Comparative study of safety and effectiveness of rivaroxaban and warfarin in patients with acute deep venous thrombosis

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Objectives
To evaluate the safety and effectiveness of the oral anti-factor Xa (rivaroxaban) in comparison with that of traditional oral (warfarin) anticoagulants in patients in acute stage of deep-vein thrombosis.

Background
Standard treatment for venous thromboembolism (VTE) consists of a heparin combined with vitamin K antagonists. Direct oral anticoagulants have been investigated for acute and extended treatment of symptomatic VTE; their use could avoid parenteral treatment and/or laboratory monitoring of anticoagulant effects.

Patients and methods
A prospective study was conducted to compare the efficacy and safety of rivaroxaban (15 mg twice daily for 21 days, followed by 20 mg once daily) with standard therapy (enoxaparin 1.0 mg/kg twice daily and warfarin or acenocoumarol). Patients were treated for 3, 6, or 12 months and followed for suspected recurrent VTE and bleeding.

Results
Our study included 200 patients in the acute stage of deep venous thrombosis. Half of them were treated by oral anti-factor Xa (rivaroxaban), which showed no significant difference in safety and effectiveness with warfarin. Partial and complete recanalization occurred in 64 and 16%, respectively, for rivaroxaban and in 48 and 24%, respectively, for warfarin, whereas pulmonary embolism and bleeding occurred in 8 and 16%, respectively, for rivaroxaban and 16 and 12%, respectively, for warfarin. Rivaroxaban was noninferior to warfarin with respect to primary efficacy and adverse effect outcome.

Conclusion
Our study results show nonsignificant difference between oral anti-factor Xa and the Low Molecular Weight Heparin (LMWH) and vitamin K antagonist technique in the treatment of acute stage of deep-vein thrombosis, but the oral anti-factor Xa (rivaroxaban) has an upper hand in being orally taken and needs less monitoring of coagulation profile.

Keywords:
acute deep venous thrombosis, rivaroxaban, warfarin

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Introduction

The venous thromboembolism (VTE), which include deep-vein thrombosis (DVT) and/or pulmonary embolism (PE), is a relatively common cardiovascular trouble. Each year, approximately one to two cases per 1000 population present with acute symptomatic VTE [1]. The complications of acute VTE, including DVT, PE, and postthrombotic syndrome, are important, as they are the most common avoidable causes of death at hospital [2]. PE, with its attendant mortality, is the most wasteful complication of acute DVT. When associated with acute DVT, most PE events may be clinically silent. In patients with symptomatic DVT, 50–80% have evidence of asymptomatic PE. Conversely, in those with symptomatic PE, asymptomatic DVT can be demonstrated in approximately 80% of cases [2]. Even with optimal anticoagulant treatment, acute symptoms of DVT such as leg pain and swelling can take weeks to subside, and 20–40% of patients develop the chronic postthrombotic syndrome, which is characterized by leg pain, heaviness, swelling, and in severe cases, skin ulcer [3]. Standard treatment for these patients consists of low-molecular-weight heparin combined with a vitamin K antagonist (VKA) [4,5]. Several direct oral anticoagulants have been estimated recently for the acute and extended treatment of symptomatic VTE [6], and their use enables for evasion of treatment and laboratory monitoring of the anticoagulant effect. These studies compared a single-drug approach

using the oral, direct factor Xa inhibitor rivaroxaban with standard treatment consisting of enoxaparin overlapping with and followed by a VKA for the treatment of DVT. These studies showed the same efficacy and a tendency toward a lower incidence of major bleeding with rivaroxaban [7].

Patients and methods

Study design and patient selection

This observational, prospective study was conducted on all consecutive patients hospitalized in the Vascular Medicine Unit of Menoufia University Hospital for acute DVT. They were analyzed for clinical criteria, comorbidities, treatment, and events during the first 6 months after the diagnosis of VTE. Patients were recruited through emergency departments of the University Hospital and regional hospitals, the Cardiology Intensive Care Unit, or referred directly by their private physicians. Patients were informed about the goal of the study and gave an oral or written consent for their participation according to the requirements of the local Ethics Committee. Patients were included if they had symptomatic DVT. The major exclusion criteria were a therapeutic dose of low-molecular-weight heparin, fondaparinux, or unfractionated heparin for more than 48 h; more than a single dose of a VKA; treatment of the current episode with mechanical thrombectomy, a vena cava filter, or thrombolytic therapy; any contraindication for anticoagulation, or acenocoumarol; or a creatinine clearance less than 30 ml/min.

Requirements for venous thromboembolism diagnosis

Imaging processes. D dimer, Duplex ultrasound, CT pulmonary angiography, ECG , Ventilation-perfusion (V/Q), Pulmonary angiography [8,9]. The initial PE and/or DVT (index event) were recorded. PE was diagnosed by either computed tomography pulmonary angiogram or ventilation perfusion lung scan. Patients with symptomatic PE were routinely screened for DVT. The presence of DVT was assessed by ultrasonography from inferior vena cava to calf vein in both lower limbs.

Treatment regimens

The type, dose, and duration of anticoagulant drug therapy were based on current recommendations [8]. Identical rivaroxaban and standard treatment regimens were evaluated in this study. Patients allocated to rivaroxaban were given 15 mg orally twice daily for 21 days, followed by 20 mg once daily. Patients allocated to standard therapy received enoxaparin subcutaneously at a dose of 1.0 mg/kg body weight twice daily and oral warfarin (international normalized ratio, 2.0–3.0), started within 48 h after randomization. Patients were treated for 3, 6, or 12 months, according to follow-up and results.

For the aim of this study, the observation period ended after 6 months from the date of the index events. All patient data were collected at the initial visit and then via phone interview at 1 month (±5 days), 3 months (±10 days), and 6 months (±15 days). The main parameters for estimation were major or nonmajor clinically relevant bleeding, recurrent VTE, major opposed cardiovascular events, and death. Major and nonmajor clinically pertinent bleeding events were classified according to the International Society on Thrombosis and Hemostasis criteria [10].

Statistical analysis

The data collected were tabulated and analyzed by using statistical package for the social science software. Quantitative data were expressed as mean and SD and analyzed by applying *t* test for comparison of two groups, and qualitative data were expressed as numbers and percentage and analyzed by applying χ^2 test. All these were used as tests of significance at *P* value equal to 0.05.

SPSS is short for Statistical Package for the Social Sciences, and it's used by various kinds of researchers for complex statistical data analysis.The SPSS software package was created for the management and statistical analysis of social science data. It was was originally launched in 1968 by SPSS Inc., and was later acquired by IBM in 2009.Officially dubbed IBM SPSS Statistics, most users still refer to it as SPSS. As the world standard for social science data analysis, SPSS is widely coveted due it's straightforward and English-like command language and impressively thorough user manual.SPSS is used by market researchers, health researchers, survey companies, government entities, education researchers, marketing organizations, data miners, and many more for the processing and analyzing of survey data.

Results

Between August 2017 and July 31, 2018, 219 patients were assessed for eligibility. Ten patients were excluded because the index episode was incidentally diagnosed during an imaging examination performed for another purpose. A total of 209 symptomatic patients were included in the baseline characteristics analysis. Five patients refused to participate after baseline analysis and four were lost to follow-up, leaving 200 patients eligible for the safety analysis. The patients who

Table 1 Risk factors of studied groups

	Rivaroxaban anticoagulant group (*N*=100) [*n* (%)]	Warfarin anticoagulant group (*N*=100) [*n* (%)]	Fisher's exact test	*P* value
Bed rest	8 (8)	8 (8)		
Postcast	12 (12)	16 (16)		
Postoperative	24 (24)	36 (36)		
Postpartum	4 (4)	24 (24)		
Posttrauma	16 (16)	12 (12)	14.45	0.07
Hormonal therapy	8 (8)	0 (0)		
Chemotherapy	0 (0)	4 (4)		
Varicose vein	4 (4)	0 (0)		
No risk factor	24 (24)	0 (0)		

Table 2 Comparison between studied groups regarding deep-vein thrombosis extension

DVT level	Rivaroxaban anticoagulant group (*N*=100)		Warfarin anticoagulant group (*N*=100)		Fisher's exact test	*P* value
Extensive	48	48	40	40		
Pop	32	32	36	36	0.88	0.92
Cuff	20	20	24	24		

DVT, deep-vein thrombosis.

Table 3 Comparison between studied groups regarding duplex after 3 months

Duplex	Rivaroxaban anticoagulant group (*N*=100) [*n* (%)]	Warfarin anticoagulant group (*N*=100) [*n* (%)]	Fisher's exact test	*P* value
Fixed thrombosis	20 (20)	24 (24)		
Start canalization	64 (64)	48 (48)	2.06	0.56
Complete canalization	16 (16)	24 (24)		
Vein fibrosis	0 (0)	4 (4)		

Table 4 Comparison between studied groups regarding complication

Complications	Rivaroxaban anticoagulant group (*N*=100) [*n* (%)]	Warfarin anticoagulant group (*N*=100) [*n* (%)]	Fisher's exact test	*P* value
Bleeding	16 (16)	12 (12)		
Pulmonary embolism	8 (8)	16 (16)	0.84	0.65
Without complication	76 (76)	72 (72)		

completed the 6-month follow-up were considered for safety analysis. Major bleeding occurred in 16 patients in the rivaroxaban group and in 12 in the VKA group. No patient died of fatal bleeding in the rivaroxaban group or in the VKA group.

Comparison between the two studied groups regarding the risk factors showed there were no significant differences between the two groups, as *P* value was more than 0.05 (Table 1).

Comparison between the studied groups regarding DVT level, showed there was nonsignificant difference between the groups, as *P* value was more than 0.05 (Table 2).

Comparison between the studied groups regarding Duplex after 3 months showed there was a nonsignificant difference between the two groups, as *P* value was more than 0.05 (Table 3).

Comparison between the studied groups regarding complication showed there is a nonsignificant difference between the two groups, as *P* value was more than 0.05 (Table 4).

Distribution of complications among the studied groups in relation to their medical history revealed that complications within diabetics showed significant variation, as *P* value was less than 0.05; complication among hypertensive patients is significant, as *P* value was

Table 5 Distribution of complications among the studied groups in relation to their medical history

	Bleeding [*n* (%)]	Pulmonary embolism [*n* (%)]	Without complication [*n* (%)]	χ^2 test	*P* value
Diabetes mellitus					
Negative	12 (42.9)	8 (116)	33.3 (78.4)	7.17*	0.02
Positive	16 (57.1)	16 (32)	66.7 (21.6)		Significance
Chronic chest disease					
Negative	28 (100)	5 (83.3)	136 (91.9)	1.22*	0.54
Positive	0 (0)	1 (16.7)	12 (8.1)		
Cardiac disease					
Negative	24 (85.7)	12 (50)	128 (86.5)	4.73	0.09
Positive	4 (14.3)	12 (50)	20 (13.5)		
Hypertension					
Negative	20 (71.4)	8 (33.3)	128 (86.5)	8.71	0.01
Positive	8 (28.6)	16 (66.7)	20 (13.5)		Significance
Smoking					
Negative	8 (28.6)	4 (16.7)	52 (35.1)	0.85	0.65
Positive	20 (71.4)	20 (83.3)	96 (64.9)		

Fisher's exact test. shows Distribution of complications among the studied groups in relation to their medical history. Complication within diabetics shows significant variation as P value < 0.05. Complication among hypertensive patients is significant as P value <0.05. Complication within chronic chest disease patients, cardiac patients and smokers is non-significant as P value > 0.05 in the two groups.

less than 0.05; complications within patients with chronic chest disease, patients with cardiac disease, and smokers are nonsignificant, as *P* value was more than 0.05 in the two groups (Table 5).

Discussion

This prospective observational study presents some novel aspects focusing on hospitalized patients, mostly with DVT, who were treated with rivaroxaban, the first direct oral anticoagulant (DOAC) licensed for VTE, and warfarin. Our study showed that there is no statistical significant difference between the two groups, regarding age and sex ($P>0.05$), and this agreed with the results of the EINSTEIN Investigators [7]. The early clinical response to the initial medication, hotness improved more in the Low Molecular Weight Heparin (LMWH) group than the oral anti-factor Xa group in the first week, as 100% of the first group in comparison to 80% in the second group, but with no significant statistical difference, and that agrees with The EINSTEIN Investigators [7]. Redness, pain, and swelling decreased in both groups, but with no significant statistical difference. Regarding the clinical improvement during the second week, there is a decrease in pain, redness, and hotness in both groups, nearly to the same extent, with no statistically significant difference. Regarding the clinical improvement during the third week in both groups, there is a decrease in pain, redness, and hotness nearly equals in the two groups, with nonsignificant statistical difference between the two groups. This agreed with The EINSTEIN Investigators [7]. Comparison of PE complications in both groups showed that 8% of cases in oral anti-factor Xa group in comparison with 16% in the LMWH/VKA group showed complications and were diagnosed clinically by chest pain and with imaging by ECG, echocardiography, and spiral computed tomography. Although there is a nonsignificant difference between the two groups, oral anti-factor Xa group revealed two cases of non-fatal PE and this represent 8% of the group and this agrees with Agnelli *et al.* [11]. Regarding bleeding in both groups, 16% of patients in oral anti-factor Xa group had bleeding in comparison with 12% of patients in LMWH/VKsA group, with statistically nonsignificant difference. The oral anti-factor Xa group had 16 (16%) patients who presented with bleeding, and this is against the studies of Agnelli *et al.* [11], which showed 3.3% with bleeding, and the EINSTEIN Investigators, which showed 8.1% of patients with bleeding. The use of a loading dose of rivaroxaban during the first 3 weeks of treatment did not result in an excess of bleeding events, confirming the results obtained in EINSTEIN studies. The follow-up of the thrombus after 3 months by duplex revealed 20% of patients of oral anti-factor Xa group showed fixed thrombus in comparison with 24% of patients of LMWH/VKA group. Overall, 64% of patients of oral anti-factor Xa group started recanalization in comparison with 48% of patients of LMWH/VKA group, and 16% of patients of oral anti-factor Xa group showed complete recanalization in comparison with 24% of patients of LMWH/VKA group. Moreover, 0% of patients of oral anti-factor Xa group showed vein fibrosis in comparison with 4% of patients of LMWH/VKA

group. So comparison between the fate of the thrombus in both groups shows a nonsignificant statistical difference ($P>0.05$), and this is in agreement with Agnelli *et al.* [11] and the EINSTEIN Investigators [7]. In this study, no patient died of intracranial hemorrhage or fatal bleeding, which is in agreement with Van Der Hulle *et al.* [12]. Nonetheless, the diagnosis of concomitant PE has been reported to be an independent predictor of death within the first months following diagnosis [13]. No enrolled patient had a concomitant PE in this study.

Because on the initial approval of rivaroxaban for DVT only, some limitations of our work should be noted. It is a single-center study and our population might not be representative of patients treated in other centers. No patient with active cancer at entry was treated by rivaroxaban and patients with newly diagnosed cancer switched to LMWH.

Conclusion

In conclusion, this proof-of-concept and dose-finding study suggests that rivaroxaban, an orally active, direct factor Xa inhibitor, may have efficacy and safety in the treatment of DVT across a two-fold daily dosing range and may be considered as effective as LMWH/VKA. Comparison of clinical outcomes with rivaroxaban or low-molecular-weight heparin/VKA across a wide spectrum of patients is needed to confirm these observations.

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Conflicts of interest

There are no conflicts of interest.

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