Comparative outcomes of catheter-directed thrombolysis plus rivaroxaban vs rivaroxaban alone in patients with acute iliofemoral deep vein thrombosis

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Abstract

Background: Since novel oral anticoagulants (NOACs) have been introduced in the past decade, the first option of deep vein thrombosis (DVT) treatment is toward NOACs. However, aggressive and early thrombus removal strategy is widely used for treating acute iliofemoral DVT. Consequently, optimal treatment duration, efficacy, and safety of rivaroxaban alone or in combination with catheter-directed intrathrombus thrombolysis (CDT) in acute iliofemoral DVT patients should be investigated.

Methods: Patients with recent acute iliofemoral DVT treated with combined CDT–rivaroxaban (CDT) or rivaroxaban alone (control) were followed for mean (standard deviation) of 25.7 (2.5) months. DVT evolution, treatment efficacy and safety, and predisposing factors for patency and postthrombotic syndrome (PTS) development were analyzed through duplex ultrasonography, plethysmography, venography, and computed tomographic venography.

Results: 43.2%, 64.9%, 75.7%, and 72.2% of the CDT patients showed complete patency at 3, 6, 12, and 24 months of treatment compared with the control patients having 8.5%, 36.2%, 55.3%, and 57.4% of cumulative patency at 3, 6, 12, and 24 months, respectively (p = 0.001, 0.017, 0.088, and 0.081, respectively). The p value of the log-rank test comparing patency rates of the two groups was 0.009. The median (interquartile range, IQR) Villalta scores at 24 months were 3 (2-5) and 6 (4-8) in CDT and control patients, respectively (p = 0·001). PTS and bleeding events during therapy were, respectively, found in 35.1% and 63.8% (p = 0.017) and in 27% and 17% of CDT and control patients (p = 0.4). The Kaplan–Meier curve analysis of cumulative patency at 24 months for 6 months of rivaroxaban treatment was significant (p = 0.016).

Conclusion: Treatment therapy and treatment duration with rivaroxaban alone or in combination with CDT are potentially associated with vein patency at 24 months, and a 6-month lysis rate and obstructive vein can influence PTS development. A larger randomized trial is warranted to confirm these findings.

Keywords: Catheter-directed intrathrombus thrombolysis; Deep vein thrombosis; Postthrombotic syndrome

1. INTRODUCTION

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism, can cause cardiovascular morbidity and mortality after myocardial infarction and ischemic stroke. Lower extremity DVT can be proximal or distal. Proximal DVT involves the popliteal or above-the-popliteal region, and distal DVT is isolated calf vein thrombosis. Both patient groups carry a great risk of recurrent DVT and postthrombotic syndrome (PTS).[2–4] The American College of Chest Physicians clinical practice guidelines recommend conventional treatment with anticoagulants (ie, low molecular weight heparin [LMWH], followed by vitamin K antagonists [VKAs] such as warfarin) or novel oral anticoagulants (NOACs; such as rivaroxaban, apixaban, and edoxaban) in all patients with acute proximal DVT.[5–8] Although conventional anticoagulants are effective for VTE, they do not directly promote efficient thrombus dissolution to reduce the thrombus burden, preserve venous valve function, or protect against PTS. In fact, 49% to 60% of patients with proximal DVT develop PTS within 2 years of anticoagulant-only treatment.[9–12]

Since NOACs were introduced in the past decade, they have replaced VKAs for treatment of the majority of patients with proximal DVT.[7,13] Rivaroxaban is effective in the treatment of proximal DVT and prevention of recurrent VTE in patients receiving 6 to 12 months of anticoagulant therapy.[14]

Iliofemoral DVT, a subgroup of proximal DVT, is associated with thrombi in the common femoral vein or iliac draining veins. In patients with acute iliofemoral DVT, a more extensive proximal thrombus renders a worse prognosis and higher risk for poor clinical outcomes compared with femoropopliteal

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DVT.[6–9] Both the Society for Vascular Surgery and American Venous Forum have proposed thrombolytic strategies for early removal of thrombi as well as improving treatment outcomes in patients with acute iliofemoral DVT.[11] A recent randomized Egyptian study and the CaVenT (catheter-directed venous thrombolysis in acute iliofemoral vein thrombosis) study have reported that catheter-directed thrombolysis (CDT) may promote early thrombus dissolution and may prevent further PTS development, with few hemorrhagic complications.[15,16]

However, the combination of thrombolysis and rivaroxaban treatment for acute iliofemoral DVT has not been studied. We compared the safety and efficacy of rivaroxaban, both alone and combined with CDT, and investigated the risk factors for PTS.

2. METHODS

Approval was obtained from the institutional review board (IRB) at Taipei Veterans General Hospital (IRB No: 2015-030-015AC). Waivers of informed consent were also obtained. From January 2014 to December 2017, 94 patients who experienced symptoms of acute iliofemoral DVT for <21 days were enrolled. In most patients, the primary symptoms were limb swelling, discoloration, pain, and venous claudication. Duplex sonography or computed tomographic venography (CTV) was used to diagnose DVT and confirm its extent. Exclusion criteria comprised active malignancy, severe anemia, severe renal failure (estimated glomerular filtration rate <30), active internal bleeding, thrombocytopenia, bilateral DVT, and contraindications to thrombolytic treatment, such as hemorrhagic stroke or another intracranial disease, major surgery within 30 days, intractable hypertension, and prolonged traumatic cardiopulmonary resuscitation.

2.1. Rivaroxaban dosage and duration

In the rivaroxaban-alone group (control group), all patients were hospitalized and administered the LMWH enoxaparin subcutaneously twice daily at 1 mg/kg for ≤3 days. After initial treatment with CDT or LMWH, all patients in both groups were treated with rivaroxaban (15 mg twice daily during the first 3 weeks, then 15-20 mg one time per day). Treatment durations (3-12 months) were based on sonographic findings and clinical conditions.

2.2. Catheter-directed thrombolysis techniques

All patients were treated with percutaneous transcatheter methods, such as thrombus removal with CDT, angioplasty, or stenting of venous obstructions. The CDT protocol of this study was modified from the CaVenT study.[16]

Before the procedure, patients' antithrombotic medication was temporarily discontinued to obtain an international normalized ratio of <1.5. At the beginning of CDT, an intravenous bolus of 3000 to 5000 U of unfractionated heparin (UFH) was administered to obtain an activated clotting time of >200 seconds. Ultrasound (US)-guided percutaneous access was secured through the lesser saphenous vein or popliteal vein. After the target vein had been punctured, a 5- or 6-Fr introducer sheath was inserted using the Seldinger technique. Venography was performed to examine the extent of the thrombus.

Urokinase solution was infused continuously at 1000 to 1500 U/kg/h over 48 to 72 hours. Serum fibrinogen, hemoglobin, and platelet count were checked daily, and the urokinase dose was adjusted accordingly to avoid hemorrhagic complications. If the value of serum fibrinogen dropped below 150 mg/d, we considered halting thrombolysis or providing fresh frozen plasma.

During CDT, UFH was infused simultaneously through the access sheath at 5 to 10 U/kg/h to prevent thrombus formation. The activated partial thromboplastin time (aPTT) was maintained at 1.5 to 2.0 times the control level. Patients receiving CDT were examined through repeat venography on the second or third day. Concurrently, angioplasty was performed to treat significant stenosis. Stenting was adopted if residual stenosis was over 70% despite repeat percutaneous transluminal angioplasty (Table 1).

After completion of all the procedures, systemic UFH was administered through the sheath to maintain the aPTT at 1.5 to 2.5 times the control level on the operation day. On the second day, all patients received rivaroxaban, which was combined with aspirin (75 mg/d) for those receiving stent implantation. Elastic bandages or thigh-high graduated elastic compression stockings were applied to all patients, and ambulation was initiated as soon as possible.

2.3. Endpoints

The endpoints were safety and efficacy outcomes.

The treated patients underwent clinical duplex US at baseline and at follow-ups after 1 week and 3, 6, 9, 12, and 24 months. The efficacy outcomes were early and immediate iliofemoral venous patency, valvular competence, recanalization of the occluded vein, evolution of thrombus burden, and occurrence of PTS. Venous patency and valvular function were evaluated with Doppler US. A valvular reflux >0.5 seconds was defined as valve incompetence, and the severity was directly proportional to the reflux time. Fifteen-color Doppler US was performed by vascular specialist physicians and experienced technicians. For analyzing the evolution of thrombosis, we used a modified thrombus score (TS) with reference to the scoring system proposed by Porter and Moneta and Haenen et al.[12,17,18] Vein segments were classified as per the standard definitions for the five proximal deep vein segments (external iliac, common femoral, proximal femoral, middle femoral, and popliteal), four distal deep vein segments (two posterior and two anterior tibial veins), and three superficial vein segments (long saphenous above and below the knee and lesser saphenous). The TS was defined by the degree of venous obstruction (0 indicates compressible and open vein free of thrombi, 1 indicates partially occluded vein with a flow Doppler signal, and 2 indicates noncompressible and completely occluded vein with no flow signal). The total TS was calculated by summing the TSs of the 12 venous segments.

Safety outcomes were bleeding events (either major or minor), recurrent DVT, and pulmonary embolism at the 24-month follow-up. All patients were examined through computed tomography (CT) at 24 months, and pulmonary embolism was documented through high-probability lung scan or chest CT.

PTS was assessed using the Villalta PTS scale at 24 months.[7] The Venous Registry Index and venography were used to classify the degree of thrombolysis before and within 48 hours after each CDT procedure.[11]

2.4. Statistical analysis

Continuous variables were calculated as means ± standard deviations or medians with interquartile ranges (IQRs), and categorical variables were figured as percentages. For numerical variables, the normality of their distributions was analyzed through the Kolmogorov–Smirnov test, and intergroup differences were determined through the independent-samples *t* test or Mann–Whitney *U* test. Chi-square testing was used for frequencies and categorical variables. Kaplan–Meier curves were obtained for time-to-patency analysis.

A two-tailed $p < 0.05$ was considered statistically significant. In addition, predisposing factors for PTS were confirmed through univariate and multivariate logistic regression methods. Statistical analyses were performed in SPSS v22.

Table 1

Demographic and clinical characteristics of study patients

Characteristics	Rivaroxaban (n = 47)	CDT (n = 37)	*p*
Age, median (IQR), y	75 (66-85)	63 (50.5-81)	0.017
Gender (female)	27 (57.4%)	21 (56.8%)	1.000
BMI, median (IQR)	24.4 (21.9-27.2)	27.6 (22.5-29.6)	0.019
Site (left)	36 (76.6%)	28 (75.7%)	1.000
Hypertension	27 (57.4%)	16 (43.2%)	0.283
DM	10 (21.3%)	12 (32.4%)	0.366
CAD	5 (10.6%)	4 (11.1%)	1.000
Hyperlipidaemia	18 (38.3%)	12 (32.4%)	0.743
Arrhythmia	11 (23.4%)	3 (8.1%)	0.116
CVA	17 (36.2%)	9 (24.3%)	0.353
Smoking	6 (12.8%)	8 (21.6%)	0.432
Constipation	11 (23.4%)	10 (27.0%)	0.899
OCT	1 (2.1%)	1 (2.8%)	1.000
Recent trauma[a]	8 (17%)	7 (18.9%)	1.000
Recent operation[b]	10 (21.3%)	12 (32.4%)	0.366
Immobilization[c]	25 (53.2%)	20 (54.1%)	1.000
Baseline TS, median (IQR)	10 (8-11)	11 (9-12)	0.007
Malignancy[d]	20 (42.6%)	5 (13.5%)	0.008
Thrombophilia[e]	14 (29.8%)	13 (33.3%)	0.73
D-dimer level, median (IQR)	8.2 (6.3-13.9)	6.4 (3.4-11.1)	0.204

Values in parentheses are percentages.

[a]Recent trauma was defined as trauma that occurred 14 to 30 d before the onset of DVT.

[b]Recent operation was defined as surgery 30 to 90 d before the onset of DVT.

[c]The range for the classification of immobilization was defined as 4 to 30 before the onset of DVT.

[d]Malignancy was defined as cancer diagnosed before the index VTE and without a recurrent or progressive event that required curative or palliative treatment.

[e]Thrombophilia was defined as documented biochemical hypercoagulable disorders, such as protein C or S deficiency, antithrombin III, and lupus anticoagulant.

BMI = body mass index; CAD = coronary artery disease; CDT = catheter-directed thrombolysis; CVA = cerebral vascular accident; DM = diabetes mellitus; DVT = deep vein thrombosis; IQR = interquartile range; OCT = oral contraceptive therapy; TS, thrombus score; VTE, venous thromboembolism.

Table 2

Intervention characteristics and adverse effects

Endpoints	Rivaroxaban (n = 47)	CDT (n = 37)	*p*
PTA	0	14	<0.0001
Adverse effects, n (%)			
Bleeding	8 (17)	10 (27)	0.267
Major bleeding	2 (4.3)	7 (18.9)	0.072
Gross hemoglobinuria	0	5	
UGI bleeding	2	1	
Spontaneous A.B.	0	1	
Minor bleeding	6 (12.8)	3 (8.1)	0.741
Microhemoglobinuria	2	2	
Gingival bleeding	1	0	
Vaginal bleeding	1	0	
Ecchymosis	2	1	
Recurrent DVT, n (%)	11 (23.4)	6 (16.7)	0.632
P.E.	5	2	0.643

Major bleeding indicates patient needed blood transfusion.

CDT = catheter-directed thrombolysis; DVT = deep vein thrombosis; PTA = percutaneous transluminal angioplasty; spontaneous A.B. = spontaneous arterial bleeding; UGI = upper gastrointestinal bleeding.

3. RESULTS

Study patients comprised 51 women and 43 men, with a mean age of 69.8 ± 16.9 years (20-90 years). Of the 94 patients, 41 were successfully treated with CDT procedure followed by rivaroxaban (CDT group), and 53 were treated with rivaroxaban alone (control group). The mean patient follow-up time was 25.7 ± 2.5 months. During the study period, 10 patients were excluded. In the control group, two patients were lost to follow up, and four died of malignancy-related organ failure during rivaroxaban treatment. In the CDT group, one patient was lost to follow up, and three died because of malignancy-related organ failure or cardiogenic shock. Therefore, 84 patients' data were included for analysis.

Patients' baseline demographics and clinical characteristics are shown in Table 1. The median (IQR) age was 63 (50.5-81) years in the CDT group and 75 (66-85) years in the control group (p = 0·017). Malignancy was observed in five (13.5%) and 20 (42.6%) of the patients in the CDT and control groups, respectively (p = 0·008).

In the CDT group, additional venography was performed to evaluate the degree of thrombolysis after CDT. Following CDT, complete lysis was observed in seven patients, and partial lysis (grade II) was discovered in 12 patients. These radiographic results were similar to the US findings, and no significant difference was observed. Furthermore, 14 of the 37 patients receiving CDT also received percutaneous angioplasty (Table 2).

3.1. Efficacy outcomes

The venous outcomes are listed in Table 3. The median treatment duration of rivaroxaban was 10 (3-25) months in the CDT group and 12 (3-48) months in the control group (p = 0.124). The thrombus resolution rate was 75.2% in the CDT group at 1 month, 84.5% at 3 months, 89.4% at 6 months, and 91.7% at 9 months, whereas it was 22.9%, 52%, 71.6%, and 81.6%, respectively, in the control group. Furthermore, early recanalization was more prominent in the CDT group after 1 week to 3 months of treatment (p < 0.001) (Table 3).

Venous patency was observed in 43.2% (16), 64.9% (24), 75.7% (28), and 75.7% (28) of the patients in the CDT group at 3, 6, 12, and 24 months, respectively, and in only 8.5%, 36.2, 55.3%, and 57.4% of patients in the control group, respectively. During the 12-month follow-up period, venous patency was significantly different between the two groups (Table 2).

The survival analysis using the Kaplan–Meier curves and life table indicating the cumulative patency after 24 months in both the CDT and control groups are presented in Fig. 1 (log-rank test, p = 0.009). In the analyses of treatment duration of rivaroxaban, the 24-month patency rate was higher in patients treated with fewer than 6 months of rivaroxaban than in patients treated with more than 6 months of rivaroxaban, and the Kaplan–Meier curve analysis indicated that the cumulative patency for 6-month treatment with rivaroxaban was statistically significant (log-rank test, p = 0.016) (Fig. 2A). However, the analysis of the 5-month subgroup (>5 months vs ≤5 months) discovered no statistically significant differences (p = 0.627) (Fig. 2B).

Valvular incompetence (VI) was observed in 62.2% of the CDT group and 66% of the control group, and no significant differences were observed in the 12th month (p = 0.719). The degree of PTS after 12 months is listed in Table 3. After 12 months, the median Villalta score was 3 (2-5) in the CDT group and 6 (4-8) in the control group (p = 0.001). The incidence of PTS was 35.1% in the CDT group compared with 63.8% in the control group (p = 0.017) (Table 3).

CTV at the 24-month follow-up revealed no statistical difference between the Doppler US and CT instruments (McNemar test, p = 0.219; data not shown).

CTV confirmed that 35 patients had obstructed veins; abnormalities discovered through CTV included a small caliber (narrowing) with an irregular wall, partial and total occlusion of the iliofemoral and femoropopliteal veins, and May–Thurner syndrome (n = 21). Anatomic locations involvement included venous stricture of the common femoral vein near the inguinal

Table 3

Treatment duration and outcomes at 24 mo

Outcomes	Rivaroxaban (n = 47)	CDT (n = 37)	*p*
Xarelto duration, median (IQR), mo	8.5 (5.6-17.5)	13 (9.7-17.1)	0.01
Cumulative patency, n (%)			
1-mo patency	0	7 (19.4%)	0.002
3-mo patency	4 (8.5%)	16 (43.2%)	0.001
6-mo patency	17 (36.2%)	24 (64.9%)	0.009
12-mo patency	26 (55.3%)	28 (75.7%)	0.088
24-mo patency	27 (57.4%)	28 (75.7%)	0.081
Resolution rate, median (IQR), %			
1-mo lysis rate	18.2 (0-44.4)	77.8 (65.2-89.9)	<0.001
3-mo lysis rate	50 (33.3-66.7)	83.3 (73.2-100)	<0.001
6-mo lysis rate	72.7 (55.6-100)	100 (77.8-100)	<0.001
12-mo lysis rate	100 (75-100)	100 (91.7-100)	0.031
VI (Reflux) at 24 mo, n (%)			
≥0.5 s	31 (66.0%)	23 (62.6%)	0.719
24-mo PTS, n (%)	30 (63.8)	13 (35.1)	0.017
24-mo Villalta score, median (IQR)	6 (4-8)	3 (2-5)	0.001

Lysis rate = (premean TS − postmean TS)/(premean TS).
CDT = catheter-directed thrombolysis; IQR = interquartile range; PTS = postthrombotic syndrome; TS, thrombus score; VI = valvular incompetence.

area (n = 22), the inferior vena cava (IVC) (n = 5), and irregular obstruction of the femoropopliteal (n = 11) and iliofemoral veins (n = 19) (Table 4).

3.2. Assessment of postthrombotic syndrome

Univariate logistic regression analysis was performed to identify clinical variables that may contribute to the development of PTS, such as age, gender, body mass index, thrombus resolution rate, treatment duration, immobilization of the involved leg, DVT division, malignancy, VI, and an obstructed vein (Table 5). The following six clinical factors were associated with an risk of PTS: treatment type (odds ratio [OR] = 3.26, 95% confidence interval [CI]: 1.3-8.01, p = 0·01), whether an obstructed vein was present on CTV image at 24 months (OR = 18.6, 95% CI: 5.9-58.65, p < 0·001), 1-month lysis rate (OR = 0.11, 95% CI: 0.03-0.44, p = 0.002), 3-month lysis rate (OR = 0.01, 95% CI: 0.001-0.09, p < 0.001), 6-month lysis rate (OR = 0.0001, 95% CI: 0.0001-0.1, p < 0.001), treatment duration (OR = 1.104, 95% CI: 1.03-1.19, p = 0.008), and recurrent DVT (OR = 4.15, 95% CI: 1.22-14.07, p = 0.022). These significant factors and those potential factors with p values of <0·2 were included in the multivariate logistic regression. Repeated multivariate regression analyses were performed to evaluate 1-, 3-, and 6-month lysis rates in relation to other potential factors of PTS at 24 months. Finally, two clinical factors were independently associated with an increased chance of PTS (obstructed vein: OR = 5.08, 95% CI: 1.34-21.24, p = 0.021; 6-month lysis rate: OR = 0.01, 95% CI: 0-0.27, p = 0.009) after adjustment for the baseline TS, treatment duration, treatment method, VI, and recurrent DVT through the anterior stepwise regression method.

3.3. Safety outcomes

During thrombolytic therapy, three patients in the CDT group did not receive complete thrombolytic treatment. The first patient (female) reported episodes of spontaneous arterial bleeding near the iliopsoas muscle and consequently required blood transfusion of more than 10 U of packed red blood cells as well as embolization therapy. The second patient (male) developed upper gastrointestinal bleeding and subsequently required endoscopic treatment. The third patient experienced massive hematuria caused by prior nephrostomy for renal stones; therefore, this patient's thrombolysis was ineffective. Other bleeding events

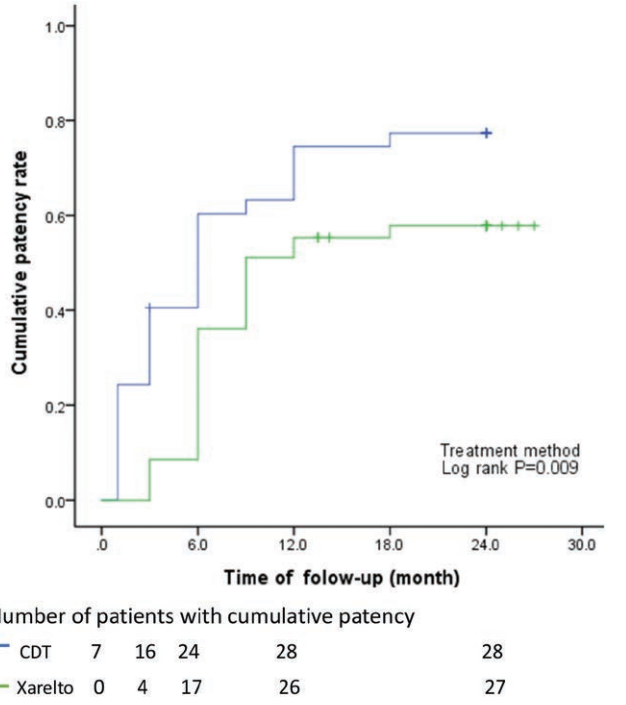

Fig. 1 Kaplan–Meier curves for the performance of time-to-patency analysis for patients treated with rivaroxaban alone and CDT–rivaroxaban (log-rank test: p = 0.009). The 24-month patency rate was higher in patients treated with CDT plus rivaroxaban than in patients treated with rivaroxaban (Xarelto) alone. CDT, catheter-directed thrombolysis.

were noted in both groups during rivaroxaban treatment, and the rivaroxaban dose was adjusted for these patients. Finally, bleeding events were observed in 27% of the CDT group compared with 17% of the control group (p = 0.267). The subgroups of major and minor bleeding events also exhibited no significant intergroup differences (Table 2).

Fewer incidences of recurrent DVT occurred in the CDT group (6/37) than in the control group (11/47) (p = 0.632). Eight patients developed recurrent DVT within 3 to 6 months of the conclusion of rivaroxaban treatment; the others had recurrent DVT within 3 months after stopping rivaroxaban. Six patients experienced thrombus progression during treatment.

No significant differences in pulmonary embolism were discovered between the two groups (Table 2).

4. DISCUSSION

This study assessed the efficacy and safety of treatments with rivaroxaban alone and rivaroxaban plus CDT in patients with acute iliofemoral DVT. Acute iliofemoral DVT usually presents a greater thrombus burden and thus potential thrombus embolization, poor prognosis, and higher risk of poor clinical outcomes. Studies have suggested that compared with rivaroxaban alone, early and effective thrombolysis provides superior venous outcomes and preserves venous function in the iliofemoral vein.

A review of the relevant literature suggests that CDT is effective in achieving short- and midterm venous patency through its satisfactory thrombus lysis rate.[11,16,18] These series of CDT have reported a 6-month patency of 60% to 85%. Information regarding the venous patency of rivaroxaban alone or CDT plus rivaroxaban in patients with acute iliofemoral DVT is limited. In the present study, the median resolution rate of the CDT group was 77.8% (65.2-89.9) at 1 month, 83.3% (73.2-100) at

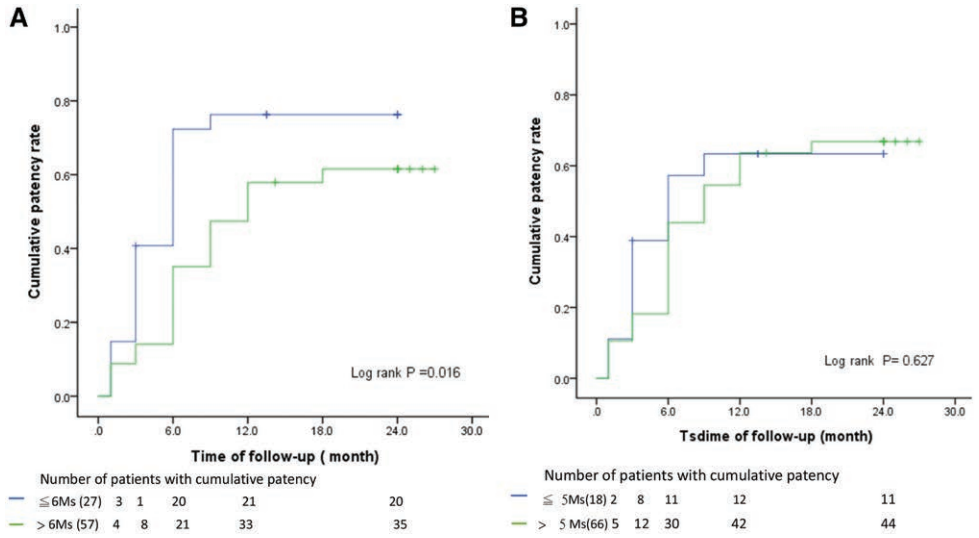

Fig. 2 A, Kaplan–Meier curves for the performance of time-to-patency analysis for patients treated with at least 6 months of rivaroxaban and more than 6 months of rivaroxaban (log-rank test: $p = 0.016$). B, Kaplan–Meier curves for performance of time-to-patency analysis for patients treated with at least 5 months of rivaroxaban and more than 5 months of rivaroxaban (log-rank test: $p = 0.627$).

3 months, 100% (77.8-100) at 6 months, and 100% (91.7-100) at 12 months, whereas that of the control group was 50 (33.3-66.7) at 3 months, 72.7 (55.6-100) at 6 months, and 100 (75-100) at 12 months. In addition, cumulative patency occurred in 43.2% (16), 64.9% (24), 75.7% (28), and 75.7% (28) of the CDT group patients at 3, 6, 12, and 24 months, respectively. Conversely, only 8.5% (4), 36.2% (17), 55.3% (26), and 55.3% (26) of the control group experienced venous patency at the respective times. The preliminary findings indicate that CDT in combination with rivaroxaban provides earlier and more effective removal of thrombi than does rivaroxaban alone. Furthermore, results of survival analysis using Kaplan–Meier curves and the life table indicating the cumulative patency after 24 months in both the CDT and rivaroxaban-alone groups were significant (log-rank test, $p = 0.009$; Fig. 1). Therefore, CDT plus rivaroxaban appeared to achieve early thrombolysis and superior venous patency (acute, short-term, and midterm) compared with rivaroxaban alone.

Some literature has suggested that CDT and LMWH have significant effects on the regression of thrombi and prevention of recurrent DVT and subsequent PTS.[15–20] Rivaroxaban is also effective for the inhibition of thrombus development and prevention of recurrent VTE in patients with acute proximal DVT.[3,14,21] However, information regarding midterm PTS development and venous function in patients with acute iliofemoral DVT treated with rivaroxaban alone or combined with CDT is scarce. In this study, significantly more patients in the CDT group had a comparatively favorable degree of PTS after 24 months. In particular, the multivariable logistic analysis demonstrated that obstructed veins (on CTV) and 6-month lysis rate were associated with PTS development. Consequently, early and effective thrombolysis may reduce thrombus burden and thus lessen inflammation, vein remodeling, and the risk of subsequent PTS.

Regular US observations proved that patients receiving CDT plus rivaroxaban experienced a rapid resolution of their symptoms that primarily resulted from effective thrombolysis and early vein recanalization. In contrast to the combined treatment, the resolution of these symptoms with the rivaroxaban-alone treatment was primarily the result of bypassing collateral veins and tiny asymmetrical recanalization. This impressive finding indicates that CDT plus rivaroxaban may provide early and direct recanalization, and reduce PTS development through superior 1- to 6-month thrombus resolution.

Over 24 months of follow-up, all patients were examined through CTV, and 35 developed vein obstructions; 28 patients were documented with vein obstructions through Doppler US plus D-dimer testing. Therefore, Doppler ultrasonography is also sensitive (89%-100%) and specific (94%-99%) for symptomatic DVT of the proximal veins. Because of the nonsignificant difference between these two instruments ($p = 0.219$), Doppler US can be conveniently used to evaluate the evolution of thrombi and vein patency accurately during follow-up,[17–20] and CTV at 24 months may provide real imaging of anatomic abnormalities, especially in the iliac vein or IVC. CTV confirmed that 35 patients had obstructed veins; the abnormalities revealed on CTV imaging included a small caliber (narrowing) (n = 14), partial and total occlusion of the iliofemoral veins, and May–Thurner syndrome (n = 21). Anatomic locations involvement included venous stricture of the common femoral vein near the inguinal area (n = 22), the IVC (n = 5), and irregular obstruction of the femoropopliteal (n = 11) and iliofemoral veins (n = 19).

Table 4

Anatomic characteristics documented through CTV

Anatomic characteristics, n (%)	Rivaroxaban (n = 47)	CDT (n = 37)	*p*
Lesion sites (left)	19 (40.4)	9 (25)	0.35
Patency, n (%)	22	26	0.016
Obstructive, n (%)	25 (53.2)	10 (27.0)	0.016
Narrowing (small caliber, irregular wall)	8	6	
Occlusion (total or partial)	15	3	
May–Thurner syndrome	2	1	
Involved anatomic location			
IVC	4	1	
Iliofemoral segment	14	5	
Common femoral segment (including saphenofemoral junction)	15	7	
Femoropopliteal segment	7	4	

CDT = catheter-directed thrombolysis; CTV = computed tomographic venography; IVC = inferior vena cava.

Table 5

Associations of risk factors with PTS through logistic regression analysis

Variable	OR (95% CI)	*p*	OR (95% CI)	*p*
Age	0.994 (0.97-1.02)	0.629		
Gender (female/male)	1.32 (0.53-1.32)	0.529		
BMI	0.983 (0.88-1.1)	0.761		
Baseline TS	0.84 (0.67-1.04)	0.112		
Involved leg (left/right)	1.22 (0.45-3.35)	0.696		
Malignancy (yes/no)	2.01 (0.67-6.05)	0.217		
Thrombophilia (yes/no)	0.84 (0.33-2.09)	0.701		
Treatment type (Xarelto/CDT)	3.26 (1.3-8.01)	0.01		
Angioplasty (yes/no)	2.14 (0.65-7.03)	0.211		
Treatment duration	1.104 (1.03-1.19)	0.008		
Lysis rate at different times				
6-mo lysis rate	0.0001 (0.0001-0.1)	<0.001	0.01 (0-0.27)	0.009
3-mo lysis rate	0.01 (0.001-0.09)	<0.001		
1-mo lysis rate	0.11 (0.03-0.44)	0.002		
Obstructive vein by CT (yes/no)	18.6 (5.9-58.65)	<0.001	5.08 (1.34-21.24)	0.021
VI	2.02 (0.82-5.01)	0.129		
Recurrent DVT	4.15 (1.22-14.07)	0.022		

ORs of obstructive vein and 6-mo lysis rate were adjusted for age, weight, gender, treatment type, baseline TS, valvular incompetence, recurrent DVT, and treatment duration.

BMI = body mass index; CDT = catheter-directed thrombolysis; CI = confidence interval; CT = computed tomography; DVT = deep vein thrombosis; OR = odds ratio; PTS = postthrombotic syndrome; TS, thrombus score; VI = valvular incompetence.

These findings indicated that anatomic abnormality of the involved leg may influence vein patency and venous complications in patients with acute iliofemoral DVT. According to CTV findings, supplementary treatment strategies may be arranged individually.

Prospective and randomized studies are required to determine whether supplementary strategies are warranted in such patients.

Bleeding complications constitute a major concern regarding thrombolysis and rivaroxaban treatment. In this study, complete CDT treatment was received by most patients (34/37 patients), and the incidence of major bleeding events in this group was similar to those reported by other studies.[15,16,18] Out of 10 patients experiencing major bleeding events, three required blood transfusions and stopped CDT treatment. Other bleeding events were noted in both groups during rivaroxaban treatment, and the rivaroxaban dose was adjusted according to clinical conditions. In total, the incidence of bleeding events was nonsignificantly higher in the CDT group. The results demonstrated that the combination of CDT and rivaroxaban is safe and effective for the treatment of acute iliofemoral DVT.

In this study, the incidence of recurrent DVT was similar in the two groups. In the control group, 11 of 47 patients had thrombus progression and recurrent DVT during follow-up. Five experienced thrombus progression during rivaroxaban treatment, and six developed recurrent thrombosis after rivaroxaban treatment. Of these patients, six had bleeding events and were positive for lupus anticoagulant, two had ischemic stroke events, and the remaining three had a history of malignancy. In the CDT group, the CDT administered was incomplete because of massive bleeding in three patients, who experienced thrombus progression within the first 3 months. During the follow-up period, recurrent thrombosis occurred in another three patients. Of them, two had ischemic stroke and protein C and S deficiencies, and one experienced malignant recurrence. Rivaroxaban therapy was prolonged by more than 3 months for all patients with recurrent DVT.

Recent studies have recommended extended duration rivaroxaban for patients with unprovoked DVT and for prevention of recurrent DVT.[2,14,24,25] However, the Kaplan–Meier curves of time-to-patency analysis in the present study demonstrated that patients treated with 6 months or less of rivaroxaban have superior venous patency at 24 months than do patients treated with more than 6 months of rivaroxaban (log-rank test, $p = 0.016$). This finding that simple rivaroxaban treatment did not provide satisfactory patency at 24 months is attributable to the CDT plus rivaroxaban treatment of 6 months resulting in effective and early removal of thrombus at 1 to 6 months and thus reaching greater cumulative patency compared with the control group. This trial enabled us to conclude that effective and early thrombolytic treatment plus rivaroxaban treatment of 6 months should be considered for acute iliofemoral DVT, and for rivaroxaban treatment alone, more than 6 months of simple oral rivaroxaban therapy may be required for acute iliofemoral DVT. Future prospective and randomized studies must exclude confounding factors to elucidate the real conditions.

In addition, 14 CDT group patients received angioplasty, and these patients exhibited no occluded lesions on CTV over the 24-month follow-up. In addition to thrombolytic and anticoagulant treatment for iliofemoral DVT, the use of ancillary treatments, specifically angioplasty and stents, should be considered for enhancing short- and long-term venous patency. Large-scale, prospective, randomized studies to compare the short- and long-term outcomes of adjuvant angioplasty and stents are warranted.

Our results did not favor routine invasive thrombolytic strategy for patients with iliofemoral DVT and multiple comorbidities. For patients with severe DVT without comorbidities, CDT can facilitate rapid resolution of thrombi and recanalization and subsequently reduce the incidence of PTS. However, such treatment might increase the various risks caused by bleeding. Medication may provide benefits through the endogenous thrombolysis caused by rivaroxaban alone. At least 6 months of oral rivaroxaban therapy should be considered for acute iliofemoral DVT treated with CDT. Nevertheless, the potential advantage of rivaroxaban-alone treatment may be safety; that advantage might be offset by a higher risk in patients with comorbidity, and extended duration therapy may be required in such patients.

Several limitations of this study should be mentioned. First, this study was nonrandomized; however, patients' clinical data were recorded prospectively. Second, the subgroup analysis was based on a small number of patients. Third, there may have been some slight selection bias caused by the heterogeneous demographics in the study. Further randomized studies should be conducted to compare the effects of rivaroxaban alone and CDT plus rivaroxaban on safety and efficacy outcomes.

In conclusion, CDT plus rivaroxaban has the advantage of a quick reduction of the thrombus burden and early recovery of venous patency compared with rivaroxaban alone. The 6-month thrombolysis rate and obstructed veins were the main factors predicting PTS development.

Our data indicate that treatment type and duration, with rivaroxaban alone or in combination with CDT, are potentially associated with vein patency at 24 months. A larger randomized trial is warranted to confirm these findings.

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