | |
| Estrogen therapy | 2 (2.2%) | 5 (5.5%) | |
| eGFR at admission (mL/min/1. 73 $m^2$) | | | |
| ≥ 30 to < 60 | 11 (12.2%) | 9 (9.9%) | 0.810 |
| ≥ 60 to < 90 | 44 (48.9%) | 43 (47.3%) | |
| ≥ 90 | 35 (38.9%) | 39 (42.9%) | |
| Comorbidities | | | |
| Hypertension | 45 (50%) | 34 (37.4%) | 0.100 |
| Hyperlipidemia | 24 (26.7%) | 19 (20.9%) | 0.387 |
| Diabetes mellitus | 18 (20%) | 11 (12.1%) | 0.161 |
| Congestive heart failure | 4 (4.4%) | 9 (9.9%) | 0.129 |
| Previous stroke | 5 (5.6%) | 1 (1.1%) | 0.103 |
| Prior myocardial infarction | 3 (3.3%) | 3 (3.3%) | 0.654 |
| Chronic obstructive pulmonary disease | 1 (1.1%) | 5 (5.5%) | 0.211 |
| Inflammatory bowel disease | 2 (2.2%) | 1 (1.1%) | 0.621 |
| VTE history > 12 months | 2 (2.2%) | 0 (0%) | 0.246 |

*eGFR* estimated glomerular filtration rate

rivaroxaban by 1.5-fold. Rivaroxaban treatment was a negative predictor of high VTE admission cost. Our findings were consistent with the cost-saving of rivaroxaban versus warfarin for VTE reported in over 20 countries [19, 20].

The cost of hospital stay was the major cost driver of all resources in VTE admission. The rivaroxaban treatment had a significantly shorter mean LOS (4.8 days) compared with warfarin treatment (8.0 days) in the present cohort, with the

**Table 2** VTE-associated cost and hospital length of stay for venous thromboembolism (VTE) index admission

| Characteristics | Rivaroxaban ($n = 90$) | Warfarin ($n = 91$) | $p$ value |
|---|---|---|---|
| Cost (USD)* (mean ± SD) | | | |
| Hospitalization | 2873 ± 1630 | 4787 ± 1807 | < 0.001 |
| Radiology service | 358 ± 194 | 334 ± 137 | 0.404 |
| Laboratory service | 193 ± 104 | 297 ± 127 | < 0.001 |
| Anticoagulants (oral and parenteral) | 33 ± 22 | 55 ± 29 | < 0.001 |
| Total | 3457 ± 1796 | 5473 ± 1914 | < 0.001 |
| Hospital length of stay (days) (mean ± SD) | | | |
| All VTE | 4.8 ± 2.7 | 8.0 ± 3.0 | < 0.001 |
| Deep venous thrombosis | 4.2 ± 2.4 | 7.6 ± 3.0 | < 0.001 |
| Pulmonary embolism | 6.4 ± 2.7 | 9.2 ± 2.8 | 0.001 |

*USD 1 = HKD 7.8

**Table 3** Factors associated with high-cost venous thromboembolism (VTE) admission

| | ≤ USD 6263 ($n = 146$) $n$ (%) | > USD 6263 ($n = 35$) $n$ (%) | Odds ratio (95% CI) | $p$ value |
|---|---|---|---|---|
| Univariate analysis | | | | |
| Pulmonary embolism | 30 (20.5) | 16 (45.7) | 3.256 (1.497–7.081) | 0.003 |
| Rivaroxaban | 80 (54.8) | 10 (28.6) | 0.330 (0.148–0.736) | 0.007 |
| Final model from multivariate analysis | | | | |
| Pulmonary embolism | | | 3.814 (1.681–8.654) | 0.001 |
| Rivaroxaban | | | 0.284 (0.122–0.658) | 0.003 |

High cost was defined as > 75 percentile of the total cost (USD 6263) for VTE index admission ($n = 181$); (USD 1 = HKD 7.8)

absolute reduction of mean LOS by 3.2 days ($p < 0.001$). These findings were similar with previously published studies that VTE treatment with rivaroxaban was associated with a reduction of 1.6–3.5 days in hospital LOS [20–22]. The longer LOS in the warfarin group was likely for anticoagulation optimization, indicated by the higher cost of parenteral anticoagulant and oral anticoagulant use in the warfarin group during VTE admission in the present study. A previous report also found that the main driver of cost-saving resulted from reduction in LOS associated with rivaroxaban, contributing to 90% of total saving [23].

The 1-year post-discharge VTE recurrence rate (2.4%) in the rivaroxaban group was compatible with the findings in the EINSTEIN trial (2.1%) [24]. The recurrent rate of VTE in the warfarin patients (7.3%) was threefold higher than that in the EINSTEIN trial (2.3%). The TTR (45.9%) of warfarin patients in the present cohort was lower than the TTR (62%) in the EINSTEIN DVT/PE pool analysis. The high VTE recurrence is likely explained by the sub-optimal anticoagulation control in the present warfarin cohort.

The cost analysis of 1-year post-discharge found significantly lower total direct medical cost in the rivaroxaban group versus the warfarin group, even though the mean medication cost was significantly higher in the rivaroxaban group (USD 470 versus USD 25; $p < 0.001$). The warfarin group consumed higher amounts of resources for routine monitoring and management of sub-optimal anticoagulation levels using resources such as LMWH (for under-coagulation), vitamin K (for over-coagulation), emergency department visits, and hospitalization for VTE-related complications (recurrent VTE and bleeding). A prior health economic study also reported that rivaroxaban significantly reduced total VTE treatment costs

**Table 4** Clinical outcomes and direct medical costs in 1-year post-discharge period

| | Rivaroxaban ($n = 84$) | Warfarin ($n = 82$) | $p$ value |
|---|---|---|---|
| Clinical outcomes | | | |
| Recurrent VTE* | 2 (2.4%) | 6 (7.3%) | 0.277 |
| All bleeding episodes | 6 (7.1%) | 11 (13.4%) | 0.209 |
| Major bleeding episodes[#] | 2 (2.4%) | 1 (1.2%) | 0.509 |
| Clinically relevant non-major bleeding episodes | 4 (6.0%) | 10 (12.3%) | 0.100 |
| Gum bleeding | 3/4 (60%) | 2/10 (20%) | |
| Hematoma | 1/4 (20%) | 2/10 (20%) | |
| Epistaxis | 0/4 (20%) | 2/10 (20%) | |
| Bruising | 0/4 (0%) | 4/10 (40%) | |
| Direct medical costs | | | |
| Outpatient visits | 613 ± 199 | 1138 ± 319 | < 0.001 |
| Oral anticoagulants | 470 ± 209 | 25 ± 3 | < 0.001 |
| Coagulation tests | 34 ± 43 | 175 ± 44 | < 0.001 |
| Emergency department visits for VTE-related complications[†] | 9 ± 33 | 25 ± 58 | 0.084 |
| Hospitalizations for VTE-related complications[†] | 145 ± 615 | 376 ± 1000 | 0.072 |
| Total cost | 1271 ± 767 | 1739 ± 1045 | < 0.001 |

*All recurrent VTE episodes were manifested as DVT

[#] Major bleeding: All episodes were associated with a fall in hemoglobin of ≥ 2 g per deciliter, transfusion of ≥ 2 units

[†] VTE-related complications included recurrent VTE and bleeding complications

during the 12 months following the index VTE event, despite higher pharmacy costs of rivaroxaban [15].

The mean TTR of 45.9% in the present cohort was lower than the recommended TTR of at least 65% [25], consistent with the sub-optimal anticoagulation control (TTR 38.8%) in atrial fibrillation patients in Hong Kong [26]. Only one-third of the patients achieved TTR of at least 65% in the 1-year post-discharge period. All recurrent VTE cases in the warfarin group occurred in the subgroup with TTR < 65%. The mean direct medical cost was significantly higher for patients with TTR < 65%. Sub-therapeutic INR levels were found to associate with a more than threefold increased risk of VTE recurrence [27]. In real-world practice, high-quality anticoagulation control with warfarin is difficult to achieve. A high degree of unpredictable variability in an individual's TTR was reported in the first 12 months of warfarin use [28]. Anticoagulation control with warfarin can be influenced by many demographic and clinical factors such as sex, age, and comorbidities [29]. In addition, low TTR control may be due to poor compliance to the drug. Frequent anticoagulant monitoring and numerous drug-drug and drug-food interactions may affect the compliance to warfarin and thus TTR control [30].

There were several limitations in this study. The retrospective design of the study affected the quality of data. The availability of data was highly dependent on the completeness and accuracy of information in the medical records. Limited by the sample size from a single center, it might not have adequate power to detect a difference for uncommon events such as major bleeding and recurrent VTE in the 1-year post-index period.

In conclusion, total direct cost and LOS for VTE admission were significantly lower in patients initiated and discharged with rivaroxaban than warfarin. Rivaroxaban was a negative predicator for high VTE admission cost. The total cost in 1-year post-discharge was also significantly lower in patients on rivaroxaban. Despite higher medication cost than warfarin, rivaroxaban appeared to be cost-saving for the management of VTE.

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## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

**Ethical Approval** The study protocol was approved by Kowloon West Cluster Research Ethics Committee of Hospital Authority prior to the initiation of the study.

**Informed Consent** For this retrospective study, formal consent was waived by the Kowloon West Cluster Research Ethics Committee of Hospital Authority.

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