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Full Length Article

# Rivaroxaban in the treatment of upper extremity deep vein thrombosis: A single-center experience and review of the literature☆

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ABSTRACT

*Introduction:* Direct oral anticoagulants (DOACs) have become widely used to treat patients with venous thromboembolism (VTE), but evidence about their use in the treatment of upper extremity deep vein thrombosis (UEDVT) is lacking.

*Objectives:* To assess rivaroxaban's efficacy and safety in the treatment of UEDVT.

*Patients/methods:* This was a single-center prospective observational study involving patients with their first UEDVT episode confirmed by duplex ultrasound scan. All patients initially received low-molecular-weight heparin for 1 to 2 days and then were switched to rivaroxaban for 3–6 months. The primary endpoint was any symptomatic episode of recurrent VTE.

*Results:* Thirty patients were included in the study, and all patients were followed for 6 months. There were no episodes of recurrent symptomatic venous thromboembolism or asymptomatic UEDVT. No episode of major bleeding was observed. Clinically relevant non-major bleeding occurred in two patients (6.7%, 95% confidence interval [CI]: 1.9–21.4%) with uterine bleeding and large skin hemorrhage. Minor bleeding was observed in two patients (6.7%, 95% CI: 1.9–21.4%) presenting with nasal and gingival bleeding. Recanalization of the upper extremity deep veins was observed in all affected limbs at three months, and it persisted up to 6 months. The signs of upper limb post-thrombotic syndrome (PTS) were found in four patients (13.4%; 95% CI: 5.4–29.8%), and the mean modified Villalta score was 2.1 ± 1.9.

*Conclusion:* Treatment of UEDVT with rivaroxaban, preceded by one to two days of LMWH, seems to be safe and effective.

## 1. Introduction

The incidence of venous thromboembolism (VTE), which includes both deep vein thrombosis (DVT) and pulmonary embolism (PE) is 1–2 per 1000 population per year [1–4]. According to the current guidelines, anticoagulant therapy for at least three months is required to prevent thrombus extension and early recurrence, as well as PE and death [5]. After that, the decision to stop or continue treatment depends on the individual balance between the benefit and risk of prolonged anticoagulation, which is associated with a reduction in the risk of recurrent VTE but an increased risk of major bleeding [6].

Upper extremity deep vein thrombosis (UEDVT) represents about 10–11% of all VTE events [7–9] with the development of PE in 6–15% and post-thrombotic syndrome (PTS) in 25–77% of all patients [11,12,30].

Direct oral anticoagulants (DOACs) have become widely used for treatment of VTE because of their non-inferiority in efficacy and superiority in safety compared with vitamin K antagonists (VKA) [13–15]. Fixed dosing and the lack of a requirement for laboratory monitoring are the most common advantages of DOACs in clinical practice. One of the most popular DOACs, rivaroxaban [16], is well established in the treatment of lower limb DVT and PE [13,14], but there is little evidence of its use in the treatment of UEDVT.

This study aimed to assess the efficacy and safety of rivaroxaban in

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the treatment of UEDVT.

## 2. Materials and methods

This single-center prospective observational study included patients with their first symptomatic UEDVT and was conducted at Clinical Hospital no.1 of the President's Administration of the Russian Federation during 2015–2017. The observation is limited by the specified time period because after that we began to use a more aggressive approach for the treatment of UEDVT with thrombolysis and decompression surgery.

Inclusion criteria were as follows: symptomatic UEDVT confirmed by duplex ultrasound scan (DUS), age over 18 years; and provision of informed consent.

Exclusion criteria were as follows: suspected or confirmed PE or recurrent UEDVT; requirement for interventional treatment (catheter-directed thrombolysis, angioplasty with stenting, and/or surgical decompression); creatinine clearance < 15 mL/min; clinically significant liver disease (acute hepatitis, chronic active hepatitis, cirrhosis, or an alanine aminotransferase level at least three or more times higher than the upper limit of the normal range), high risk of bleeding, pregnancy, postpartum period, or breastfeeding.

Duplex ultrasound was performed in all patients who were admitted to the hospital with suspected UEDVT using the Voluson E8 (GE Medical Systems, Zipf, Austria) with a linear transducer in the frequency range of 5–13 MHz. The standard B-mode with an assessment for vein compressibility and color flow Doppler was used, according to the previously described technique [17]. The criteria for DVT were incompressibility of the potentially compressible superficial and deep veins located under the axillary cavity; and the absence of spontaneous blood flow or blood flow that was stimulated by manual compression or by flexion-extension of a fist in all veins located under and over the axillary cavity, as well as vessels in the costoclavicular space and thoracic cavity. In addition to DUS, all patients were assessed clinically, especially for well-known individual VTE risk factors [18].

After UEDVT was confirmed, all patients received initial treatment with low-molecular-weight heparin (LMWH), enoxaparin (1 mg/kg subcutaneously twice daily), for 24–48 h followed by rivaroxaban 15 mg twice daily for the first 3 weeks and then 20 mg once daily for 3 months or more. The initial therapy with LMWH was aimed to provide an opportunity for thrombolysis if it was appropriate. Patients were followed up for 6 months with monthly evaluations, including a clinical assessment and DUS. An unscheduled DUS was available in any case of suspicion for recurrent upper extremity or lower extremity DVT and PE.

The primary endpoint was a combination of radiologically confirmed symptomatic lower extremity DVT, symptomatic recurrent UEDVT, and symptomatic PE. The secondary efficacy endpoints were separate components of the primary endpoint, as well as asymptomatic recurrence of UEDVT, recanalization of the affected veins, and development of the upper extremity post-thrombotic syndrome within the first six months after the index episode.

The symptomatic lower extremity DVT was defined as the appearance of classic symptoms, including pain, edema, cyanosis, and prominent subcutaneous veins. Symptomatic UEDVT recurrence was defined as an appearance of typical symptoms (pain, edema, cyanosis, and prominent subcutaneous veins) in the intact limb or an increase in symptom severity in the affected arm. Symptomatic PE was defined as the sudden appearance of dyspnea, chest pain, cough, hemoptysis, and collapse. Recanalization was suggested in the presence of any blood flow in the affected veins that was revealed by DUS. The asymptomatic recurrence of UEDVT was defined as total occlusion in a previously recanalized venous segment or any thrombotic lesion in the previously unaffected veins that was revealed by DUS. The modified Villalta score was used to assess PTS of the upper limb at six months after index UEDVT. This modification was published by Czihal and consists of 5 patient-reported symptoms (pain, cramps, heaviness, pruritus, and paresthesia) and 6 physician-reported clinical signs (edema, prominent subcutaneous arm veins, prominent collateral veins, tenderness, redness, dependent cyanosis - when the arm is in the down position). Each symptom or sign was graded from 0 (absent) to 3 (severe). A score of 5 or more is considered to be a PTS diagnosis [19].

The secondary safety endpoints were major bleeding, clinically relevant non-major (CRNM), and minor bleedings. Major bleeding was defined according to the International Society on Thrombosis and Haemostasis (ISTH) criteria [20]. CRNM bleeding was suggested for those who did not meet the criteria for major bleeding but who required preliminary interruption of anticoagulation, and/or any medical intervention for hemostasis, and/or unscheduled contact with the physician. Minor bleeding was defined as bleeding that did not meet the criteria for major or CRNM bleeding.

This study was approved by the local Institutional Reviewal Board.

Statistical analysis was performed using the IBM SPSS Statistics v.19 software package (IBM, Armonk, NY, USA). All absolute values are presented as the mean value with the standard deviation (mean ± SD). For relative values, the 95% confidence interval (CI) was calculated by the Wilson method. $P < 0.05$ was considered to be significant.

## 3. Results

Thirty-five patients with UEDVT confirmed by DUS were consecutively admitted and treated at the Clinical Hospital no.1 of the President Administration of the Russian Federation from April of 2015 to March of 2017. Among them, 30 patients (85.7%) were included in the study. Five did not meet the inclusion criteria as follows: three patients were excluded because catheter-directed thrombolysis was performed (8.6%), and two patients (5.7%) did not give informed consent. Thirteen men and 17 women aged 28–78 years (mean age, 52.4 ± 17.3 years) were included. UEDVT was triggered by physical effort in five patients (16.7%) and by pacemaker implantation through the veins of the affected extremity within 6 months before symptoms manifestation in four patients (13.3%). Uterine cancer was revealed in one woman (3.3%) 9 months before the index event. The other 19 patients (63.3%) had no distinct triggering factors for UEDVT development at the moment of manifestation. Additionally, most patients (76.6%) had well-known individual risk factors for VTE, which are presented in Table 1. Lung cancer was diagnosed in one patient within one month after UEDVT presentation. The clearance of creatinine estimated by Cockcroft-Gault equation was over 30 mL/min in all patients (mean value, 114,1 ± 29,0).

A subclavian vein lesion was detected in all patients: in five patients (16.7%), the thrombosis extended to the jugular vein; in 14 patients (46.7%), it extended to the axial vein; and in 10 patients (33.3%) it extended to the brachial vein. The mean duration of symptoms before diagnosis was 1.8 ± 1.7 days.

Duration of the initial enoxaparin therapy was 1.2 ± 0.8 days. Treatment with rivaroxaban was limited to 3 months in 28 patients (93.3%), and in two patients (6.7%), it was prolonged for 6 months because of active malignancy.

**Table 1**
Individual risk factors for VTE.

| Individual risk factors for venous thromboembolism | n | % |
|---|---|---|
| Age > 60 years old | 11 | 36.6% |
| Chronic venous disease | 9 | 30.0% |
| Chronic heart failure (NYHA functional class 2–4) | 10 | 33.3% |
| BMI > 25 kg/m$^2$ | 11 | 36.6% |
| Surgical intervention | 1 | 3.3% |
| Active malignancy | 2 | 6.7% |
| Hormone therapy | 1 | 3.3% |
| Individual history of VTE | 5 | 16.7% |

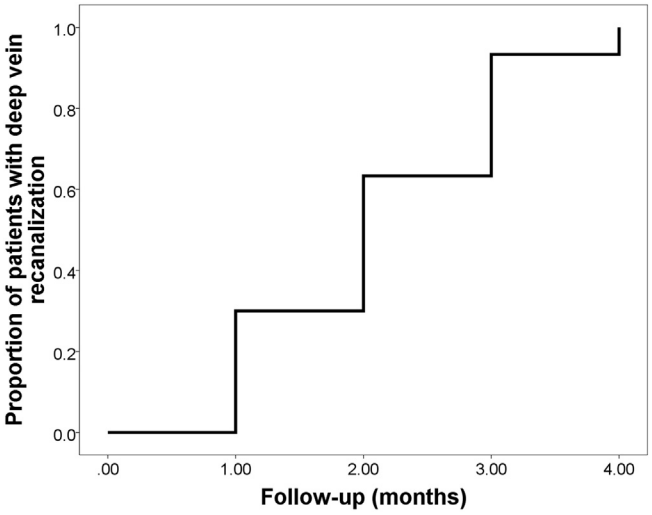


**Fig. 1.** Cumulative incidence of deep vein recanalization.

Thirty patients were followed for 6 months. The primary endpoint was not observed in any patient (0%, 95% CI: 0.0–11.4%), and there was no asymptomatic recurrence of UEDVT. Recanalization was observed in all deep veins in all patients (100%, 95% CI: 88.7–100.0%), and time to recanalization is presented in Fig. 1. At 6 months no residual thrombi were observed in the compressible superficial and deep veins under the axillary cavity and enlarged subcutaneous collaterals of the chest and shoulder were found in 3 patients (10%; 95% CI: 3.5–25.6%).

Signs of upper extremity PTS were found in 4 patients (13.4%; 95% CI: 5.4–29.8%), and the mean score was 2.1 ± 1.9, as assessed using a modified Villata score. None of these UEDVT was associated with physical effort or pacemaker implantation. There was a history of previous lower extremity DVT in two patients. The incidence of detected PTS symptoms is presented in Table 2.

No episode of major bleeding was observed. CRNM bleeding occurred in two patients (6.7%: 95% CI: 1.9–21.4%) who presented with uterine bleeding and extensive skin hemorrhage. Minor bleeding was observed in two patients (6.7%, 95% CI: 1.9–21.4%) who presented with nasal and gingival bleeding. Thus, the cumulative bleeding incidence was 13.4% (95% CI: 5.4–29.8%). Discontinuation of anticoagulant therapy was not required in patients with minor bleeding and one patient with CRNM bleeding. One clinically relevant uterine hemorrhage required short-term discontinuation of anticoagulant therapy, which was resumed after hemostasis was achieved.

**Table 2**
The prevalence of symptoms and signs of PTS.

| Clinical presentation | n | % |
|---|---|---|
| Symptoms | | |
| Pain | 2 | 6.6% |
| Cramps | 6 | 20.0% |
| Heaviness | 7 | 23.3% |
| Pruritus | 4 | 13.3% |
| Paresthesia | 7 | 23.3% |
| Clinical signs | | |
| Edema | 5 | 16.6% |
| Prominent subcutaneous arm veins | 5 | 16.6% |
| Prominent collateral veins (shoulder/anterior chest wall) | 3 | 10.0% |
| Tenderness | 2 | 6.6% |
| Redness | 2 | 6.6% |
| Dependent cyanosis | 5 | 16.6% |

## 4. Discussion

Although UEDVT was initially considered to be uncommon (occurring in < 2% of all cases of venous thrombosis) and associated with little residual disability, the results of more recent epidemiologic investigations have been inconsistent with those findings. In 2004, an analysis of a U.S. VTE registry reported that UEDVT accounted for as much as 11% of all DVT, that PE could be detected in 6–15% of all UEDVT patients, and that PTS developed in 25–77% of affected individuals [7,11,12,21,30].

Currently, there is no optimal treatment approach for UEDVT. Some guidelines suggest anticoagulant therapy alone, while others consider additional active surgical intervention. According to the American Venous Forum, patients with subclavian vein thrombosis with a background of thoracic outlet syndrome should be treated with thrombolysis followed by surgical decompression [30]. However, this guideline emphasizes that mandatory anticoagulation should be provided for all patients with UEDVT regardless of surgical intervention. They suggest several options for this: low-molecular-weight heparin (LMWH) switched to vitamin K antagonists (VKA), oral thrombin inhibitors (dabigatran), or oral Xa factor inhibitors (rivaroxaban or apixaban) as an alternative for traditional anticoagulation. However, these guidelines are not based on safety and efficacy data for DOACs in UEDVT treatment.

The American College of Chest Physicians' guidelines support only conservative treatment with anticoagulation and recommend against thrombolysis [5,6]. However, these guidelines highlight the absence of randomized clinical trials in this group of patients and highlight that all recommendations are based on indirect evidence from studies performed in patients with lower limb DVT, observational studies (generally small), and understanding the natural history of UEDVT. Thus, there is a current gap in the evidence for the best UEDVT treatment.

Over the last decades, DOACs have been widely used to treat lower extremity DVT and PE. In randomized clinical trials, DOACs appeared to be safer and at least as effective as traditional anticoagulation with LMWH/VKA. Meta-analyses have shown that using DOACs is associated with a lower risk of major bleeding, especially intracranial hemorrhages, compared with VKA, particularly in patients with VTE [22,23].

Despite the extensive experience in treating lower extremity DVT using DOACs, there are only sporadic reports about the possible use of novel drugs in patients with UEDVT [24,25]. In 2017, data from the Swedish oral anticoagulation registry were published [24]. In 5 years, they identified only 55 patients with UEDVT who were treated using DOACs: 46 patients (84%) were prescribed rivaroxaban, seven (13%) were prescribed apixaban, and two (4%) were prescribed dabigatran. Among 69% of the patients, therapy was started with an LMWH injection, which was then switched to oral anticoagulants for 3–6 months. One episode (2%) of recurrent VTE was reported, and one occurrence (2%) of nasal bleeding was classified as clinically relevant, each in a patient treated with rivaroxaban. Analysis of the Mayo clinic's database for the period from March 1, 2013, to April 30, 2017, identified 20 patients with UEDVT who were treated with rivaroxaban or apixaban. The authors did not report any episodes of bleeding or VTE recurrence during the 3-month follow-up [25]. Thus, our results correspond well with Sweden's and the Mayo clinic's databases and suggest that UEDVT treatment with rivaroxaban seems to be effective and rather safe (Table 3). However, to make a strong conclusion, more powerful, randomized clinical trials or registry data are needed.

The critical outcome for DVT is development of PTS, which develops over an extended period and can be identified on the lower limbs by the Villata score [26]. The same score was adapted for use in the upper limbs by Czihal [19]. In this modified version, five subjective symptoms, such as pain, cramps, pruritis, heaviness, and paresthesia, were not changed. The objective signs were modified, and the score does not include hyperpigmentation but contains venous ectasia that was divided into two items as follows: prominent subcutaneous veins in

**Table 3**
Efficacy and safety of rivaroxaban in the treatment of UEDVT.

| | Montiel FS, 2017 [24] | Houghton DE, 2017 [25] | Current study |
|---|---|---|---|
| Number of patients | 55 | 20 | 30 |
| Duration of therapy | 3–6 months | 3 months | 3–6 months |
| Recurrent VTE | 2.0% | 0 | 0 |
| Major bleeding | 0 | 0 | 0 |
| CRNM bleeding | 2.0% | 0 | 6.7% |
| Minor bleeding | 0 | 0 | 6.7% |

the arm and prominent collateral veins in the shoulder or chest. Additionally, a new item, dependent cyanosis, was added. Edema, tenderness, and redness were not changed.

In the current study, we detected the signs and symptoms of upper limb PTS (scores of 5 or more using a modified Villalta score) in four patients (13%). Previous studies reported a higher incidence of complication, ranging from 25% to 77% [11,12,30]. This may be because of the different criteria that were used for PTS verification. However, using the same tool, Czihal et al. detected upper limb PTS in 40.5% of patients treated by LMW/VKA [19], and this figure is higher than in the current study with rivaroxaban. This difference may be explained by the specific influence of rivaroxaban on deep vein recanalization. Previously, it has been shown that therapy with rivaroxaban allows better recanalization and reduces the amount of PTS in patients with lower limb DVT [27–29]. Contrariwise, a small number of patients may be the other reason for the lower incidence of PTS observed in the current study. However, obtained 95% CI is overlapping with the previously reported figures.

The limitations of this study include small sample size, absence of a control group, inability to completely assess for residual thrombi in the subclavian vein using DUS, inability to correlate residual venous lesions or underlying thoracic outlet syndrome with the occurrence of PTS, and limited length of follow-up.

## 5. Conclusion

Rivaroxaban can be an alternative option to treat UEDVT. Treatment of UEDVT with rivaroxaban, preceded by one to two days of low-molecular weight heparin, appears to be effective, rather safe, and associated with a low rate for post-thrombotic syndrome.

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## Author contributions

Ilya Schastlivtsev and Kirill Lobastov contributed to the concept and design of the research and wrote the manuscript. Ilya Schastlivtsev, Sergey Tsaplin, and Irina Kanzafarova performed acquisition of patient data, and Kirill Lobastov performed statistical analyses. Victor Barinov, Leonid Laberko, Grigory Rodoman, and Sergey Zhuravlev reviewed the manuscript.

## Declaration of Competing Interest

The authors are not aware of any competing interests with the publication of this study. Ilya Schastlivtsev discloses participation in a speakers' bureau and receipt of honoraria from Bayer. Kirill Lobastov discloses participation in a speakers' bureau and receipt of honoraria from Bayer. Victor Barinov discloses participation in a speakers' bureau and receipt of honoraria from Bayer. The other authors state that they have no conflicts of interest.

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