Surgery 166 (2019) 1076–1083

Contents lists available at ScienceDirect

Surgery

journal homepage: www.elsevier.com/locate/surg

Vascular

Comparison of the recanalization rate and postthrombotic syndrome in patients with deep venous thrombosis treated with rivaroxaban or warfarin

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ARTICLE INFO

Article history:
Accepted 25 May 2019
Available online 2 July 2019

ABSTRACT

Background: In this article, we report the outcomes of patients with deep venous thrombosis in the lower limbs treated with the oral anticoagulant rivaroxaban or warfarin, focusing on the recanalization rate (measured with duplex ultrasound) and the incidence of postthrombotic syndrome.

Methods: This was a prospective, consecutive, randomized, blind cohort study of patients admitted with deep venous thrombosis to the Division of Vascular and Endovascular Surgery, Hospital do Servidor Público Estadual, São Paulo, Brazil, between March 2016 and July 2018. The patients were randomized into 2 groups and treated with oral anticoagulation for 6 months: either rivaroxaban (group 1) or warfarin (group 2). The study was registered at clinicaltrials.gov under NCT 02704598.

Results: Eighty-eight patients with deep venous thrombosis were admitted to the Vascular Surgery Department and randomized into the 2 groups. The follow-up time was 360 days. Analyses were performed at 180 and 360 days. Four patients were excluded from the study during follow-up because of a diagnosis of ovarian cancer (1 patient), head and neck cancer (1 patient), lung cancer (1 patient), and stomach cancer (1 patient). Therefore, 84 patients were evaluated: 46 patients in group 1 and 38 in group 2. The incidence of postthrombotic syndrome was 17.9% (15 cases) in the total cohort, but was significantly higher in group 2 (11 cases, 28.9%) than in group 1 (4 cases, 8.7%; $P < .001$; odds ratio, 4.278). The rate of total venous recanalization at 360 days was 40.5% (34 patients) in the total cohort, but was significantly higher in group 1 (35 patients, 76.1%) than in group 2 (5 patients, 13.2%; $P < .001$). The incidence of partial venous recanalization was 46.4% and was significantly higher in group 2 (28 patients, 73.7%) than in group 1 (11 patients, 23.9%; $P = .016$). Five patients in the total cohort (6%) showed no venous recanalization, all of them in group 2 ($P = .016$).

Conclusion: In this study, patients who received oral rivaroxaban displayed a lower incidence of postthrombotic syndrome and a better total vein recanalization rate after 6 and 12 months than patients who received warfarin.

Introduction

Deep venous thrombosis (DVT) is a very common and life-threatening disease, with an incidence of 900,000 cases per year in the United States.[1,2] The prevalence of pulmonary embolism is 21% to 39%.[3] About 4% of patients who survive pulmonary embolism develop pulmonary hypertension, which results in a poor quality of life and severe respiratory complications.[3]

However, apart from the pulmonary and fatal complications, 25% to 50% of patients with DVT develop postthrombotic syndrome (PTS),[4] a very serious condition that causes pain, swelling, heaviness, fatigue, itching, cramping at night, and venous ulcer in the affected limb.[4] There have been no studies of the cost of PTS on the Brazilian healthcare system, but the mean cost of PTS treatment in the United States has been estimated to be $7,000 per patient per year.[5] In this study, it was estimated that the total per-patient cost

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https://doi.org/10.1016/j.surg.2019.05.030
0039-6060/

of DVT with PTS during a 2-year period was almost 50% higher than for DVT patients without PTS.[5]

No gold standard laboratory, imaging, or functional test can establish a diagnosis of PTS. The Villalta PTS scale[6] has been adopted by the International Society on Thrombosis and Haemostasis as the gold standard method for diagnosing and grading the severity of PTS in clinical studies.

The PTS risk increases (2-fold) if the level of anticoagulation is inadequate (eg, subtherapeutic international normalized ratio [INR] >50% time) during the first 3 months of treatment with vitamin K antagonists.[7] Another factor that increases the risk of PTS during follow-up is the presence of residual thrombosis on ultrasound (eg, 3–6 months after acute DVT).[8] However, there is no consensus in the literature on how the use of the new direct, target-specific oral anticoagulants used to treat DVT influence the risk of PTS compared with low-molecular-weight heparin and vitamin K antagonists.[9] In the EINSTEIN Clinical Trial Program,[10] rivaroxaban was shown to be at least as effective as enoxaparin or vitamin K antagonist in the acute treatment and secondary prevention of recurrent venous thromboembolism in patients with creatinine clearance >30 mL/min.[10,11] A post hoc analysis of the EINSTEIN DVT trial suggested that rivaroxaban is associated with a reduced incidence of PTS.[12]

Therefore, the objective of this study was to compare the recanalization rate measured with duplex ultrasound (DUS) and PTS in patients with DVT who were treated with oral rivaroxaban or warfarin.

Methods

This study was approved by the Research Ethics Committee of the Hospital do Servidor Público Estadual, São Paulo, Brazil, and was registered at clinicaltrials.gov under NCT 02704598. This prospective, randomized, consecutive, blind cohort study included patients treated for acute iliofemoral or femoropopliteal DVT of a lower limb at the Division of Vascular and Endovascular Surgery, Hospital do Servidor Público Estadual, São Paulo, Brazil, between March 2016 and July 2018. Patient informed consent was obtained for the study, according to the principles outlined in the Declaration of Helsinki. Patient data were collected during a routine follow-up appointment and recorded using the proper protocols. The randomization protocol was performed by a computer-generated program. The data obtained included the patient's general and demographic characteristics and the information recorded during the outpatient follow-up visits. This research received no specific funding.

The prerandomization exclusion criteria were pregnancy, age <18 years or >80 years, chronic renal failure, chronic hepatic failure, inferior vena cava thrombosis, contraindication for any type of anticoagulation, previous DVT on the ipsilateral affected limb, any type of active cancer, and refusing to participate in the study.

The postrandomization exclusion criteria were predefined before the start of the study and were defined as several hemorrhagic complications that required the discontinuation of anticoagulation, death after <30 days, allergic reaction to any anticoagulant, a diagnosis of active cancer during follow-up, loss to follow-up, difficulty in achieving proper anticoagulation owing to patient nonadherence to the treatment protocol, and incomplete data.

The diagnosis of DVT was made with clinical signs and symptoms, laboratory tests such as D-dimer, and routine DUS of the affected limb. The criteria used to confirm acute DVT with DUS were the absence or diminution of venous flow, incompressibility of the vessel, visible thrombus, enlarged vein diameter, immobility of the valves, and loss of respiratory phasicity.[13]

All patients diagnosed with acute DVT were hospitalized and received initial anticoagulation with subcutaneous enoxaparin (1 mg/kg/dose) every 12 h (12/12 h) or intravenous unfractionated heparin (IUH; loading dose 80 UI/kg, and 18 UI/kg/h) for at least 48 to 72 hours. The infusion dose of IUH was adjusted to achieve the therapeutic activated partial thromboplastin time established by the hospital laboratory within every 4- to 6-hour period. After initial admission, the patients were randomized into 2 groups: group 1 patients received oral rivaroxaban, with a loading dose of 15 mg 12/12 h for 21 days after the initial dose and 20 mg/day for 6 months; group 2 patients received oral warfarin, sufficient to maintain an INR of 2 to 3 for 6 months. Patients diagnosed with thrombophilia during the follow-up period received extended anticoagulation therapy for >6 months. The patients in group 2 were kept in the hospital on subcutaneous enoxaparin or IUH until their INR was 2 to 3. The patients were discharged after their INR achieved the therapeutic dose. All patients in the study were prescribed 30 to 40 mm Hg elastic compression stockings and were instructed to wear them only on the affected limb. Compliance with the use of the elastic compression stockings was evaluated with a questionnaire filled out by patients.

During the follow-up visits, all patients were subjected to a DUS analysis by a vascular surgery physician who was blinded to the type of drug therapy. The same physician in the same laboratory performed the DUS using defined protocols that assessed the compressibility of the external iliac vein, common femoral vein, superficial femoral vein, and popliteal vein. Flow recanalization was evaluated by confirming the total vein flow (without residual thrombi and complete venous flow inside the vessel), partial vein flow (residual thrombi and partial venous flow inside the vessel), or the absence of vein flow. All vessels evaluated were tested for the absence or presence of reflux and the grade of reflux.

The following ultrasound criteria were used to determine the absence of recanalization flow: partial compressibility of the vein, diminution of the vessel diameter, heterogeneous and hyperechoic thrombus, multiple channels of flow inside the veins, reflux, and collateral circulation. Femoral and popliteal vein reflux was defined as retrograde flow >1 s after calf and thigh compression release while the patient was in the standing position.[13]

All patients were followed-up with outpatient visits at 1, 3, 6, and 12 months after discharge by a vascular surgery physician who was blinded to the type of drug therapy. At each visit, results of the physical examination, DUS, laboratory tests such as D-dimer, and the Villalta scale were recorded for all patients. Group 2 patients were seen once a week to ensure that their INR remained at 2 to 3 and to confirm adequate anticoagulation. During the physical examination, a tape measure was used to determine the diameter of the thigh in the medium segment and the legs in the proximal segments to objectively assess the improvement in the swelling and edema of the leg.

A diagnosis of PTS was made with the Villalta scale when the patient's symptoms had remained unresolved for 6 months after treatment by a physician blinded to the type of drug therapy.[9] Each of the scale's components (5 symptoms and 6 signs) were rated on a 4-point severity scale, and the points were summed to produce a total score. A score >4 indicated PTS. The 5 symptoms (pain, cramps, heaviness, pruritus, and paresthesia) were assessed by patient self-report, and the 6 signs (edema, skin induration, hyperpigmentation, venous ectasia, redness, and pain during calf compression) were evaluated by a clinician. The severity of each symptom and sign was rated as 0 (absent), 1 (mild), 2 (moderate), or 3 (severe). These were summed to yield the total Villalta PTS score: 0 to 4, no PTS; 5 to 9, mild PTS; 10 to14, moderate PTS; ≥15 or presence of an ulcer, severe PTS.

Table I
Clinical characteristics

Variable	Total (n = 84)	Group 1 (n = 46, 54.7%)	Group 2 (n = 38, 45.3%)	*P* value
Age, y	55.10 ± 8.8	54.93 ± 3.08	55.61 ± 2.3	.55
Females	43 (51.2%)	26 (56.5%)	17 (44.7%)	.19
Hypertension	30 (35.7%)	15 (32.6%)	15 (39.5%)	.33
Diabetes	12 (14.3%)	5 (10.9%)	7 (18.4%)	.25
Heart disease	8 (9.5%)	5 (10.9%)	3 (7.8%)	.49
Tobacco use	12 (14.2%)	5 (10.9%)	7 (18.4%)	.25
Provoked DVT	43 (51.2%)	26 (56.5%)	17 (44.7%)	.19
Trauma	11 (25.5%)	5 (10.8%)	6 (15.7%)	.25
Immobilization	6 (14%)	3 (6.5%)	3 (7.9%)	.33
Previous surgery	26 (60.5%)	3 (28.2%)	13 (34.2%)	.35

The purpose of this study was to examine the outcomes (after 6 and 12 months) in the 2 groups of patients after treatment for DVT, by comparing the DUS-detected recanalization rates and the occurrence of PTS. The secondary endpoints of the analysis were the prevalence of pulmonary embolism, death, and complications of treatment.

Sample size calculation and statistical analysis

$$n = [(Z\alpha/2 + Z\beta)2 \times \{2(ó)2\}]/(\mu1 - \mu2)2$$

n = sample size required in each group,

μ1 − μ2 = mean clinically significant difference = 0.5 PTS between rivaroxaban and Warfarin.

ó = standard deviation = 1.195

Zα: level of significance, for 5% this is 1.96

Zβ: power, for 80% this is 0.84

n = 37.81 patients each group

Statistical analyses were performed with SPSS 15.0 for Windows (SPSS Inc., Chicago, IL). The χ^2 test and Student *t* test were used to compare univariate data and differences between groups. Logistic regressions were used in the univariate and multivariable analyses, and the results are reported as adjusted odds ratios (ORs) with the accompanying 95% confidence intervals (CIs). Analysis of variance and a post hoc test were used in the analysis of groups.

Results

Initially, 88 patients with DVT were admitted to our Vascular Surgery Department and randomized into 2 groups: group 1 was treated with rivaroxaban and group 2 with warfarin. The follow-up period was 360 days. Four patients were excluded from the study during follow-up with a diagnosis of ovarian cancer (1 patient), head and neck cancer (1 patient), lung cancer (1 patient), and stomach cancer (1 patient). After these exclusions, 84 patients were evaluated, with 46 patients in group 1 and 38 patients in group 2. The analyses were performed after 360 days and PTS analysis within 180 and 360 days.

The general characteristics of the patients are shown in Table I. There were no differences in comorbidities between the groups. The mean age in the total cohort was 55.10 years, with no difference between groups (54.93 years in group 1 vs 55.61 years in group 2; $P = .55$). There was a higher prevalence of provoked DVT (51.2%) than unprovoked DVT, which was mainly attributable to previous surgery (60.5%), trauma (25.5%), or immobilization (14%), with no difference between the groups (56.5% in group 1 vs 44.7% in group 2; $P = .19$). Among the patients with unprovoked DVT, there were 3 cases of thrombophilia diagnosed during follow-up, one case of homozygous Leiden V factor deficiency (group 1), one case of heterozygous Leiden V factor deficiency (group 1), and one case of prothrombin gene mutation (group 2). These patients continued receiving anticoagulation therapy for >6 months, and there were no statistically significant differences between both groups ($P = .27$). The compliance rate of elastic compression stockings in the total cohort was achieved by 85.1% of patients, which was related to daily use of the stockings, and there were no differences among groups (82.3% in group 1 vs 87.5% in group 2; $P = .35$).

The mean Wells criteria score at admission was 3.79, with no difference between the groups (3.63 for group 1 vs 3.37 for group 2; $P = .31$). Most patients presented with edema (92.9%) in the affected limb, with no statistical difference between the groups (95.7% in group 1 vs 89.5% in group 2; $P = .25$), followed by pain (79.8%), with a higher prevalence in group 2 (89.5%; $P = .039$). There was a higher incidence of DVT in the left limb (51 cases, 60.7%), with no difference between the groups (60.9% in group 1 vs 60.5% in group 2; $P = .57$). Most patients in the whole cohort presented with femoropopliteal DVT (71 cases, 84.5%), but this differed significantly between groups (76.1% in group 1 vs 94.7% in group 2; $P = .018$). However, there was a higher incidence of iliofemoral DVT in group 1 (11 cases, 23.9%) than in group 2 (3 cases; 5.6%; $P = .018$). D-dimer was positive in 83 patients (98.8%), with no difference between groups. There were 2 cases of symptomatic pulmonary embolism, diagnosed during admission, both in group 2 (2.4%; $P = .01$). There was a prevalence of chronic venous disease in 39 patients (46.4%), with no differences between groups (21 patients [45.7%] in group 1 versus 18 patients [21.4%] in group 2; $P = .52$). As an initial treatment, 86.9% of patients received subcutaneous enoxaparin, with no difference between the groups (89.1% in group 1 versus 84.2% in group 2; $P = .365$). A subanalysis showed no difference among the type of anticoagulation initial treatment and the length of hospitalization (6.09 days for unfractionated heparin and 5.23 days for enoxaparin; $P = .64$). These data are summarized in Table II.

The mean period of hospitalization was 5.35 days and was higher in group 2 (7.45 days) than in group 1 (3.61 days; $P < .001$). The mean time to achieve the target INR in group 2 was 6.29 days. There were no cases of major bleeding in the total cohort. There was one case of minor bleeding in group 2, a minor epistaxis that required no further intervention. There were no deaths during the follow-up period.

The Villalta scores were higher in group 2 than in group 1 (Table III). Most patients in group 2 presented with mild PTS (18.4%). Only 4 patients displayed moderate PTS, all of them in group 2. There were no cases of severe PTS (Villalta score >15). The incidence of PTS was 17.9% (15 cases) in the total cohort at 12 months. There was a higher incidence of PTS in group 2 (11 cases, 28.9%) than in group 1 (4 cases, 8.7%), and this difference was statistically significant ($P < .001$, OR = 4.27). A subanalysis performed at 6 months also showed a higher incidence of PTS in group 2 (14 cases, 37.8%) than in group 1 (4 cases, 8.7%; $P < .001$). A

Table II
Clinical characteristics upon admission

Variable	Total (n = 84)	Group 1 (n = 46, 54.7%)	Group 2 (n = 38, 45.3%)	*P* value
Wells criteria	3.79 ± 0.85	3.63 ± 0.95	3.37 ± 0.65	.31
Pain	67 (79.8%)	33 (71.7%)	34 (89.5%)	.039
Edema	78 (92.9%)	44 (95.7%)	34 (89.5%)	.25
Left limb	51 (60.7%)	28 (60.9%)	23 (60.5%)	.57
Segment affected				
Femoropopliteal	71 (84.5%)	35 (76.1%)	36 (94.7%)	.018
Iliofemoral	14 (15.5%)	11 (23.9%)	3 (5.3%)	.018
D-dimer positive	83 (98.8%)	45 (97.8%)	38 (100%)	.54
Symptomatic PE	2 (2.4%)	0 (0%)	2 (5.3%)	.010
CVD	39 (46.4%)	21 (45.7%)	18 (21.4%)	.52
Enoxaparin	73 (86.9%)	41 (89.1%)	32 (84.2%)	.36
UH	11 (13.1%)	5 (10.9%)	6 (15.8%)	.36

CVD, chronic venous disease (varicose veins); PE, pulmonary embolism; UH, unfractionated heparin.

Table III
Villalta score and PTS at 6 months and 12 months

Variable	Total (n = 84)	Group 1 (n = 46, 54.7%)	Group 2 (n = 38, 45.3%)	*P* value
<5	66 (78.5%)	42 (91.3%)	24 (63.1%)	.025
5–9	14 (16.6%)	4 (8.7%)	10 (26.3%)	.012
10–14	4 (4.9%)	0	4 (10.5%)	.007
PTS at 6 mo	18 (21.4%)	4 (8.7%)	14 (37.8%)	<.001
<5	69 (82.1%)	42 (91.3%)	27 (71.1%)	.025
5–9	11 (13.1%)	4 (8.7%)	7 (18.4%)	.012
10–14	4 (4.8%)	0	4 (10.5%)	.007
PTS at 12 mo	15 (17.9%)	4 (8.7%)	11 (28.9%)	< .001
Segment affected and PTS at 12 mo*				
Femoropopliteal	10 (14%)	3 (8.6%)	8 (22.2%)	< .001
Iliofemoral	4 (28.6%)	1 (9.1%)	3 (100%)	< .001

* Percent referred to the incidence of DVT in the segment.

Table IV
Ultrasound data on venous flow at admission, 3, 6 months, and after 360 days

Variable	Total (n = 84)	Group 1 (n = 46, 54.7%)	Group 2 (n = 38, 45.3%)	*P* value
At admission				
Occlusion	78 (92.9%)	43 (93.5%)	35 (92.1%)	.56
Partial flow	6 (7.1%)	3 (6.5%)	3 (7.9%)	.56
At 3 mo				
Occlusion	8 (9.5%)	1 (2.2%)	7 (18.4%)	.006
Partial flow	60 (71.4%)	33 (71.7%)	27 (71.1%)	.006
Total Flow	16 (19%)	12 (26.1%)	4 (10.5%)	.006
At 6 mo				
Occlusion	5 (6%)	0 (0%)	5 (13.2%)	.001
Partial flow	50 (59.5%)	21 (45%)	29 (76.3%)	.001
Total flow	25 (29.8%)	22 (47.8%)	3 (7.9%)	.001
At 360 days				
Occlusion	5 (6%)	0 (0%)	5 (13.2%)	< .001
Partial flow	38 (45.2%)	10 (21.7%)	28 (73.7%)	< .001
Total patency	41 (48.8%)	36 (78.3%)	5 (13.2%)	< .001

subanalysis was performed to evaluate the segment affected and PTS at 12 months, and in both subgroups (femoropopliteal and iliofemoral), group 2 had higher rates of PTS ($P < .001$). These data are summarized in Table III.

The DUS performed at admission showed an absence of venous flow in 78 patients (92.9%), with no difference between the groups (93.5% in group 1 vs 92.1% in group 2; $P = .56$) and partial venous flow in 6 patients (7.1%), also with no difference between the groups (6.5% in group 1 vs 7.9% in group 2; $P = .56$). Common femoral vein reflux occurred in 11.9% (10) of patients, all in group 2 ($P < .001$), at 360 days. The incidence of popliteal vein reflux was 28.6% (24 cases) in the total cohort at 360 days and was significantly higher in group 2 (22 patients, 57.9%) than in group 1 (2 patients, 4.3%; $P < .001$). In contrast, DUS at 360 days showed a statistically significant improvement in venous flow, with total patency in 41 patients (48.8%); results were significantly better for group 1 (36 patients, 76.1%) than for group 2 (5 patients, 13.2%; $P < .001$). Five patients had no venous flow, all of them in group 2 ($P < .001$). These data are summarized in Table IV with the DUS data at admission and 3, 6, and 12 months.

We used univariate and multivariate logistic regression analyses to identify the factors associated with PTS. Among all the factors tested, warfarin use instead of rivaroxaban ($P < .001$; OR = 4.27), the presence of popliteal vein reflux ($P = .012$; OR = 4.33), and

Table V
Univariate and multivariate logistic regression analyses of factors related to postthrombotic syndrome

Variable	Univariate analysis				Multivariate analysis			
	B	OR	95% CI	P value	B	OR	95% CI	*P* value
Warfarin use	3.256	4.278	1.241–2.360	.000	3.256	4.278	1.820–2.680	.000
D-dimer positive	0.542	0.890	0.188–1.051	.345	0.542	0.890	0.538–4.567	.831
Segment of DVT	0.412	7.698	1.221–10.501	.166	1.885	0.412	1.411–14.294	.166
Obesity	0.722	5.480	1.331–21.429	.341	0.032	5.571	1.531–24.234	.341
Female	0.631	1.331	0.542–1.543	.172	0.711	0.915	0.339–12.230	.249
Femoral vein reflux	1.953	1.731	0.324–2.111	.111	4.243	5.314	0.334–5.433	.123
Popliteal vein reflux	1.953	4.433	1.093–3.012	.012	1.596	4.433	1.212–3.555	.012
Partial/absent venous recanalization	1.897	8.232	1.119–4.112	.000	1.987	8.232	1.050–4.568	.000
CVD	0.155	0.879	0.334–3.546	.489		3.432	0.556–1.234	.234

B, coefficient.

Table VI
Univariate and multivariate logistic regression analyses of factors related to total vein recanalization

Variable	Univariate analysis				Multivariate analysis			
	B	OR	95% CI	P value	B	OR	95% CI	*P* value
Rivarobaxan use	3.256	0.400	0.175–0.625	.001	2.124	0.400	0.175–0.625	.001
D-Dimer positive	0.542	0.890	0.188–1.051	.345	0.542	0.890	0.538–4.567	.831
Segment of DVT	0.412	7.698	1.221–10.501	.346	1.885	0.412	1.411–14.294	.346
Obesity	0.722	5.480	0.662–0.111	.341	0.032	5.571	1.531–24.234	.341
Female	0.631	0.365	0.220–0.151	.172	0.711	0.915	0.339–12.230	.249
Femoral vein reflux	1.953	1.731	0.324–2.111	.111	4.243	5.314	0.334–5.433	.123
Popliteal vein reflux	1.953	0.386	0.662–0.811	.007	1.596	0.386	0.662–0.811	.007
CVD	0.567	0.987	0.567–1.224	.345	2.345	0.987	0.887–1.223	.245

B, coefficient.

absent or partial venous recanalization ($P < .001$; OR = 8.23) were associated with PTS (Table V).

We also used univariate and multivariate logistic regression analyses to identify the factors related to total recanalization. Among all the factors tested, rivaroxaban use instead of warfarin ($P = .001$; OR = 0.40) and the absence of popliteal vein reflux ($P = .007$; OR = −0.38) were associated with total recanalization (Table VI).

The rate of total venous recanalization at 360 days was 40.5% (34 patients) in the total cohort. The total venous recanalization rate was significantly higher in group 1 (35 patients, 76.1%) than in group 2 (5 patients, 13.2%; $P < .001$). The incidence of partial venous recanalization was 46.4% in the total cohort and was significantly higher in group 2 (28 patients, 73.7%) than in group 1 (11 patients, 23.9%; $P = .016$). There were 5 cases (6%) of nonvenous recanalization in the total cohort, all of them in group 2 ($P = .016$).

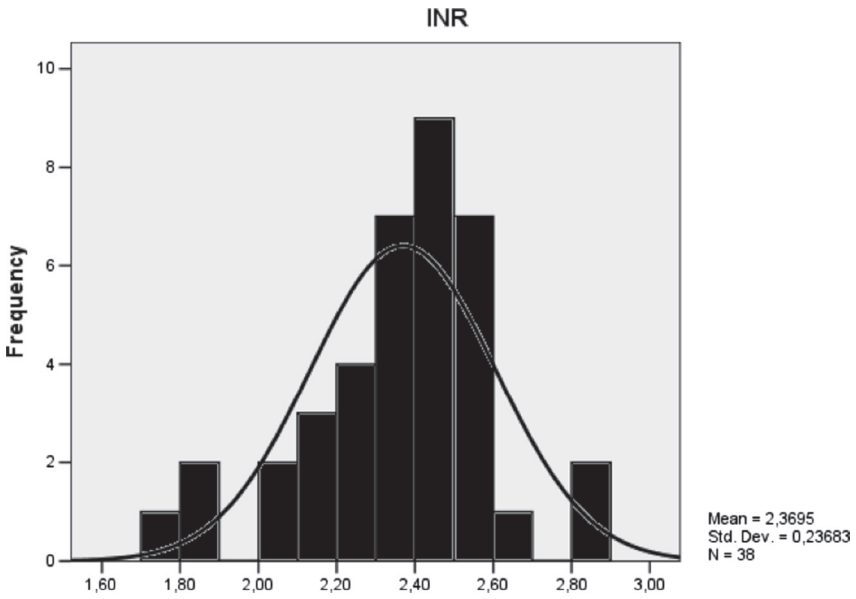
When the recanalization rates were compared with the occurrence of PTS, 39 patients displayed total recanalization, with one case of PTS (1.2%); 40 patients displayed partial recanalization, with 9 cases of PTS (10.7%), and 5 patients displayed no venous recanalization, all of whom developed PTS (6%). A χ^2 test and cross-tabulation showed that partial recanalization and an absence of recanalization were related to PTS ($P < .001$, OR = 8.23).

The mean INR in group 2 was 2.369 (95% CI, 1.85–2.84), and the median was 2.405 (Figure 1). The INR averages for group 2 were divided into periods, and the mean INR was 2.19 or 2.45 in the acute phase (Figure 1).

Discussion

In this study, we evaluated and compared 2 groups of patients diagnosed with DVT and administered specific medical treatments. The patients who received oral rivaroxaban showed a lower incidence of PTS (8.7%) and a better total vein recanalization (76.1%) rate within 12 months. In contrast, patients treated with warfarin had a higher incidence of PTS (28.9%) and a worse rate of total venous recanalization (13.2%) at 12 months. The lower rate of PTS in patients who received oral rivaroxaban is similar of that reported by Cheung et al,[12] who performed a post hoc analysis of a small subset of patients with DVT (without symptomatic pulmonary embolism) enrolled in the EINSTEIN-DVT randomized controlled trial, in which they assessed the impact of rivaroxaban versus enoxaparin bridging to warfarin in preventing PTS. Forty-five of 162 participants treated with rivaroxaban developed PTS during follow-up (estimated rate 5.8% per year), as did 66 of 174 participants treated with enoxaparin or warfarin (estimated rate 8.0% per year; hazard ratio [HR] 0.76; 95% CI: 0.51–1.13; $P = .18$). Coleman et al[14] evaluated 10,463 users of rivaroxaban and 26,494 users of warfarin, and a total of 2,418 PTS events were identified during follow-up. Cox's proportional hazard regression showed that rivaroxaban was associated with a significantly reduced (23%) risk of developing PTS compared with warfarin (adjusted rates: 3.6 vs 4.7 events per 100 person-years, respectively). The lower risk of developing PTS when treated with rivaroxaban was consistent across subgroups (HR range, 0.60–0.85; all $P < .05$). These data are similar to the results of the present study, in which the use of warfarin instead of rivaroxaban for the treatment of DVT increased the risk of PTS at 360 days by 4.278-fold. Despite the higher rate of PTS in the warfarin-treated group in this study, it is important to note that most patients had mild PTS (63.6%), defined as a Villalta score of 5 to 9. Only 4 patients in this cohort had moderate PTS, defined as a Villalta score of 10 to 14.

When the anatomic venous segment of DVT was analyzed, most patients in this cohort had femoropopliteal DVT (84.5%), with a significantly higher incidence in the warfarin group. However, the rivaroxaban group had a significantly higher incidence of iliofemoral DVT (23.9%). These findings are similar to those in a large cohort of 1,289 consecutive patients with DVT, in which Partsch also detected iliofemoral DVT in 28% of patients.[15] Although the incidence of iliofemoral DVT was higher in the rivaroxaban group, this



Percentiles	5	10	25	50	75	90	95
Mean INR (weighted)	1.85	2.08	2.23	2.40	2.54	2.60	2.84
Mean INR (Tukey's)			2.25	2.40	2.54		

Periods	1 - 2 weeks	2 weeks-3 months	3 - 6 months
Mean INR (weighted)	2.19	2.08	2.23
Mean INR (Tukey's)	2.45	2.24	2.25

Figure 1. Histogram of mean INR and median INR in patients in group 2.

group had a lower rate of PTS and a higher rate of total venous recanalization on DUS. A logistic regression analysis of this cohort showed that the anatomic venous segment was not related to PTS or venous recanalization on DUS. A subanalysis was also conducted among the segments of DVT (iliofemoral and femoropopliteal segment) and PTS development at 12 months, and in both segments, the warfarin group had statistically significantly higher rates of PTS at 12 months. Prandoni et al[16] concluded that the factors potentially related to the development of PTS were older age, obesity, a history of previous ipsilateral DVT, iliofemoral location of the current thrombosis, failure to promptly recover from acute symptoms, and poor-quality oral anticoagulant therapy. However, with the new oral anticoagulation drugs that are available, especially rivaroxaban (used in the cohort reported here), iliofemoral DVT no longer plays a crucial part in the development of PTS and did not affect the recanalization rate on DUS. Another important finding of the present study was the higher incidence of DVT in the left limb. The predominance of left-sided DVT is consistent with previous findings of other large-cohort studies[17,18] and may be attributable to the frequent compression of the left common iliac vein by the overriding right common iliac artery. This may cause increased venous stasis on the left side, secondary to the compression at the iliac level.[19] Cockett syndrome was not investigated in this study because it was not the main objective. Therefore, there was a low incidence of PTS in the rivaroxaban group, despite the higher incidence of iliofemoral DVT, indicating that the treatment is safe and provides adequate results, without interventional endovascular therapy.

The rivaroxaban group had significantly better and more consistent total venous recanalization rates than the warfarin group. Moreover, the partial or absent venous recanalization rate was higher in the warfarin group and was related to the greater incidence of PTS in the warfarin group. It is important to note that upon admission, both groups had statistically similar ultrasound findings for venous flow. However, when DUS was performed 360 days after treatment, the rivaroxaban group showed more-improved venous flow (total venous flow patency of 78.3%) than the warfarin group (only 13.2%). This difference was statistically significant and compatible with the recanalization rates in the 2 groups. According to Dronkers et al,[20] 2 ultrasonographic parameters measured during or after the treatment of DVT in the leg predicted PTS: residual vein thrombosis (pooled OR, 2.17; 95% CI, 1.79–2.63) and venous reflux at the popliteal level (pooled OR, 1.34; 95% CI, 1.03–1.75). These findings are similar to those of our study, in which warfarin use instead of rivaroxaban, the presence of popliteal vein reflux, and absent or partial venous recanalization were associated with PTS. Another study by Jeraj et al[21] suggested that patients with residual thrombi were at greater risk of PTS than patients with total recanalization (OR, 6.0; 95% CI, 1.7–21.9; $P = .006$). No difference in the presence of reflux was observed in

these patients. They concluded that incomplete or absent recanalization was associated with a higher incidence of PTS, probably as a consequence of reduced blood flow and increased venous pressure. It remains unclear whether the development of venous reflux after DVT is a risk factor for the development of PTS, whether it is a marker of PTS itself, or whether it is a consequence of severe PTS. Additional studies are required to determine the temporal associations between reflux, venous obstruction, and the development of PTS.[22] However, it is clear that popliteal reflux indicates more severely reduced blood flow and a severe obstruction of venous return, once the calf-muscle pump and the one-way valves within the veins cannot allow the flow of blood proximally out of the legs, leading to venous hypertension and its dire consequences.

Possible explanations for the worse rate of venous recanalization and the higher incidence of PTS in the warfarin group include inadequate or difficult anticoagulation in these patients, which can be attributable to drug interactions and variations in their INR levels. However, INR was at the therapeutic level (which is considered adequate anticoagulation) in 95% of the patients in the warfarin group in this cohort. The patients were monitored weekly by phone to control their INR, so the appropriate warfarin posology and adequate INR levels could be maintained. Several previous studies have suggested that providing anticoagulation at an appropriate intensity (and duration), particularly during the first week of DVT, is an important way of preventing PTS.[4] An important factor in this controlled study was the assurance of adequate anticoagulation, especially in the first week of treatment, by the hospitalization of all patients who were diagnosed with DVT upon admission. Besides, the mean INR was under therapeutic dose in the acute onset of DVT, at 1 to 2 weeks, and at 2 weeks to 3 months in group 2, ensuring proper control of INR in the warfarin group. The mean period of hospitalization was higher in group 2 than in group 1. The mean time to achieve the target INR in group 2 was 6.29 days. This was expected because the achievement of adequate anticoagulation with warfarin is slow and generally takes at least 72 hours to initial change of the target INR. Therefore, a subanalysis was performed and showed no difference among the types of anticoagulation initial treatment and the lengths of hospitalization. A considerable number of studies have demonstrated that patients with DVT spend only about one-half of their time in the target INR range of 2.0 to 3.0, with a strong tendency toward subtherapeutic anticoagulation (42% of patients were below the target range in the first month of treatment, 35% at 1–3 months, and 24.1% at 1–6 months).[23] Possible bias was avoided in the present study by the aggressive and proactive control of INR levels and the prompt adjustment of the warfarin dose if necessary. In contrast, rivaroxaban is a direct-acting oral anticoagulant that induces the rapid onset of anticoagulation and has a predictable pharmacological profile, which allows it to circumvent the early subtherapeutic anticoagulation frequently observed in patients treated with warfarin.

This was a prospective, randomized, controlled trial performed at a single center, and it provides new perspectives on results for medical therapies for DVT. There are some limitations regarding this study, in particular the small sample size, differences in the sample selection (ie, the segment of DVT among both groups), and the 17% difference in enrollment between the 2 groups (46 patients in group 1 vs 38 patients in group 2) that could have made occurrences of PTS in group 2 worse. The sample size calculation showed that 37.81 patients in each group were satisfactory to perform the study. Despite the small size of the patient sample, the results are statistically significant and applicable. However, larger, multicenter, prospective studies are required to better analyze these findings and extend them to clinical practice.

In this study, patients who received oral rivaroxaban displayed a lower incidence of PTS and a better total vein recanalization rate after 6 and 12 months than patients who received warfarin. The main factors associated with PTS were warfarin use instead of rivaroxaban, the presence of popliteal vein reflux, and absent or partial venous recanalization. In contrast, the factors associated with better total recanalization rates were rivaroxaban use instead of warfarin and the absence of popliteal vein reflux.

Conflict of interest/Disclosure

The authors declare that they have no conflicts of interest.

Funding/Support

The authors have indicated that they have no conflicts of interest (or funding) regarding the content of this article.

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