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Original Research Article

Extended warfarin treatment versus rivaroxaban treatment for first episode of symptomatic unprovoked pulmonary embolism: A prospective cohort study

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Abstract

Purpose: *To compare the benefits and risks of extra 6 months of warfarin therapy with those of rivaroxaban treatment in patients with initial unprovoked pulmonary embolism (PE) episode who completed 3- or 6-month of therapy on heparin/vitamin K antagonist standard regime.*
Methods: *This prospective observational study included 212 patients with follow-up from July 2013 to July 2018. The primary endpoint was symptomatic recurrent venous thromboembolism (VT), composite of non-fatal symptomatic PE or deep vein thrombosis or fatal VT, and major bleeding (non-fatal/fatal) up to 6 months. Secondary endpoints were death not related to PE or major bleeding.*
Results: *During the 6-month therapy period, the primary endpoint was seen in 3 out of 106 patients (2.83 %) in warfarin category, and in rivaroxaban category, for a hazard ratio (HR) of 1.22 [95 % confidence interval (CI) = 0.09 - 11.18; p = 0.813]. With warfarin therapy, 2 patients (1.89 %) had recurrent VT, while 3 patients (2.83 %) had VT with rivaroxaban. Major bleeding was observed in 2 patients (1.89 %) on warfarin, and in one patient (0.94 %) on rivaroxaban. During the entire 18-month period, the primary endpoint was seen in 15 patients (14.15 %) treated with warfarin, and in 18 patients (16.98 %) treated with rivaroxaban (HR 0.84; 95 % CI = 0.47 - 1.84; p = 0.431). Major bleeding was observed in 5 patients (4.72 %) under warfarin (one fatal), relative to 3 patients (2.83 %) under rivaroxaban (R 1.67; 95 % CI = 0.62 - 5.95; p = 0.09).*
Conclusion: *Rivaroxaban showed higher efficacy than warfarin in recurrent VT prevention, with lower risk of major bleeding. However, the extended therapeutic benefit was not maintained post-therapy.*

Keywords: *Pulmonary embolism, Rivaroxaban, Warfarin, Heparin, Vitamin K, Hazard ratio*

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INTRODUCTION

Patients with episodes of initial unprovoked venous thromboembolism (VT) have greater recurrence risk when anticoagulant treatment is halted after 3 to 6 months of therapy, relative to patients with VT provoked by risk-factors (e.g., surgery). In such higher risk patients, prolonging anticoagulant therapy past 3 to 6 months is associated with recurrence risk reduction if continuous treatment is provided. However, it is not certain whether such advantage remains constant, since most previous studies did not carry out follow-up of patients after

discontinuation of therapy [1-5]. Only two studies included patients with initial unprovoked pulmonary embolism (PE), out of studies that evaluated the effect of prolonged duration of anticoagulants for secondary prophylaxis post-unprovoked VT. Since the fatality of recurrent VT is about four times greater post-PE than that of deep vein thrombosis (DVT), the risk-benefit ratio of prolonged use of anticoagulants differs in all probability between PE and DVT, and hence should be determined independently [3,5].

Although the incidence of PE in China is unknown, the disorder is gaining greater recognition by the medical services domain in China. This pattern may have emerged because of growing awareness by physicians and the accessibility of minimal/non-invasive diagnostic methods. Records of VT therapy outcomes in Chinese patients are scanty, although there is, by all accounts a general notion that bleeding risk is more in patients on standard therapy, and that treatment with vitamin K antagonists ought to be dosed cautiously, with a goal of achieving low values of international normalized ratio (INR). Likewise, bleeding concerns are applicable to direct oral anticoagulant therapy.

Rivaroxaban falls under direct Factor Xa inhibitors with fast onset of action that requires no regular coagulation monitoring. It has minimal interaction with drugs, and it does not interact with food. These desirable properties have been corroborated in a study conducted on Chinese patients [6]. In EINSTEIN DVT and PE studies, rivaroxaban monotherapy was demonstrated to be as efficacious as two-drug treatment involving enoxaparin overlapped with, and accompanied by vitamin K antagonist, with low incidents of major bleeding [7,8].

The aim of the present study was to conduct a prospective investigation on patients with an initial unprovoked PE episode who were on three- or six-monthly anticoagulant treatment. The purpose was to evaluate the benefits as well as risks of extra 6 months of therapy with warfarin relative to rivaroxaban in patients who completed three or six-months of therapy with heparin/vitamin K antagonist standard regime. In addition, examination of results for one year after cessation of the studied medications was done.

METHODS

General information

This prospective cohort study was carried out in Vascular Surgery Department of Shanghai Fifth People's Hospital. Approval was received from Institutional Review Board of the hospital (approval no. 2013SP10524), and informed consent was received from participants. Patient confidentiality was strictly maintained. The review was carried out as per the V2008 Helsinki Declaration [9].

Study population

Patients older than 18 years who were on three- or six-monthly anticoagulants treatment, with an initial unprovoked PE episode, and on extra 6 months of therapy (with either warfarin or rivaroxaban) were included. Unprovoked PE was defined as symptomatic PE which was confirmed objectively, and manifested with no major reversible risk factors for VT within 3 months prior to diagnosis. Other criteria included regional/general anesthesia (>30 min) surgery, trauma with/without lower limb plaster cast, as well as >72 h bed rest and no active cancer presence or cancer resolved at least two years before diagnosis.

The exclusion criterion included patients with provoked PE, proximal/distal DVT, recurrent VT or bleeding while on initial anticoagulant therapy, major thrombophilia, vitamin K antagonist indication for other reasons, and raised bleeding risk. Moreover, patients with serious kidney, cardiovascular, liver, lung, and brain disorders, as well as those who were pregnant, breastfeeding, or planning pregnancy, were excluded. Treatment selection depended on physician and patient's choice of either warfarin or rivaroxaban.

Endpoints

The primary endpoint was symptomatic recurrent VT (composite of non-fatal symptomatic PE or DVT or fatal VT) and major bleeding (non-fatal/fatal) up to 6 months. The secondary endpoints were death not related to PE and major bleeding during the 6-month therapy period and 18-month study period. The decision of the composite endpoints to assess depended on the outcomes of studies demonstrating recurrent VT, as well as incidence of major bleeding fatality [3,10]. Symptomatic recurrent DVT or PE was confirmed using spiral computerized tomographic angiography, ultrasonography, pulmonary angiography, or ventilation-perfusion lung scanning. Bleeding was deemed major when it was fatal, or had critical organ involvement, or overt and in association with decreased hemoglobin level of ≥2 g/dL, or required transfusion with a minimum of 2 units of packed red blood cells.

Statistical analysis

Values for categorical variables are expressed as numbers with percentages, while results for continuous variables are expressed as mean ± standard deviation (SD). Analysis of all data collected was done using SPSS version 21.0 (SPSS Inc, Chicago). Student's *t*-test was used for analysis of continuous variables, and non-parametric tests were utilized for comparison of group differences. An estimate of $p < 0.05$ was selected for statistical significance. Kaplan-Meier method was utilized for estimating time-to-event outcomes, while log rank test was utilized for between-group comparisons. Cox regression was utilized for the hazard ratio comparisons with reference standard warfarin.

RESULTS

Between July 2013 and July 2018, 212 patients were selected in the present study. Six-month extended rivaroxaban therapy was given to 106 patients, while the other 106 patients received 6-month extended warfarin therapy. The clinical and demographic characteristics of the included patients were well balanced at baseline, the exception being that more women and patients with body mass index (BMI) greater than 29 received warfarin (Table 1).

During the 6-month therapy period, the primary endpoint was observed in 3 of 106 patients (2.83 %) in the warfarin category as well as in the rivaroxaban category, for a hazard ratio (HR) of 1.22 (95 % CI = 0.09 - 11.18*;* $p = 0.813$) (Table 2). In the warfarin category, 2 patients (1.89 %) had recurrent VT, which were unprovoked and presented post-discontinuation of warfarin. In the rivaroxaban category, 3 patients (2.83 %) had unprovoked recurrent VT. Major bleeding was observed in 2 patients (1.89 %) in the warfarin category (one with retroperitoneal bleeding, and the other with epistaxis). In the rivaroxaban category, one patient (0.94 %) had major bleeding. However, these events were non-fatal (Table 2).

Table 1: Clinical/demographic characteristics of patients

Characteristic	Warfarin (n = 106)	Rivaroxaban (n = 106)
Age (years)*	61.23 ±16.14	59.54 ±17.92
>65 years, n (%)	38 (35.85 %)	36 (33.96 %)
Female, n (%)	63 (59.43 %)	43 (40.57 %)
Body mass index (BMI; kg/m^2)*	28.2 ±4.4	28.7 ±4.1
BMI ≥30, n (%)	34 (32.08 %)	24 (22.64 %)
Comorbid conditions		
Chronic heart failure	3 (2.83 %)	4 (3.77 %)
Prior cancer	5 (4.72 %)	3 (2.83 %)
Chronic respiratory failure	22 (20.75 %)	20 (18.87 %)
Prior distal DVT	12 (11.32 %)	11 (10.38 %)
Creatinine clearance, n (%)		
< 30 mL/min	0	0
≥ 30 to <50 mL/min	11 (10.38 %)	10 (9.43 %)
≥50 mL/min	95 (89.62 %)	96 (90.57 %)
Diagnostic method, n (%)		
Ventilation perfusion lung scanning	26 (24.53 %)	27 (25.47 %)
Spiral computed tomography	77 (72.64 %)	76 (71.69 %)
Pulmonary angiography	3 (2.83 %)	3 (2.83 %)
PE characteristics		
Residual DVT, n (%)	16 (15.09 %)	19 (17.92 %)
Perfusion defect (≥10 %), n (%)	36 (33.96 %)	33 (31.13 %)
D-dimer level (ng/mL)	376.4 ±559.3	352.1 ±483.4
Systolic pulmonary arterial pressure, mmHg	31.2 ±7.1	30.8 ±8.0
Thrombophilia, n (%)		
Major	5 (4.72 %)	6 (5.66 %)
Minor	29 (27.36 %)	25 (23.58 %)
Compression stockings usage, n (%)	61 (57.55 %)	64 (60.38 %)
Major concomitant treatments, n (%)		
Statins	22 (20.75 %)	20 (18.87 %)
Antiplatelet agents	11 (10.38 %)	8 (7.55 %)
Bleeding risk, n (%)		
Low	25 (23.58 %)	29 (27.36 %)
Moderate	36 (33.96 %)	39 (36.79 %)
High	46 (43.39 %)	43 (40.57 %)

*Values are expressed as mean ± SD. DVT = deep vein thrombosis; PE = pulmonary embolism

Table 2: Primary and secondary endpoints

Characteristic	Warfarin (n = 106)	Rivaroxaban (n = 106)	Hazard Ratio (CI)	*P*-value
During 6-month therapy period				
Primary endpoint	3 (2.83 %)	3 (2.83 %)	1.22 (0.09-11.18)	0.813
Recurrent VT	2 (1.89 %)	3 (2.83 %)	0.81 (0.49-1.63)	0.344
Nonfatal symptomatic PE	1	2		
Nonfatal symptomatic DVT	1	1		
Fatal PE	0	0		
Major bleeding	2 (1.89 %)	1 (0.94 %)	2.18 (0.41-4.84)	0.04
Nonfatal	2	1		
Fatal	0	0		
Death from other causes	1 (0.94 %)	1 (0.94 %)	1.19 (0.34-9.61)	0.336
During 18-month entire period				
Primary endpoint	15 (14.15 %)	18 (16.98 %)	0.84 (0.47-1.84)	0.431
Recurrent VT	12 (11.32 %)	15 (14.15 %)	0.79 (0.28-2.14)	0.626
Nonfatal symptomatic PE	8	13		
Nonfatal symptomatic DVT	2	2		
Fatal PE	2	1		
Major bleeding	5 (4.72 %)	3 (2.83 %)	1.67 (0.62-5.95)	0.09
Nonfatal	4	3		
Fatal	1	0		
Death from other causes	4 (3.77 %)	3 (2.83 %)	1.26 (0.11-5.88)	0.148

CI = 95% confidence interval; DVT = deep vein thrombosis; PE = pulmonary embolism; VT = venous thromboembolism

In the follow-up post-therapy, the primary endpoint was seen in 12 patients who took warfarin (11.32 %), and in 15 patients who received rivaroxaban (14.15 %). In the warfarin category, 10 patients (9.43 %) had recurrent VT, all with no anticoagulants, and there were 6 unprovoked events (60 %) and 2 fatal events. In the rivaroxaban category, 13 patients (12.26 %) had recurrent VT, all with no anticoagulants, and there were 9 unprovoked events (69.23 %) and 1 fatal event. Major bleeding was observed in 2 patients (1.89 %) in the warfarin category (one fatal and another non-fatal), whereas one patient (0.94 %) had major bleeding in the rivaroxaban category (non-fatal), for a HR of 2.18 (95 % CI = 0.41 - 4.84*; p* = 0.04).

On the whole, the primary composite endpoint was seen in 15 patients (14.15 %) on warfarin treatment, and in 18 patients (16.98 %) on rivaroxaban therapy, with a HR of 0.84 (95% CI = 0.47 - 1.84*; p* = 0.431). Major bleeding was observed in 5 patients (4.72 %) in the warfarin category (one fatal) when compared to 3 patients (2.83 %) in the rivaroxaban category (non-fatal), for a HR of 1.67 (95% CI = 0.62 - 5.95*; p* = 0.09).

DISCUSSION

In present study involving patients with an initial unprovoked PE episode who were given extra 6 months of therapy with either warfarin or rivaroxaban, there was no significant difference in the composite primary endpoint, but a significantly lower percentage of major bleeding was found in the rivaroxaban group. However, this benefit of extended therapy was not seen post-therapy.

Consistent with prior studies that assessed significantly extended anticoagulant therapy for initial unprovoked VT or PE episode, greater percentage recurrent VT was seen in warfarin and rivaroxaban treatment categories [3-5,11-13].The relative benefit in terms of efficacy and safety of rivaroxaban compared to warfarin in present study is in line with results of other global studies [7,8].

The treatment guideline utilized in China is similar to the standard treatment utilized in the EINSTEIN studies, i.e., heparins overlapped with, and accompanied by adjusted vitamin K antagonist treatment [7,8]. Previous studies have shown that when patients suffer recurrent VT episode, it normally took a form similar to the initial event [3-5,10]. Such situation was seen in present study too. Notwithstanding whether patients were under warfarin or rivaroxaban, nearly 80 % of recurrent VT episodes constituted another symptomatic PE episode. Moreover, the greater number of recurrent VT episodes in both study categories were unprovoked (>80 %), as seen in other studies [3-5]. Thus, prolonging anticoagulant therapy to 6 months had no effect on the clinical manifestation of recurrent VT. Most recurrent VT episodes were non-preventable and amounted to the most serious type of VT.

The present study outcome recommends that patients have need for long-term maintenance measures. However, the incorporation of precise therapies with new anticoagulants, vitamin K antagonists, or aspirin, or therapies customized as per risk factors (including raised D-dimer levels) of patients requires further investigations.

Limitations of the study

Certain intrinsic limitations should be considered while interpreting the outcomes of this study. Being a one-center study with very limited number of patients, one should be cautious in generalizing the results. The primary endpoint constituted two distinctive result estimates that might not be equivalent clinically, though each has comparable and high fatality rate [3,14].

CONCLUSION

In patients with an initial unprovoked PE episode who received extra 6 months of warfarin or rivaroxaban therapy, rivaroxaban showed more efficacy than warfarin in recurrent VT prevention, with lower major bleeding risk. However, this benefit of extended therapy was not maintained post-therapy.

DECLARATIONS

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Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

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