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Clinical outcomes in lower extremity deep vein thrombosis treated with a direct oral anticoagulant: A retrospective cohort study

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Ethics Committee Approval
The ethical approval was obtained from the Ethics Committee of the Medical Faculty of the Erciyes University (number 2019/491).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Rivaroxaban and apixaban were shown to be non-inferior and somewhat superior to warfarin in preventing pulmonary embolization and venous complications. However, there is still a need for further evidence concerning the efficacy and safety of direct oral anticoagulants in the treatment of patients with deep vein thrombosis **(**DVT) and pulmonary embolism (PE). This study aimed to analyze patients with DVT and PE who received a direct oral anticoagulant (apixaban) during their hospitalization and thereafter.

Methods: Data of all consecutive subjects admitted for lower limb DVT who received apixaban for DVT treatment in our department between January 2015-April 2019 were analyzed. Apixaban was directly administered after the diagnosis of DVT in 68 subjects, following discontinuation of warfarin due to the lack of success in maintaining appropriate INR values in 56 subjects and following the discontinuation of the rivaroxaban due to gastrointestinal complications in 7 subjects.

Results: Apixaban was administered for a median duration of 12.0 (12.0-24.0) months. The most common predisposing factors for venous thromboembolism were thrombophilia and major surgery history. Among all, 62.59% of the DVT were at and proximal to the femoral vein. Concomitant PE was encountered in 16.03% of the study subjects. Those with distal DVT and those who received apixaban immediately after diagnosis of the DVT less frequently developed PE compared to those who received post-rivaroxaban or post-warfarin apixaban. Treatment with apixaban leads to a significant decline in D-dimer levels from the first month of the treatment ($P<0.001$). Recurrent DVT and PE occur in 10% and 16%, respectively, under apixaban treatment.

Conclusions: Among patients with proximal DVT, those receiving apixaban following a period of treatment with rivaroxaban or warfarin compared to direct administration constitute the majority of the PE cases. Apixaban seems like an effective treatment option in patients with DVT and PE.

Keywords: Deep vein thrombosis, Direct oral anticoagulant, Apixaban, Recurrence, Pulmonary embolism, Anticoagulation

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Introduction

Deep vein thrombosis (DVT) which commonly affects the lower limb has an incidence of 1.6 per 1000 of the general population [1, 2]. Distal lower limb veins are the most frequently affected sites with a rate of 40% [3]. Femoral, common femoral, and iliac veins are involved in about 55% of the cases. Surgery under general anesthesia, prolonged hospitalization, pregnancy, cesarean section, estrogen therapy, and leg injury are common transient predisposing factors for the development of lower limb DVT [4], while an active malignancy or inflammatory bowel disease and systemic lupus erythematosus are persistent risk factors [5].

Deep vein thrombosis was shown to lead to excessive morbidity due to post-thrombotic syndrome and venous ulceration, which are encountered in one-third of the subjects [6]. However, PE develops in 6-32% of the subjects with DVT and may be fatal in 5%-10% of cases [7, 8]. Anticoagulation with low-molecular-weight heparin (LMWH) and warfarin are traditionally used in the treatment of DVT to prevent clot extension and embolization. However, recent guidelines from NICE and ACCP recommend direct oral anticoagulants (DOACs) as a first-line treatment for DVT [9]. Rivaroxaban and apixaban, which do not require initial treatment with LMWH before the commencement of the DOAC, were shown to be non-inferior and somewhat superior to warfarin in the prevention of pulmonary embolization and venous complications [10, 11]. However, there is still a need for further evidence concerning the efficacy and safety of DOACs in the treatment of patients with DVT and PE.

This study aimed to analyze patients with DVT and PE who received apixaban during their hospitalization and thereafter.

Materials and methods

In this cohort study, data of all consecutive subjects admitted for lower limb DVT who received apixaban for the treatment of the DVT in Erciyes University Medical School, Department of Cardiovascular Surgery between January 2015 and April 2019 were analyzed.

Ethical approval was obtained from the Ethics Committee of the Medical Faculty of the Erciyes University (number 2019/491). Written informed consent was obtained from all subjects and the study was conducted following the Helsinki declaration.

The criteria for inclusion in the study were as follows: Being over 18 years of age, DVT confirmed by Doppler ultrasonography, post-warfarin, post-rivaroxaban, or direct apixaban treatment initiation. Those receiving warfarin, LMWH, and DOACs other than apixaban were not included in the final analysis. Exclusion criteria were as follows: Creatinine clearance <25 mL/min, presence of advanced liver failure, moderate to high-risk PE, and contraindications for anticoagulant treatment. Apixaban was directly administered after the diagnosis of the DVT in 68 subjects, following discontinuation of warfarin due to the lack of success in maintaining appropriate INR values in 56 subjects and following the discontinuation of the rivaroxaban due to gastrointestinal complications in 7 subjects. Apixaban was administered 10 mg twice daily for the first 7 days. After completion of the first week, the dose was adjusted to 5 mg twice daily.

The patients who used apixaban were followed up closely in our clinic with complete medical records. Thus, all patients who received apixaban were included in the study.

Demographic data including age, gender, and previous medical history, D-dimer results, and ultrasonography findings including the location of the DVT were retrieved from an institutional digital database. Factors associated with recurrent DVT, PE, and the locations of the DVT were analyzed.

Statistical analysis

Statistical analyses were conducted using SPSS for Windows, version 17 (SPSS, Chicago, IL, USA). The normality of data distribution was assessed using the Shapiro-Wilk test. Continuous variables were presented as mean (standard deviation) or median (1^{st} and 3^{rd} quartiles) according to data distribution and categorical variables as frequency (n) and percentage (%). Pairwise comparisons were performed using Student's t-test, Mann–Whitney U-test, $\chi 2$ -test, or Fisher's exact test, where appropriate. Friedman test was used for comparison of baseline, 1^{st} month, and 3^{rd}-month D-dimer measurements. A two-sided *P*-value of ≤ 0.05 was interpreted as statistically significant.

Results

Longitudinal data was available for 131 subjects (mean age: 56.73 (18.31) years, 48.86% males). The demographic characteristics of the study group are listed in Table 1. Apixaban was administered for a median duration of 12.0 (12.0-24.0) months. The most common predisposing factors for venous thromboembolism were thrombophilia and major surgery history with rates of 25.19%, and 16.79%, respectively. Among all, 62.59% of the DVTs were at or proximal to the femoral vein. Concomitant PE was encountered in 16.03% of the study subjects. D-dimer levels at first and sixth months of the treatment were lower than baseline values [1050.0 (550.0-1080.0) µg/L, 750.0 (550.0–1080.0) µg/L vs. 1200.0 (8900.0-2700.0) µg/L, $P<0.001$]. Baseline D-dimer levels of subjects with a sub-femoral DVT were lower than that of the subjects with a DVT located at the femoral vein or proximal to it [980.0(765.0 - 14600) µg/L vs. 1765.0(987.5 - 3815.0) µg/L, $P<0.001$].

Table 1: Demographic and clinical characteristic of the study patients

	n=131
Age, years	56.73 (18.31)
Gender	
Female, n	67 (51.40%)
Male, n	64(48.86%)
D-dimer baseline	1200.0(895.0-2600.0)
D-dimer 1st month	1050.0(750.0-2200.0)
D-dimer 6th month	750.0 (550.0-1080.0)
BMI, kg/m^2	27.6 (3.75)
Apixaban duration, months	12.0 (12.0-24.0)
Location of the DVT	
Sub-femoral, n	49 (37.40%)
Femoral and above, n	82 (62.59%)
Coronary artery disease, n	17 (12.97%)
Atrial fibrillation, n	25 (19.08%)
Hypertension, n	39 (29.77%)
Previous malignancy, n	18 (13.74%)
Recurrent DVT, n	13 (9.92%)
Predisposing factors	
Major Surgery History, n	22 (16.79%)
Thrombophilia, n	33 (25.19%)
Immobilization, n	11 (8.39%)
Active cancer, n	11 (8.39%)
Concomitant Pulmonary Embolism, n	21 (16.03%)

Recurrent DVT occurred in 13 (10%) patients, the data of which are presented in Table 2. Thrombophilia was more frequent among subjects with recurrent DVTs compared to those without (61.54% vs. 21.19%, $P<0.001$). There were 21 (16%) patients with concomitant PE (Table 3). The DVTs of 95.24% of the subjects with PE were at the femoral vein or proximal to it. Thrombophilia (47.62% vs. 20.91%, $P=0.010$), history of major surgery (42.86% vs. 11.82%, $P<0.001$) and malignancy (38.1% vs. 9.09%, $P<0.001$) were more frequent in subjects with PE compared to those without. Those who received apixaban immediately after diagnosis of the DVT less frequently developed PE compared to those who received post-rivaroxaban or post-warfarin apixaban ($P<0.001$).

Table 2: Comparison of the demographic and clinical features of the subjects with and without recurrent deep vein thrombosis

	Recurrent DVT		*P*-value
	Yes (*n*=13)	No (*n*=118)	
Age, years	50.23 (14.99)	57.44 (18.55)	0.179
Male gender, n	6(46.15%)	58(49.15%)	1.000
BMI, kg/m2	27.69 (2.75)	27.54 (3.86)	0.892
Atrial fibrillation, n	0(0.0%)	25(21.2%)	0.065
Coronary artery disease, n	2(15.38%)	15(12.7%)	0.785
Hypertension, n	2(15.38%)	37(31.36%)	0.232
Previous malignancy, n	0(0.0%)	18(15.25%)	0.129
Major surgery, n	3(23.08%)	19(16.1%)	0.523
Thrombophilia, n	25(61.54%)	8(21.19%)	<0.001
Immobilization, n	0(0.0%)	11(9.32%)	0.250
Active cancer, n	0(0.0%)	11(9.32%)	0.250

Table 3: Comparison of the demographic and clinical features of the subjects with and without pulmonary embolism

	Pulmonary Embolism		*P*-value
	Yes (n=21)	No (n=110)	
DVT location			
Subfemoral, n	1(4.76%)	48(43.64%)	<0.001
Femoral and above, n	20(95.24%)	62(56.36%)	
Major surgery, n	9(42.86%)	13(11.82%)	<0.001
Thrombophilia, n	10(47.62%)	23(20.91%)	0.010
Immobilization, n	3(14.29%)	8(7.27%)	0.288
Hypertension, n	6(28.57%)	33(30.0%)	0.896
Female gender, n	15(71.43%)	52(47.27%)	0.042
Coronary artery disease, n	2(9.52%)	15(13.64%)	0.607
Atrial fibrillation, n	0(0.0%)	25(22.73%)	0.015
Previous malignancy, n	8(38.1%)	10(9.09%)	<0.001
Apixaban administration			
Direct Apixaban, n	3(14.29%)	65(59.09%)	<0.001
Post-Rivaroxaban, n	2(19.52%)	5(4.54%)	
Post-Warfarin, n	16(76.19%)	40(36.36%)	
Recurrent DVT, n	4(19.05%)	9(8.18%)	0.127
Active cancer, n	3(14.29%)	8(7.27%)	0.288

Discussion

Venous thromboembolism, which includes DVT and PE, is a significant source of morbidity and mortality. Recurrent DVT, *post-pulmonary embolism syndrome*, chronic thromboembolic pulmonary hypertension, and post-thrombotic syndrome are long-term complications of venous thromboembolism [12]. Proximal DVT of the lower extremities, symptomatic calf vein (distal) DVT, and PE require immediate treatment with anticoagulant agents unless anticoagulation is contraindicated because of high bleeding risk [13]. More aggressive therapies, such as systemic thrombolysis, catheter-directed thrombolysis, pharmaco-mechanical therapies, or surgical intervention are reserved for patients with PE and complicated proximal DVT [14].

Anticoagulants are the first-line agents in the treatment of DVT both in the acute and extended treatment phases. Unfractionated heparin, LMWH, warfarin, fondaparinux, and DOACs are used for this purpose. LMWHs are used in the first week of DVT for transitioning to warfarin, dabigatran, or edoxaban for long-term anticoagulation and the agents of choice in pregnant women and those with malignancies [15, 16]. Apixaban and rivaroxaban do not need a pretreatment period with LMWH before administration and can be used as monotherapy for the initial treatment of DVT [17]. Lack of the need for INR monitoring in long-term treatment, rapid onset of action, and shorter half-life make DOACs the most popular treatment option due to more predictable anticoagulant effects. The earlier EINSTEIN-DVT study has shown that rivaroxaban was non-inferior to warfarin in terms of safety and efficacy in the acute treatment of DVT [10]. Further research including patients with PE has demonstrated that rivaroxaban was also non-inferior to warfarin in this patient population [18]. Moreover, major bleeding events were less frequent in patients receiving rivaroxaban compared to those receiving warfarin in the EINSTEIN-PE study. Apixaban, another oral factor Xa inhibitor, was non-inferior to conventional warfarin therapy for the treatment of acute venous thromboembolism with less bleeding risk in the AMPLIFY trial [11]. Nevertheless, there is currently no head-to-head comparison of DOACs in the treatment of patients with DVT. Real-life data concerning the use of apixaban and clinical and demographical features of the subjects who received apixaban for DVT are also limited.

Findings of the present study indicate that thrombophilia and history of a major surgery were the most common underlying causes for the development of DVT. Previous data indicate that inherited deficiency of protein C, protein S, and antithrombin, and mutations in factor V and prothrombin genes account for up to one-third of the cases with venous thromboembolism [5, 8, 19]. Prolonged immobilization after a major surgical procedure has also been reported as an important risk factor for the development of DVT [20]. We found that one-half of the DVTs were at or proximal to the femoral vein. Recurrent DVT occurred in 10 % and PE occurred in 16% of the study population. Thrombophilia and history of a recent major surgery were more common in those who developed PE compared to those who did not. Those directly receiving apixaban compared to the subjects receiving apixaban after warfarin or rivaroxaban tend to have less PE. Majority of the subjects who developed PE while receiving treatment for DVT were prescribed apixaban following discontinuation of warfarin due to inappropriate INR during follow-up. We speculate that subjects directly receiving apixaban compared to those receiving apixaban following a period of treatment with rivaroxaban or warfarin may have a lower risk for the development of PE. However, further research is required to address whether apixaban is superior to warfarin in the prevention of PE in DVT.

Subjects with femoral or supra-femoral DVTs constituted 95% of the PE cases whereas only 5% of the patients with PE had distal DVT. Previous evidence indicates a higher risk of PE in proximal lower extremity DVT compared to distal DVT.

Limitations

The current study has some limitations. First, the study was conducted retrospectively and in a single center, both of which limit the generalizability. Second, the study did not contain a control group. Lastly, the follow-up of patients was not long.

Conclusion

The majority of the DVT occurs in proximal veins of the lower extremity and thrombophilia and history of major surgery are the most common predisposing factors. Treatment with apixaban leads to a significant decline in D-dimer levels from the first month of the treatment. Recurrent DVT and PE occur in 10%

and 16%, respectively, under apixaban treatment. Those with proximal DVTs and receiving apixaban following a period of treatment with rivaroxaban or warfarin compared to direct administration constitute the majority of the PE cases.

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