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Endovascular Management of Acute Lower Extremity Deep Vein Thrombosis

Rationale for Use and Lessons Learned from Emerging Clinical Trials

Kush R. Desai, MD[a,*], Simer Grewal, MD[a], Raj Shah, BS[b], Suresh Vedantham, MD[c]
[a]Department of Radiology, Northwestern University Feinberg School of Medicine, 676 North St. Clair Street, Suite 800, Chicago, IL 60611, USA; [b]University of Arizona College of Medicine, 1501 North Campbell Avenue, PO Box 245017, Tucson, AZ 85724, USA; [c]Mallinckrodt Institute of Radiology, Washington University School of Medicine, 510 South Kingshighway Boulevard, Campus Box 8131, St Louis, MO 63110, USA

KEYWORDS
• Deep vein thrombosis • Postthrombotic syndrome • Catheter-directed thrombolysis

KEY POINTS
- Approximately 50% of patients develop postthrombotic syndrome (PTS) after deep vein thrombosis, which can lead to significant impact on quality of life.
- Smaller historical studies suggest that catheter-directed thrombolysis (CDT) may have a significant impact on the development of PTS by decreasing valve damage and the development of deep venous reflux.
- The Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis trial demonstrates that pharmacomechanical CDT does not reduce the development of PTS, although it does seem to improve the severity of PTS in specific subsets of patients; further evaluation of specific subgroups is needed to determine which patients are most likely to benefit.

INTRODUCTION

Venous thromboembolism (VTE) affects approximately 0.1% of the United States population annually, with the prevalence predicted to double by the year 2050 [1,2]. Acute deep vein thrombosis (DVT) accounts for approximately 1% of all hospital admissions in the United States, with death occurring in approximately 6% of patients within 1 month of diagnosis [3]. Of patients with symptomatic acute DVT, 20% to 50% go on to develop postthrombotic syndrome (PTS), with up to one-third developing severe disease despite treatment with anticoagulation [4,5]. PTS is a chronic condition with a wide spectrum of severity; it is variably characterized by pain, intractable edema, stasis dermatitis, subcutaneous fibrosis, and in severe cases chronic ulceration of the overlying skin. Prospective assessments of the impact of PTS on quality of life (QOL) have shown that it is comparable to patients with arthritis, chronic lung

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*Corresponding author, *E-mail address:* kdesai007@northwestern.edu

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disease, or diabetes; those suffering from severe PTS have QOL similar to patients with cancer or congestive heart failure [6].

Development of PTS also places a large financial burden on patients and the health care system. In the United States, the average cost of PTS treatment is approximately $7000 per patient per year [7]. Patients with severe PTS have been shown to incur at least 4-times greater annual cost of treatment than those with mild to moderate disease within the first year after diagnosis [8]. Furthermore, it has been shown that patients with venous-origin skin ulcerations incur at least 3.5-times the annual treatment cost compared with patients with healed ulcers due to loss of employment and the potential need for surgical intervention [9]. Given the prevalence, potential morbidity, chronicity, and overall financial impact, studies have directed their aim to evaluating preventative therapies for PTS.

PATHOPHYSIOLOGY OF POSTTHROMBOTIC SYNDROME

The exact mechanism that contributes to the development of PTS is not completely understood, although venous hypertension is believed to play a central role. Studies have shown that outflow obstruction and venous reflux from valve incompetence lead to venous hypertension and are strongly associated with development of PTS symptoms [10]. Deposition of thrombus at the venous valve can incite acute and chronic local inflammation, resulting in damage to venous valve leaflets, subsequently resulting in reflux of blood. This inflammatory process also can result in luminal obstruction due to sclerosis of the venous wall. These processes are theorized to result in chronic venous insufficiency with its various clinical manifestations.

Relative to the unaffected population, patients with a history of a DVT collectively have a 26-fold increase in developing chronic venous insufficiency [11]. Additional risk factors include age greater than 65, suboptimal anticoagulation, and symptoms that persist greater than 1 month after diagnosis of initial VTE event [12]. The rates at which patients develop venous insufficiency are correlated directly with the length of time before the resolution of thrombosis; patients with proximal, iliofemoral DVT have been shown to have significantly lower rates of recanalization than patients with femoropopliteal DVT as well as higher rates of reflux [13], clinically reflected in studies that demonstrate that patients with iliofemoral DVT are approximately twice as likely to develop a recurrent DVT and more than 50% more likely to develop PTS [14]. Additionally, it has been shown that derangement of previously nonthrombosed veins can result after episodes of venous thrombosis, with increased rates of venous insufficiency in veins not affected by the initial venous thrombosis [11].

Despite these theories, published literature has not established whether reflux or obstruction plays a larger role in the development of PTS. Haenen and colleagues [13] found a positive correlation between increased PTS severity and valvular reflux while also noting that thrombus volume was not correlated with PTS severity. Two additional studies corroborated these findings, noting that reflux seemed to play a larger role than thrombus volume in PTS pathophysiology [10,11].

Other studies have reported, however, that venous obstruction plays a significant role in PTS development when assessed at 3 months after the formation of the initial DVT [15]. These findings were corroborated by Prandoni and colleagues [16], noting that patients with persistent venous obstruction 6 months after DVT formation developed PTS at an increased rate. Although the pathophysiology is not completely understood, these studies support the open-vein hypothesis, thereby justifying the investigation of catheter-directed thrombolysis (CDT) as a treatment tool for DVT for preventing or reducing the severity of PTS.

ASSESSMENT OF POSTTHROMBOTIC SYNDROME

Much like the uncertainty in the pathophysiology of PTS, there has been debate about the optimal method of defining and classifying PTS. The Villalta scoring system was developed in 1994 as a disease-specific assessment to both diagnose and categorize the severity of PTS and is now considered one of the standard classification systems for PTS [17,18]. Points are assigned based on a combination of 5 symptoms and 6 clinical signs. If a venous ulcer is present, the severity of the condition is classified as severe regardless of the other signs or symptoms. A score of greater than 5 indicates a diagnosis of PTS; a score of 5 to 9 indicates mild disease, 10 to 14 indicates moderate disease, and greater than 14 and/or presence of an ulcer indicates severe disease [17]. This scale has been used in many clinical studies of DVT and PTS and has been endorsed by the International Society on Thrombosis and Haemostasis [19].

The clinical-etiological-anatomic-pathophysiologic (CEAP) system was designed to descriptively classify chronic venous disease based on clinical signs, etiology, anatomic distribution, and pathophysiologic condition [20]. Clinical signs are scored based on objective signs of disease with from 0, no visible disease, to 6, active

ulceration. Etiology is classified as congenital, primary, or secondary. Anatomic sites are subdivided based on superficial, deep, or perforator venous system involvement with the possibility of any or all systems being involved. Pathophysiologic condition is categorized by presence of venous reflux, obstruction, or both. CEAP is a useful way to categorize patients to enable comparison across studies but is not designed as a measure to be used for longitudinal outcome assessment.

The Venous Clinical Severity Score is based on the elements of the CEAP classification that can exhibit change over time and applies a score of 0 to 3 for 9 clinical descriptors, with an additional 0 to 3 points assigned for use of compressive therapy. This system was made to allow for assessment of disease for change over time. The Venous Clinical Severity Score scale elements tend to focus on the more severe end of the venous disease spectrum and, aside from pain, do not measure symptoms [17,21].

RATIONALE FOR THROMBOREDUCTIVE THERAPIES

Systemic anticoagulation, the current standard of care for DVT treatment, can prevent thrombus extension but does not clear thrombus that is already present; rather, the body's own endogenous lytic mechanisms perform this function over time. It is theorized that the prompt removal of thrombus in DVT patients may have a positive impact the development of PTS, because this would create an open vein with relief of outflow obstruction as well as removal of the nidus for inflammatory change that is believed to lead to valve dysfunction [5,22]. CDT permits local delivery of high concentrations of thrombolytic agent to provide prompt, active thrombus clearance. This hypothesis has been supported by clinical studies that have observed a reduction in the development of PTS in DVT patients treated with CDT and that also have linked findings of residual thrombus to valve incompetence and recurrent DVT [15,17,23–25]. When compared with anticoagulation alone, there was an estimated risk reduction of 0.64 for developing PTS after undergoing CDT in 1 meta-analysis [26]. A vast majority of the studies, discussed previously, however, were of low methodological quality (ie, limited protections against bias), and the meta-analysis does not include the largest and most rigorous randomized trial that has been completed.

EARLY SUPPORTIVE STUDIES

As time progressed, studies found CDT provided significant improvement in outcome measures for PTS. In 2000, Comerota and colleagues [27] conducted a retrospective case-control study of 98 patients with proximal iliofemoral DVT, where 68 patients who were successfully treated with urokinase CDT in additional to conventional anticoagulation were compared with 30 retrospectively defined patients who had been treated with anticoagulation alone. There was a statistically significant improvement in overall physical functioning and QOL measures along with fewer PTS symptoms in patients who had undergone CDT plus conventional anticoagulation therapy compared with those who were treated with conventional anticoagulation alone. The investigators concluded that patients with iliofemoral DVT who are treated with CDT plus anticoagulation have better functioning and well-being compared with those treated with standard anticoagulation alone. This study was limited by a small sample size, retrospective nature, and lack of balance in the cohorts in some parameters (eg, the control patients were older).

The following year, AbuRahma and colleagues [28] conducted a small, single-center, prospective study of 51 patients that compared conventional anticoagulation of iliofemoral DVT to multimodality treatment with anticoagulation and CDT followed by percutaneous transluminal balloon angioplasty and stent placement in select patients with residual iliac venous stenoses. Patients were able to choose their treatment arm, with 18 patients choosing the multimodality treatment arm and the remaining 33 patients choosing standard anticoagulation alone. The multimodality treatment group had greater 6-month patency of the affected vein along with greater long-term symptom resolution at 5 years compared with those who underwent anticoagulation alone (83% vs 24% and 78% vs 30%, respectively). The investigators concluded that lysis in additional to mechanical methods was a more effective treatment than anticoagulation alone in patients with iliofemoral DVT. This study was limited by its nonrandomized design, lack of blinding, and overall small size of the study.

PROSPECTIVE EVALUATION OF CATHETER-DIRECTED THROMBOLYSIS IN POSTTHROMBOTIC SYNDROME PREVENTION: THE CATHETER-DIRECTED VENOUS THROMBOLYSIS IN ACUTE ILIOFEMORAL VEIN THROMBOSIS TRIAL

The first rigorous randomized trial to examine the role of CDT in PTS prevention was performed by the Catheter-Directed Venous Thrombolysis in Acute Iliofemoral Vein Thrombosis (CaVenT) group from Norway; they conducted an open-label randomized controlled trial

evaluating whether anticoagulation plus CDT (n = 90) versus anticoagulation alone (n = 99) reduced the development and severity of PTS as well as the 6-month vein patency rates. This study assessed presence and severity of PTS via the Villalta scale. All patients received subcutaneous low-molecular-weight heparin followed by warfarin. All patients were advised to wear compression stockings for 24 months. For the CDT cohort, use of adjunct balloon angioplasty and stenting for those with residual stenosis was left to the discretion of the operator. The investigators found a 26% relative risk reduction of PTS at 2 years in patients who underwent CDT—41% of patients who underwent CDT went on to develop PTS compared with 56% who underwent anticoagulation alone. There was a 9% rate of major or clinically relevant bleeding; all were without permanent sequelae. At 5-year follow-up, absolute risk reduction broadened to 28% in patients who underwent CDT; however, there was no significant difference in QOL measures at any time point beyond 6 months. The investigators concluded that additional CDT should be considered in patients with a high proximal DVT and a low risk of bleeding [29–31]. The study was limited by lack of standardization in use of adjunct therapy, angioplasty, and stent placement in the CDT cohort. Additionally, the open-label design has the potential for reporting biases given some elements of the Villalta scale are patient reported. This study's statistical power was limited due to the modest sample size (n = 209), and there possibly could be some degree of limitation to its generalizability to populations outside Norway and to other endovascular treatment methods.

PHARMACOMECHANICAL THROMBECTOMY AND THE ACUTE VENOUS THROMBOSIS: THROMBUS REMOVAL WITH ADJUNCTIVE CATHETER-DIRECTED THROMBOLYSIS TRIAL

Conventional CDT procedures involve multiday procedures during which patients require intensive-level care with prolonged exposure to lytic agents; for example, the CaVenT study had treatment durations ranging from 1 day to 4 days [30]. Devices for venous thrombolytic applications, where mechanical and pharmaceutical thrombectomy can be combined, have been introduced with the intent of accelerating the removal of thrombus and shortening treatment duration. Pharmacomechanical CDT (PCDT) also may permit reduction in length of lytic exposure time and, therefore, a theoretic reduction in bleeding risk as well as decreasing the need for ICU-level care and overall hospital length of stay. These benefits have been suggested in observational studies; a single-center, retrospective review of 46 CDT procedures and 52 PCDT procedures demonstrated a significant reduction in ICU and hospital length of stays in favor of the CDT cohort. Overall, this led to a significant cost reduction in the PCDT group relative to the CDT group on subsequent hospital cost analysis. At 1-year follow-up, the CDT cohort and the PCDT cohort did not significantly differ in vein patency rates, 64% and 68%, respectively. This study concluded PCDT provided a similar treatment success with reduced length of stays and hospital costs compared with CDT [32].

The Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis (ATTRACT) trial is the only multicenter, randomized controlled trial to address the role of PCDT as a treatment modality for acute proximal DVT in the prevention of PTS. The investigators conducted a phase 3, multicenter, open-label, assessor-blinded, randomized trial of 692 patients to determine whether PCDT prevents PTS in patients with proximal DVT, measured over 24 months. The study included patients with acute proximal DVT that extended above the popliteal vein. This study used the Villalta scale to diagnose PTS with a score of higher than 5; the primary endpoint was cumulative PTS rate measured by the Villalta scale between 6 months and 24 months (inclusive). To a far greater extent than preceding studies, ATTRACT featured robust precautions against bias that included central automated randomization, allocation concealment, stratification by thrombus extent (iliofemoral vs femoropopliteal), separation of the study's conduct from the data management, minimization of confounding (ie, standardization of treatment in both arms), blinding of outcome assessors and clinical event adjudicators, and use of an independent adjudication committee, among others. Anticoagulation was delivered per published clinical practice guidelines; initial therapy predominantly was with low-molecular-weight heparin and unfractionated heparin; however, rivaroxaban and fondaparinux also were used in some study patients. These were followed in most patients by warfarin therapy for at least 3 months, with the duration determined by the ongoing risk of recurrence, per published guidelines. Sized-to-fit, elastic compression stockings were provided at 10 days to patients in both arms, and patients were encouraged to wear them daily for the entire 2-year period of follow-up. Alteplase was used as the thrombolytic drug in PCDT recipients. Physicians were required to attempt single-session therapy when the popliteal vein had good inflow and the inferior vena cava was not involved. For patients who had

inferior vena cava involvement or popliteal vein occlusion, physicians used infusion-first therapy, in which an alteplase infusion catheter was left in place for no longer than 30 hours. For patients with residual stenosis, physician discretion determined adjunct use of balloon angioplasty or stent placement.

The ATTRACT investigators found no significant differences in cumulative PTS rates in the PCDT group versus the control group receiving anticoagulation alone (47% vs 48%, respectively) after 24 months. There was a statistically significantly higher rate of major, nonfatal bleeding in the PCDT group compared with the conventional therapy group, 1.7% versus 0.3% ($P = .049$), respectively. The investigators concluded that the addition of PCDT to anticoagulation did not reduce the occurrence of PTS, the study's primary endpoint [33]. PCDT did, however, enhance early resolution of leg swelling and pain and reduced PTS severity. Elderly patients (>65 year old) were less likely to benefit from PCDT, and most of the major bleeding complications were observed in this group.

The primary study report included all randomized patients. The randomization originally was stratified, however, by whether the iliac vein and/or common femoral vein was involved (iliofemoral DVT, n = 391) or not (femoral-popliteal DVT, n = 300). Subsequent subgroup analyses can be summarized as follows: (1) PCDT did not influence the occurrence of PTS or recurrent VTE in either subgroup; (2) patients with femoral-popliteal DVT did not experience any benefit with use of PCDT; and (3) patients with iliofemoral DVT who received PCDT experienced greater improvement in early leg pain and swelling through 30 days ($P<.01$), reduced PTS severity ($P<.01$), and reduced occurrence of moderate or severe PTS ($0.01<P<.05$) through 2 years and greater improvement in venous disease–specific health-related QOL ($P = .029$) over 2 years, compared with the control-arm patients [34,35]. Hence, the study suggests that most patients with proximal DVT should not receive PCDT due to lack of PTS prevention efficacy and increased major bleeding. PCDT seems appropriate, however, for patients with acute iliofemoral DVT, low expected bleeding risk, severe presenting symptoms, and amenability to a catheter-based procedure.

The ATTRACT trial had limitations that could have affected outcomes in some respects. The study included several PCDT methods in the endovascular treatment arm and, therefore, did not have the ability to assess specific methods with strong statistical power. There was a large number of patients lost to follow-up, with more loss in the control group, which could have resulted in an underestimate of the effect of PCDT treatment. Sensitivity analysis with multiple imputation did not, however, document a statistically significant PTS prevention effect; in both patient subsets (femoropopliteal and iliofemoral DVT), there was no significant reduction in overall prevention of PTS.

FUTURE DIRECTIONS

At this time, 2 rigorous randomized trials have identified benefits with use of CDT or PCDT in patients with DVT, justifying additional study of the open vein hypothesis. Neither demonstrated a large, compelling benefit, however, that might justify large-scale use of thrombolytic therapy, given the risk of bleeding. The CaVenT trial identified a reduction in PTS but not QOL with use of CDT, and ATTRACT did not find a PTS prevention effect for PCDT in the entire study population or either major anatomic subgroup. In the 2 studies together, 44% of lysed patients developed PTS. These findings suggest that the development of PTS is governed primarily by mechanisms that are not influenced by the thromboreductive effect of fibrinolytic therapy. As such, additional studies are needed to better define the pathophysiology of PTS.

Endovascular DVT treatment, however, has shown the ability to reduce early and late symptom severity in patients with iliofemoral venous involvement, supporting the validity of the open vein hypothesis to a degree. Studies show that there is an increased risk of bleeding with thrombolytic therapy, so finding new ways to eliminate thrombus and open veins that do not increase bleeding risks may be important. As a chronic condition with significant QOL and financial burden on both individuals and the health care system, new ways to prevent and treat PTS are needed.

Treatment and prevention of PTS are likely to be a multimodality, interdisciplinary effort that requires further research to study new devices and techniques in the treatment of acute DVT, elucidate the risk factors for development of clinically significant disease, and to better delineate the population most likely to benefit. Through a selective, individualized approach, clinicians then can identify the appropriate patient population most likely to benefit from thromboreductive therapies. As of now, there is a potential role, supported for the first time by high-quality randomized controlled trial data, for targeted thrombolytic therapy in patients with DVT involving the common femoral vein or more central veins, with moderate to severe symptoms,

without contraindications to fibrinolytic drugs, and with long life expectancies with robust baseline activity levels.

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