

# Long-Term Results of Catheter-Directed Thrombolysis Combined with Iliac Vein Stenting for Iliofemoral Deep Vein Thrombosis

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**Purpose:** We were going to assess the effect of catheter-directed thrombolytic therapy (CDT) on post-thrombotic syndrome (PTS) and the long term effects of iliac vein stenting in acute iliofemoral deep vein thrombosis (IFDVT).

**Materials and Methods:** Fifty-six limbs in fifty-one patients (46 unilateral, 5 bilateral) were included from November 2001 through December 2007. Patients were classified based on the method of treatment: with stent implantation (n=37) and without stent implantation (n=19). The Villalta scale was chosen to assess for severity of PTS. The validated outcome measures were compared between the treatment groups. Statistical analysis was estimated according to the Kaplan-Meier test and Pearson chi-square test.

**Results:** Mean age was 57±13 years (range, 27-76 years). Mean follow up duration was 56±12 months (range, 24-144 months). Overall 5-year primary patency rate was 66.1% (77.8% in the stenting group and 42.1% in the non-stenting group) and showed statistically significant difference between the two groups (P=0.02). The recurrence rate of deep vein thrombosis was 10/37 (27.1%) in the stenting group and 11/19 (57.9%) in the non-stenting group, respectively, which showed statistically significant difference between the two groups (P=0.024). Overall incidence of mild PTS was 8/30 (26.7%): 4/13 (30.8%) in the stenting group and 4/17 (23.5%) in the non-stenting group. None of the other factors showed statistically significant difference between the groups.

**Conclusion:** Long term results of CDT in IFDVT were acceptable, and stent implantation to the iliac segment seems to have a good effect on the long term results. Therefore CDT with simultaneous stenting is recommended to improve long term results of IFDVT, if indicated.

**Key Words:** Acute iliofemoral deep vein thrombosis, Iliac vein stenting, Post-thrombotic syndrome, Villalta scale

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## INTRODUCTION

Each year, one in every 1,000 people is affected by deep vein thrombosis (DVT) of the lower limbs and is associated

with substantial morbidity [1]. International guidelines for antithrombotic therapy form the basis of adequate treatment [2]. Although anticoagulation effectively prevents thrombus extension, pulmonary embolism, and recurrence

of DVT, it rarely dissolves the clot, and many patients develop post-thrombotic syndrome (PTS). PTS is the single most frequent complication following DVT [3], occurring in 25% to 46% of the patients [4,5]. PTS is thought to be caused by obstruction due to the presence of residual thrombus, and valvular reflux due to venous damage by acute thrombosis [6,7]. This syndrome is characterized by pain, swelling, heaviness, edema, pigmentation, and deterioration of the skin including venous ulcers in severe cases [8]. PTS is also associated with reduced individual health-related quality of life and a substantially increased economic burden [9]. Even with adequate anticoagulation and daily use of elastic compression stockings, many patients are at risk of a chronically impaired long-term outcome, so improved treatment to reduce PTS development is greatly needed.

It has been thought that PTS may be prevented by providing rapid thrombus elimination. A recent systematic review suggested that accelerated removal of thrombus material by systemic thrombolysis can prevent vein dysfunction and PTS [10], but such treatment was associated with an unacceptable risk of bleeding. To reduce this complication, catheter-directed thrombolytic therapy (CDT) has been tried as a novel modality in which a catheter is introduced into the affected vein and advanced through the thrombotic segment. Additionally CDT has been suggested as a reasonable therapy for iliofemoral deep vein thrombosis (IFDVT) because it can remove thrombus and restore venous patency, preventing recurrent thrombosis and PTS. Currently, randomized trials for determining the effect of CDT in acute DVT are under way. In our study, we studied the effects of CDT on PTS, assessed by the Villalta score, and the long term effects of iliac vein stenting compared with a non-stenting group for acute IFDVT.

## MATERIALS AND METHODS

### 1) Study design and patient population

This was a retrospective study of 69 patients with acute symptomatic IFDVT that had been admitted to the Department of Vascular Surgery, Wonkwang University School of Medicine & Hospital between November 2001 and December 2007. However, 18 patients were ineligible for the study due to missing outcome data as a result of withdrawal of consent or death, and therefore the remaining 51 patients were included in this study. Because 5 patients had DVT on bilateral lower extremities, finally 56 limbs were included in this study. The average patient age was 57-13 years (range, 27-76 years). Mean follow up duration was 56-12 months (range, 24-144 months).

Diagnosis of DVT was established with level of D-dimer (cut off: >0.5 mg/dL) and computed tomography (CT) angiography. All patients underwent catheter directed thrombolytic therapy, and at the end of thrombolytic therapy, a completion venography was taken to assess the results of thrombolysis and the presence of underlying stenosis. We performed venous stent implantation in cases of severe stenosis associated with blood stagnation or in patients who had May-Thurner syndrome as underlying disease. Endovascular iliac stent was inserted in 37 limbs (stenting group), while the remaining 19 limbs were not indicated (non-stenting group). After the procedure, all the patients received oral warfarin/sodium for at least 1 year to maintain an international normalized ratio in the range of 1.5-2.5. After that, we tailored the duration of anticoagulation therapy according to risk factors of thromboembolic recurrence and residual thrombus on follow up venography. All patients wore graduated compression stockings for at least 6 months. All patients visited the outpatient clinic every month during the first 6 months, and every 2 months thereafter. We underwent one of the following methods every year to evaluate thrombus recurrence, in-stent restenosis and patency: CT venography, duplex ultrasonography, or conventional venography. Table 1 shows the demographic characteristics of the patients included in this study. Mean duration of illness was less than 14 days in both groups. The extent of DVT was evaluated on the basis of the clinical, etiological, anatomical and pathological elements (CEAP) anatomical classification. The number of involved segments was counted. The degree of thrombus extent did not show a statistically significant difference between the two groups. We assessed common risk factors for thrombosis before treatment: protein C, protein S, antithrombin, homocysteine and factor V levels. There was no significant statistical difference between the two groups.

**Table 1.** Patient demographic characteristics (n=51; 46 unilateral, 5 bilateral)

Characteristic	Stenting group (n=37)	Non-stenting group (n=19)	P-value
Sex (male:female)	15:13	12:11	0.647
Age (y)	56.7±15.0	55.0±17.8	0.672
Symptom duration (d)	9.3±8.5	8.4±8.4	0.332
Thrombus extent <sup>a</sup>	6.6±1.1	5.8±1.9	0.671
Risk factors <sup>b</sup>	1.6±1.1	1.3±0.6	0.561

<sup>a</sup>From inferior vena cava to popliteal vein; inferior vena cava, common iliac vein, external iliac vein, internal iliac vein, common femoral vein, deep femoral vein, superficial femoral vein, popliteal vein. <sup>b</sup>Protein C or Protein S deficiency, antithrombin deficiency, dysfibrinogenemia, anatomic defect, malignancy.

## 2) Treatment procedures

For patients with lower leg edema, several basic laboratory tests were checked such as D-dimer, albumin, BUN and creatinine. In case of D-dimer positive findings, we performed further confirmatory procedures such as CT or duplex ultrasonography. For CDT, a catheter was inserted via an adequate vein under ultrasonographic guidance, most commonly the ipsilateral popliteal vein. Details of the CDT procedure have been reported in numerous reports [11]. A venography was done at the start of the procedure to establish the topography of the thrombus. After local anesthesia, an infusion catheter with multiple side-holes (Uni\*Fuse Infusion Catheter; Cook, Latham, NY, USA), was introduced across the thrombosed segment. Urokinase was used as thrombolytic agent at hourly infusion doses ranging from 30,000 IU to 60,000 IU. Dose adjustment was done according to the patient's condition and clinical responses. We tried to finish the procedure as soon as possible, within 96 hours at maximum. Unfractionated heparin was given simultaneously at 100 units/hour through a sheath to prevent thrombus around the puncture site. Additional antiplatelet treatment was not given (Table 2). Residual venous outflow obstruction or severe stenosis after clot lysis was corrected by endovascular methods. We used balloon catheters for predilation and deployed self-expanding stents (diameter: 12-14 mm, length: 40-100 mm; Smart Stent; Cordis, Natick, MA, USA). All the stent implantation sites were the left iliac vein. We determined the length of stent based on the lesion and the position of the proximal landing zone (>20 mm). The distal stent extended approximately 1.0 cm into the inferior vena cava (IVC). IVC filter was implanted in 36 patients (70.6%). All the IVC filters that were implanted in the patients with acute DVT were successfully retrieved within 3 weeks after thrombolysis and stent implantation. No complications related to IVC filter implantation or retrieval occurred.

## 3) Outcome assessment

The results of thrombolytic therapy were analyzed by re-

**Table 2.** Urokinase hourly mean dose and infusion time for the two groups

Variable	Data
Total urokinase dose/patient (IU)	3,204,000±988,000
Hourly mean dose (IU)	30,000-60,000
Mean infusion duration (h)	57.6±20.6 (18-96)

Values are presented as mean±standard deviation (SD), range, or mean±SD (range).

viewing the post-procedural venograms. According to the final postprocedural venograms, complete resolution was defined as >90% lysis, and partial resolution as 50%-90% lysis of the initial thrombus. Patency, in-stent restenosis and thrombotic recurrence were evaluated with regular radiologic follow-up studies. Recurrent DVT was defined as imaging-proved DVT involving a new venous segment or a previously involved venous segment for which symptomatic and radiologic improvement had been obtained in a patient with at least one prior episode of DVT. Primary patency was defined as the time from the intervention to the first occurrence of either thrombosis of the treated segment or to an intervention to maintain patency. During the follow-up, the degree of PTS was calculated by the Villalta scale: A total score of <5 indicated absence of PTS, a score of 5-9 indicated mild PTS, a 10-14 indicated moderate PTS, and a score of >15 or leg ulcer indicated severe PTS.

## 4) Statistical analysis

The validated outcome measures were compared between the two treatment groups using PASW Statistics ver. 18.0 (IBM Co., Armonk, NY, USA). Statistical analysis was estimated according to the Kaplan-Meier test and Pearson chi-square test.  $P<0.05$  was accepted as a significant value.

## RESULTS

### 1) Initial results of thrombolytic therapy

The overall complete resolution rate was 83.9%. In the stenting group, 32 out of 37 procedures (86.5%) resulted in complete resolution, and in the non-stenting group, 15 out of 19 procedures (78.9%) had complete resolution. There was no significant difference between the groups ( $P=0.529$ ; Table 3).

### 2) Complications

In all patients, bleeding complications related to CDT occurred in 15 patients. There were no major bleeding complications in our study. Hematuria was the most commonly encountered bleeding complication related to CDT (Table 4).

**Table 3.** Initial results of thrombolytic therapy (n=51)

Group	Complete resolution	Partial resolution	Success rate (%)
Stenting group (n=37)	32	5	86.5
Non-stenting group (n=19)	15	4	78.9

### 3) Recurrence rate of DVT

The overall recurrence rate was 37.5% (21/56). The time to recurrence was variably distributed in both groups (1-127 months). About 61.9% (13/21) of limbs were rescued by repeated thrombolytic therapy. In 8 limbs, re-thrombolytic therapy was not successful. Table 5 shows the recurrence rate of thrombosis in both groups. The DVT recurrent rate

of the non-stenting group (57.9%) was higher than that of the stenting group (27.1%) (P=0.024; Table 5).

**Table 4.** Bleeding complications of catheter-directed thrombolytic therapy in all patients

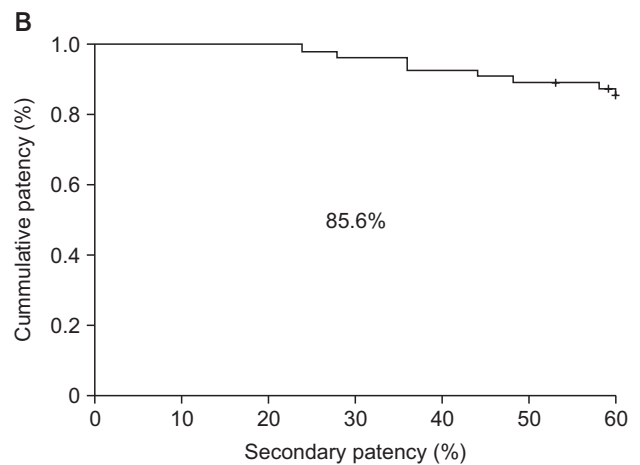
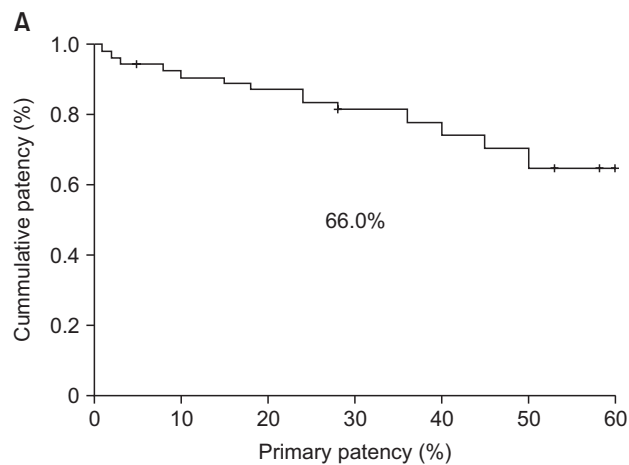
Complication	Value
Total	15
Hematuria	7
Sheath bleeding	6
Hematoma	1
Vaginal bleeding	1

### 4) Primary/secondary patency rate

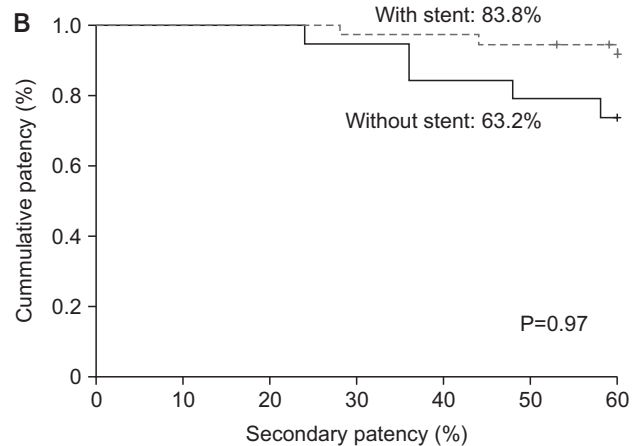
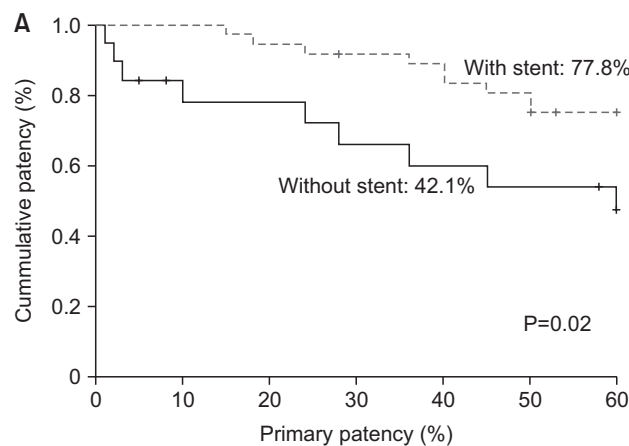
At 5 years, the overall primary patency rate was 66.0%, and the overall secondary patency rate was 85.6% (Fig. 1). The primary patency rates at 5 years for the stenting group and the non-stenting group were 77.8% and 42.1%, respectively, which was statistically significant (P=0.02; Fig. 2). The secondary patency rates at 5 years were 83.8% and 63.2%, respectively and there was no statistically sig-

**Table 5.** Recurrence rate of thrombosis

Group	No recur (n, %)	Recurred (n, %)
Stenting group (n=37)	27 (72.9)	10 (27.1)
Non-stenting group (n=19)	8 (42.1)	11 (57.9)



**Fig. 1.** Overall primary/secondary patency rates. Kaplan-Meier curves illustrating primary and secondary patency rate over time (month). (A) Primary patency, (B) secondary patency.



**Fig. 2.** Kaplan-Meier curve for primary/secondary patency rates in both groups. (A) Primary patency, (B) secondary patency.

**Table 6.** Mean Villalta Score

Group	Mean±SD (score)	Range
Stenting group (n=17)	3.18±2.60	0-9
Non-stenting group (n=13)	4.46±3.15	2-9

SD, standard deviation.

nificant difference between the two groups ( $P=0.97$ ; Fig. 2).

#### 5) Severity of post-thrombotic syndrome

Only 30 limbs had a Villalta score available at 57 months (mean) post treatment because we did not include the Villalta score initially, and because of follow-up loss. The mean Villalta scores were  $3.18\pm 2.60$  and  $4.46\pm 3.15$  for the stenting and non-stenting groups, respectively. There was a tendency for a lower Villalta score in the stenting group compared with the non-stenting group, yet it failed to reach statistical significance (Table 6). Table 7 shows the distribution of the Villalta scale in both groups. The Villalta scales of both groups belonged only to either 'None' or 'Mild PTS'.

## DISCUSSION

Acute DVT is usually regarded as a multicausal disease, arising from the interaction of multiple genetic, environmental, and behavior risk factors [12,13]. Various treatment modalities for DVT have developed during the past 30 years and each method still has its strengths and limitations. Conventional anticoagulant treatment was considered the standard treatment of DVT and it put emphasis on preventing recurrent venous thromboembolism and thrombus propagation [14]. However it may not resolve thrombi and this would not prevent the development of PTS. Especially, patients with IFDVT have a higher risk for developing PTS. It has been well known that more than 60% of patients with IFDVT complain about edema and chronic limb pain, and 5% develop venous leg ulcers despite adequate anticoagulation [5,15-17]. For these lesions, more aggressive and proper treatment has been required, and CDT has been tried as an advanced method because it can remove thrombus and restore venous patency, and may prevent recurrent thrombosis and PTS. Additionally, the benefit of CDT is also its ability to detect and treat any underlying stenotic lesions with endovascular treatment such as angioplasty and stenting. Stent implantation is used worldwide to mainly treat peripheral arterial obstruction or stenosis [18,19], and there is little data on the efficacy and long-term patency of stents that are implanted for venous disease. Many authors have performed catheter-directed thrombolysis for acute

**Table 7.** Distribution of Villalta Scale

Group	None	Mild	Moderate	Severe
Stenting group (n=17)	13	4	0	0
Non-stenting group (n=13)	7	4	0	0

IFDVT, but they have often experienced recurrence soon after successful thrombolysis despite administration of anticoagulation therapy within the therapeutic range. Residual venous outflow obstruction or stenosis after clot lysis can lead to recurrence of DVT because of venous stasis and/or endothelial injury. The importance of underlying anatomic factors, such as nonthrombotic iliac vein lesions [20], was not considered when conventional anticoagulation was the only therapeutic option. However, with the development of image-guided techniques for early thrombus removal, including surgical thrombectomy and thrombolytic strategies, it has become clear that compressive or obstructive iliac vein lesions contribute to many cases of iliofemoral DVT. The most common cause of outflow obstruction or stenosis is thought to be an extrinsic compression of the iliac vein (May-Thurner syndrome). A pooled analysis of 19 published studies, including 1,046 patients treated with catheter-directed or pharmacomechanical thrombolysis, reported the use of stents in 46% of patients [21]. Although the total number of limbs with stenosis or obstructive lesions uncovered by lytic therapy in the National Venous Registry was not reported, 33% of limbs required treatment with metallic stents [22]. The 1-year patency was significantly better in limbs treated with iliac stents (74%) than in limbs without stent placement (53%;  $P=0.01$ ). In this study, we performed venous stent implantation in cases of severe stenosis associated with blood stagnation due to residual stenosis after thrombolytic therapy. Endovascular iliac stent was inserted in 37 limbs (stenting group), but the remaining 19 limbs were not indicated (non-stenting group). We examined the short- and long-term efficacy and safety of venous stent implantation for iliac venous stenosis. This study showed that CDT with or without stenting led to complete resolution in 83.9% of cases. The resolution rate was not different with that of historical results. Additionally, the primary patency rate for all patients was 66% at 5 years. The 5-year primary patency rates of the stenting group and the non-stenting group were 77.8% and 42.1%, respectively, and statistically significant differences were shown between the two groups ( $P=0.02$ ). This result is similar with other reports [22]. The DVT recurrent rate of the non-stenting group (57.9%) was higher than that of the stenting group (27.1%) ( $P=0.024$ ). Iliac vein stenting is thought to be an effective way to prevent DVT recurrence for those patients with anatomical



defects in the iliac vein. There were no major bleeding complications in our study. Hematuria was the most commonly encountered bleeding complication related to CDT. In-stent restenosis occurred in 11 cases. Among these cases, three cases were rescued by balloon angioplasty and restenting. As a result of the wide range of clinical presentations, it has been proven difficult to achieve a consensus on a clear definition of PTS. PTS is considered when a patient has had a DVT and has complaints in the ipsilateral leg [23] that have developed or persisted a few months after DVT [24]. PTS is a syndrome and there is no gold standard diagnostic test. An ad hoc conference organized by the European Venous Forum defined PTS as chronic venous symptoms/signs secondary to DVT [25]. In the past 20 years, a few scales have been introduced to help assess whether a patient has PTS or not. These include the Venous Clinical Severity Score, CEAP classification, Widmer classification, PTS scoring system according to Brandjes, Ginsberg scale and Villalta scale. Recently, the subcommittee on control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis recommended that the Villalta scale should be adopted in clinical studies to diagnose and grade the severity of PTS [23]. The specific reasons for recommending the Villalta scale were the use of both clinical signs and subjective symptoms with severity and range taken into account, demonstrated validity, ease to use and the advantage of being able to use the scale in multiple ways (binary, categorical or continuous) and also the fact that it has been successfully used in clinical trials [26]. The Villalta scale is a validated score for assessing PTS [27]. The scale consists of subjective symptoms reported by the patient and the second part of the scale consists of objective signs observed by the clinician. Together the scale consists of 11 elements that are scored from 0 to 3, with 0 meaning absent, 1 meaning mild, 2 meaning moderate and 3 meaning severe. It also has a visual guide for the six signs of the Villalta score. Leg ulceration is also present in the scale, but is only scored as either present or absent. Scores of <5 indicate absence of PTS, a score of 5-9 indicates mild PTS, 10-14 indicates moderate PTS, and a Villalta score of >15 or ulceration indicates severe PTS. As the PTS can

develop anywhere in the years following a DVT, it is important to keep track of progression. During each follow-up, PTS can be assessed using the Villalta scale. We wanted to know the effect of CDT and stenting on PTS in our patients. Therefore, we chose the Villalta scale to evaluate incidence and severity of PTS. Only 30 limbs had a Villalta score available at 57 months (mean) post treatment, because we did not include the Villalta score initially, and because of follow-up loss. Therefore, the many missing data can be a vulnerability of this study. Anyway, the Villalta score was lower in the stenting group compared with the non-stenting group (though not statistically significant) and Villalta scales of both groups belonged only to either 'None' or 'Mild PTS'. This result means that CDT with no stenting (if necessary) could be a useful method to reduce the incidence of PTS and severity of PTS. These results provide two important points for iliofemoral DVT. First, the long term results of catheter-based intervention for IFDVT were acceptable, with low PTS incidence. Second, additional stent implantation to the iliac segment to correct the underlying disease can improve long term patency rates, and reduce DVT recurrent rates. However there are several limitations in this study. Firstly, this study was a retrospective observational study. Secondly, the Villalta score for only a small number of patients was included in this study. A multicenter randomized trial is currently in progress to evaluate whether CDT for acute iliofemoral DVT can improve long-term outcomes, which may give us a more confirmatory answer about the long term effects of CDT. Although the effectiveness of CDT has not been proved yet, it could be recommended for iliofemoral DVT patients to improve long term results and prevention of PTS.

## CONCLUSION

Long-term results of CDT in IFDVT were acceptable, and stent implantation to the iliac segment to correct the underlying disease seems to have a good effect on the long term results. Therefore, it should be recommended that CDT and simultaneous stenting be performed if indicated to improve long term results of IFDVT.

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