The Role of Thrombolysis in the Clinical Management of Deep Vein Thrombosis

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Abstract—The cornerstones of current management of deep vein thrombosis (DVT) are the routine use of anticoagulant therapy, graduated elastic compression stockings, and early ambulation. Thrombolytic therapy was previously reserved only for patients with life-, limb-, or organ-threatening complications. However, the postthrombotic syndrome has been increasingly recognized as a frequent and serious long-term complication of DVT. In parallel, endovascular thrombolytic methods have evolved considerably in recent years, prompting discussion and controversy as to whether they should be more liberally used. In some centers, pharmacomechanical catheter–directed thrombolysis is now routinely used in the treatment of acute iliofemoral DVT. Randomized trials are currently under way to determine when the use of pharmacomechanical catheter–directed thrombolysis is appropriate in patients presenting with acute proximal DVT. (Arterioscler Thromb Vasc Biol. 2011;31:479-484.)

Key Words: thrombolysis ■ venous thrombosis ■ catheter-directed thrombolysis ■ postthrombotic syndrome

Venous thromboembolism (VTE) is estimated to occur in 350 000 to 600 000 persons per year in the United States alone, of which more than 250 000 cases represent first episodes of deep vein thrombosis (DVT).1 The management of DVT has traditionally been anchored in a longstanding view of the disease as an “acute” condition involving an initial period of high risk of pulmonary embolism, followed by progressively reduced risk of patient harm over time. As a result, DVT therapies have been judged primarily on their ability to prevent symptomatic pulmonary embolism, early thrombus progression, and recurrent VTE.2 However, contemporary prospective studies suggest that this concept of DVT-related health impairment needs to be modernized substantially. In particular, it is now clear that achievement of the above therapeutic goals often does not suffice to provide optimal clinical outcomes for patients.

DVT and the Postthrombotic Syndrome

It has long been known that hypercoagulability, stasis of blood flow, and venous endothelial injury, collectively known as the “Virchow’s triad” of procoagulant risk, are major factors in the pathophysiology of DVT. More recently, it has become apparent that susceptibility to venous disease is also governed by a complex interplay of gene expression, inflammation, lipid biology, and other processes.3 Because these processes remain incompletely characterized, standard treatment for DVT remains focused on reducing recurrent events via the use of anticoagulant drugs. For most patient groups, initial therapy consists of administration of a parenteral anticoagulant drug (unfractionated heparin, a low–molecular weight heparin, or fondaparinux) with subsequent transition to long-term oral vitamin K antagonist therapy for at least 3 months, with the duration of therapy dependent on the presence or absence of ongoing risk factors for recurrence.2 The preferred initial approach to most DVT patients with active cancer is low–molecular weight heparin monotherapy for at least 3 to 6 months.2,4,5

Despite the use of anticoagulant therapy, the postthrombotic syndrome (PTS) develops in 25% to 50% of patients who experience a proximal DVT episode.6,7 PTS most commonly causes chronic, daily limb pain/aching, fatigue, heaviness, or swelling. In severely affected patients, limiting venous claudication, stasis dermatitis, subcutaneous fibrosis, or skin ulceration may develop. PTS clearly impairs quality of life (QOL), and the recent Venous Thrombosis Outcomes cohort study found the presence and severity of PTS to be the leading predictors of patients’ health-related QOL 2 years after a DVT episode.7–11 PTS also leads to venous leg ulcers that are difficult to treat and that often recur. The direct medical costs of treating PTS and the indirect costs of the related work disability have been shown to result in substantial economic burden to the healthcare systems of several North American and European countries.12–15

The pathogenesis of PTS is complex and incompletely understood, particularly at a microscopic level. Studies have demonstrated that an initial inflammatory response to thrombosis strongly influences thrombus resolution, organization, and subsequent vein wall injury.16,17 Among the elements that
play a role in the ultimate outcome are inflammatory and growth factor mediators, extracellular matrix–derived factors, blood-borne elements, and endothelial factors.\textsuperscript{19} The ultimate result of this process on the cellular composition of the adjacent vein wall appears to be an increase in thickness and reduced compliance, among other abnormalities.

At a macroscopic level, it is currently thought that the continued presence of thrombus within the deep venous system during the initial weeks after an acute DVT leads to PTS by at least 2 pathways. First, even with anticoagulant therapy, incomplete clearance of thrombus is common, so residual thrombus that is present over the long run physically blocks venous blood flow (obstruction). Second, the inflammatory response to acute thrombosis directly damages the venous valves and alters the adjacent vein wall, leading to valvular reflux.\textsuperscript{19,20} Uninvolved distal deep veins and superficial collateral veins may dilate and become incompetent as well. When reflux or obstruction is present, ambulatory venous hypertension develops and ultimately leads to edema, tissue hypoxia and injury, progressive calf pump dysfunction, subcutaneous fibrosis, and skin ulceration.\textsuperscript{21–28} Recurrent ipsilateral DVT and large initial thrombus extent (specifically, involvement of the iliac or common femoral veins) increase PTS risk, but other factors that predispose DVT patients to develop PTS are largely unknown.\textsuperscript{6,29} Daily use of graduated elastic compression stockings for 2 years after a proximal DVT episode has also been shown in several single-center randomized trials to significantly reduce the rate of PTS.\textsuperscript{30,31}

### The Open Vein Hypothesis

It has been hypothesized for many years that rapid thrombus elimination and restoration of unobstructed deep venous flow may prevent valvular reflux, venous obstruction, and PTS. Proof-of-concept support for this “open vein hypo­thesis” can be found in studies of DVT patients who were treated with anticoagulation alone. In a series of ultrasound studies, Meissner et al found that venous segments that developed valvular reflux had longer (2.3 to 7.3 times) endogenous clot clearance times than segments that did not \( (P<0.04) \) and that reflux developed much less frequently in veins that remained free from DVT propagation or rethrombosis (26% to 35% versus 61% to 80%, \( P<0.005, n=204 \)).\textsuperscript{24,28} In a study published in 2005, Prandoni et al found that PTS developed more frequently in proximal DVT patients who had residual venous thrombus or popliteal valvular reflux at 6-month follow-up \( (n=180, 47\% \text{ versus } 23\%, \ P<0.01) \).\textsuperscript{23} In 2005, Hull et al performed a metaanalysis of 11 randomized DVT treatment trials and found a strong correlation between the amount of residual thrombus after a course of anticoagulant therapy and the subsequent incidence of recurrent VTE.\textsuperscript{32} Moreover, a published randomized trial found the use of contemporary surgical venous thrombectomy with anticoagulation to result in better venous patency and reduced PTS than anticoagulation alone.\textsuperscript{33,34} However, this procedure has not been widely adopted because of its invasiveness and dependence on specialized surgical expertise. Nevertheless, the above studies together suggest that successful thrombus elimination is correlated with better long-term venous function and improved clinical outcomes.

### Systemic Thrombolytic Therapy

Systemic DVT thrombolysis, which refers to venous thrombus dissolution using a fibrinolytic drug given via an intravenous line distant from the affected limb, has been evaluated in a number of randomized trials of DVT patients. In studies that evaluated streptokinase, a first-generation fibrinolytic drug, \( >50\% \) clot lysis (by quantitative analysis of venograms) was observed more frequently in patients treated with streptokinase than in patients treated with heparin alone (62% versus 17%, \( P<0.0001 \)).\textsuperscript{35} In 1979, Elliot et al found that PTS developed less frequently in acute DVT patients treated with streptokinase compared with heparin alone after a mean of 19 months follow-up (35% versus 92%, \( n=51 \)).\textsuperscript{36} In 1982, Arnason et al found that venographic obstruction (56% versus 100%) and PTS (24% versus 67%) were less frequent in patients treated with streptokinase compared with anticoagulation alone at a mean of 6.5 years follow-up \( (P<0.01, n=42) \). It should be noted that the PTS assessments in these studies were not performed using any validated instrument. Moreover, bleeding complications were much more frequent in the patients who were treated with streptokinase (14% versus 4% in a pooled analysis of 6 randomized clinical trials [RCTs]).\textsuperscript{35} For this reason, systemic streptokinase infusions are not used for DVT treatment in current practice.

Systemic infusion of recombinant tissue plasminogen activator (rt-PA), a drug with greater fibrin affinity than previous fibrinolytic agents, has also been studied for the treatment of DVT. In a 1990 study of 59 proximal DVT patients, Turpie et al found that a 4-hour systemic rt-PA infusion \( (0.5 \text{ mg/kg}) \) achieved \( \geq 50\% \) clot lysis more often than heparin alone (58% versus 0%, \( P=0.002 \)), with a trend toward reduced PTS in patients who had \( >50\% \) clot lysis (25% versus 56%, \( P=0.07 \)).\textsuperscript{37} In a 1990 multicenter randomized trial of 64 proximal DVT patients, Goldhaber et al found \( >50\% \) clot lysis to be more frequently achieved in patients treated with rt-PA \( (0.05 \text{ mg/kg/h infused for up to 24 hours, maximum dose 150 mg}) \) than in patients treated with heparin alone (29% versus 0%, \( P=0.04 \)).\textsuperscript{39} In this study, \( >50\% \) clot lysis was far more frequent in patients with nonocclusive thrombi rather than occlusive thrombi (59% versus 14%, \( P<0.005 \)), raising the possibility that inadequate access of rt-PA to its target sites within the thrombus may have contributed to its limited effectiveness.\textsuperscript{40} These studies showed that rt-PA can lyse human DVT but also strongly suggest that the systemic administration route may not reliably achieve a therapeutic rt-PA concentration at its target sites within the thrombus, resulting in only modest (29% to 58%) clot removal efficacy. In the 2 studies above \( (n=123) \), there was 1 nonfatal intracranial bleed.\textsuperscript{38,39} Two patients had extracranial bleeding (1 subcutaneous ecchymosis and 1 hemarthrosis which occurred 10 days after hip surgery). The use of intermittent rt-PA injections into nearby veins in the affected leg has also been studied in a RCT but was not superior to systemic thrombolytic therapy either in safety or in efficacy.\textsuperscript{41}

### Modern Endovascular Thrombolytic Techniques

In current practice, thrombolytic drugs are delivered using catheter-based techniques to achieve a higher local intratherombus drug concentration (enhancing efficacy) and thereby
enable successful clot lysis with a reduced drug dose (enhancing safety). Catheter-directed intrathrombus thrombolysis (CDT) refers to the infusion of a fibrinolytic drug directly into the venous thrombus via a multisidehole catheter which is embedded in the thrombus using imaging guidance.\textsuperscript{42-43} After the acute thrombus has been eliminated, the underlying veins are evaluated by venography and any venous obstructive lesion identified is treated with balloon angioplasty or stent placement. Limitations of this technique include the long infusion times required to lyse extensive DVT (typically 1 to 3 days) and the healthcare resources used. In an early prospective multicenter registry, major bleeding occurred in 11% of DVT patients treated with urokinase CDT infusions.\textsuperscript{44} In more recent experiences using infusions of rt-PA at low doses (0.5 to 1.0 mg/h), major bleeding has occurred in 3% to 4% of patients.\textsuperscript{45-47} Reasons for this difference may be improved patient selection and the incorporation of routine ultrasound-guided venipuncture, which has largely eliminated the problem of local access site bleeding.

The development of pharmacomechanical catheter–directed thrombolysis (PCDT; the combined use of CDT and catheter-based thrombectomy devices) techniques has enhanced the ability to efficiently remove large thrombus volumes. Two general types of PCDT may be used. (1) First-generation PCDT methods involve use of thrombectomy devices along with traditional CDT and appear to reduce fibrinolytic drug infusion time and dose by nearly 50%.\textsuperscript{48} This is thought to enhance treatment safety. (2) Single-session PCDT methods enable rapid intrathrombus dispersion of thrombolytic drug bolus and can enable complete on-table removal of thrombus in a single 1- to 3-hour procedure, obviating the need for further drug infusion.\textsuperscript{49-52} Whichever method is used, patients also receive anticoagulation before, during, and after endovascular treatment. Either unfractionated heparin or low–molecular weight heparin may be used during therapy; when unfractionated heparin is used, one generally aims for a subtherapeutic partial thromboplastin time. At present, there is no evidence to support altering the type or duration of long-term anticoagulation because CDT or PCDT was performed. Like other DVT patients, patients who have undergone CDT or PCDT should also be provided graduated elastic compression stockings (30 to 40 mm Hg ankle pressure) for PTS prevention long-term.\textsuperscript{30,31}

**RCTs of Endovascular DVT Thrombolysis**

At present, there remains no published, adequately designed multicenter RCT that has evaluated the ability of CDT or PCDT to prevent long-term PTS in patients with proximal DVT. The ability of CDT/PCDT to rapidly remove venous thrombus and prevent PTS in proximal DVT patients is supported by several studies, each with significant methodological limitations. In 2000, Comerota et al analyzed data from 68 CDT-treated acute iliofemoral DVT patients from a multicenter prospective CDT registry and found that they had fewer PTS symptoms ($P=0.006$), better physical functioning ($P=0.046$), less stigma of chronic venous insufficiency ($P=0.033$), and less health distress ($P=0.022$) at a mean follow-up of 16 months than 30 retrospectively “matched” patients who were treated with anticoagulation alone.\textsuperscript{53} However, this comparison was limited by marked age differences in the 2 cohorts. In 2001, AbuRahma et al described a prospective study in which 51 acute iliofemoral DVT patients were permitted to choose to receive adjunctive CDT (with urokinase or rt-PA)+anticoagulation or anticoagulation alone. The patients treated with CDT had more frequent venous patency at 6 months (83% versus 24%, $P<0.0001$) and absence of symptoms at 5 years (78% versus 30%, $P=0.0015$).\textsuperscript{54} However, this study was limited by nonrandomized design, performance in a single center, and small sample size. In 2002, Elsharawy et al described a single-center Egyptian randomized trial comparing adjunctive CDT (with streptokinase) versus anticoagulation alone in 35 patients with acute iliofemoral DVT. At 6 months, patients treated with CDT had a higher rate of normal venous function (72% versus 12%, $P<0.001$) and less valvular reflux (11% versus 41%, $P=0.04$).\textsuperscript{55} However, this study was limited by small sample size and performance in a single center, and it did not evaluate clinically meaningful outcomes, such as PTS and QOL. In 2009, Enden et al described the 6-month follow-up results from the first 100 patients randomly assigned to either CDT+anticoagulation or anticoagulation alone in the Norwegian multicenter CaVenT Trial.\textsuperscript{56} Venous patency was significantly superior in the CDT-treated patients (64% versus 36%, $P<0.05$), but valvular reflux was no different (60% versus 66%, $P=0$ significant). In 2010, Sharifi et al described the results of a 183-patient single-center RCT (the TORPEDO Trial) in which CDT+anticoagulation proved superior to anticoagulation alone at 6 months follow-up in preventing PTS (3.4% versus 27.2%, $P<0.001$) and recurrent VTE (2.3% versus 14.8%, $P<0.003$).\textsuperscript{57} However, a validated measure of PTS was not used, and the follow-up period was short.

Of note, the CaVenT Trial noted above has finished enrollment, and 6-month follow-up has also been completed for the entire cohort (personal communication with Tone Enden, 2010). Follow-up of enrolled patients is ongoing. As the study’s primary outcome is the occurrence of PTS at 2-year follow-up, its results are expected to become available within 2 to 3 years.

The ongoing Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis (ATTRACT) Trial, sponsored by the National Heart Lung and Blood Institute (http://www.clinicaltrials.gov, NCT00790335), is a National Institutes of Health–funded, Phase III, multicenter, open-label, assessor-blinded, parallel 2-arm RCT. For this study, 692 patients with symptomatic proximal DVT are being randomly assigned to 50 to 60 US clinical centers to receive either PCDT+standard DVT therapy (anticoagulant therapy+elastic compression stockings) or standard DVT therapy alone. The study is powered to determine whether the initial adjunctive use of PCDT (using rt-PA as the investigational drug) reduces the occurrence of PTS by one third over 2 years of follow-up. PTS is assessed at follow-up visits every 6 months during the 2-year follow-up period using the Villalta PTS Scale, a validated measure of PTS that is endorsed by the International Society of Thrombosis and Hemostasis.\textsuperscript{58} The Villalta Scale incorporates patient self-assessment of 5 common symptoms of PTS along with a blinded clinician’s assessment...
of 6 common PTS signs on physical examination. Secondary outcomes being assessed include venous disease-specific and generic QOL using the Venous Insufficiency Epidemiological and Economic Study-QOL and SF-36 measures, respectively; resolution of acute DVT symptoms (pain and swelling); rates of major bleeding, symptomatic pulmonary embolism, recurrent VTE, and death; and cost-effectiveness (dollars per quality-adjusted life-year). To date, 100 patients have been enrolled in ATTRACT, and the monthly accrual rate continues to increase. Key challenges include the large number of patients who must be excluded from thrombolytic studies because of bleeding risk, as well as challenges in conveying clinical equipoise to patients on a clinical question that tends to be viewed very differently by different medical subspecialties. It is hoped that this study’s methodological rigor and leadership by a diverse steering committee of national DVT research experts will enable this important question to be answered to the mutual satisfaction of medical physicians, endovascular specialists, and DVT patients alike.

Determining Whom to Treat

There is great heterogeneity of clinical and biological phenotypes with the patient population with DVT. Given the clinical importance of PTS to the long-term health of the patient and the invasiveness, risks, and costs of thrombolytic therapy, it is important for clinical decision-making to be guided by rigorously performed randomized trials. While these are ongoing, sound judgment should be applied to use these procedures in those patients who are most likely to benefit and least likely to be harmed. These factors may reasonably influence such decisions.

Projected Risk of Bleeding

All patients in whom thrombolytic therapy is being considered must undergo careful evaluation for factors that may increase the risk of bleeding, including (but not limited to) ongoing or recent active bleeding; recent major surgery, trauma, pregnancy, cardiopulmonary resuscitation, or other invasive procedure; the presence of lesions that could bleed in critical areas, such as the central nervous system; and renal failure. Decisions as to whether to exclude patients from receiving thrombolysis on the basis of these risk factors should be individualized based on the clinical severity of DVT and the other factors noted below.

Clinical Severity of DVT

Urgent endovascular thrombolysis is indicated to prevent life-, limb-, or organ-threatening complications of acute DVT in situations such as phlegmasia cerulea dolens or extensive inferior vena cava thrombosis (especially with suprarenal extension, which may lead to fatal pulmonary embolism or acute renal failure). The use of endovascular thrombolysis in these situations is justifiable because of the absence of other viable treatment options and may sometimes be necessary even when moderate risk factors for bleeding are present. In addition, in the authors’ view, nonurgent second-line endovascular thrombolysis is reasonable when initial anticoagulation alone has failed to achieve therapeutic objectives—there is major anatomic DVT progression, an increase in clinical severity of DVT, or patient inability or unwillingness to tolerate ongoing major DVT symptoms (ie, pain and swelling that are not relieved or that preclude physical activity). In these situations, a low threshold should be applied to exclude patients from thrombolytic therapy if there are risk factors for bleeding.

Anatomic Extent of DVT

Patients with iliofemoral DVT, defined as DVT involving the iliac vein or common femoral vein, are at significantly increased risk of both PTS and recurrent VTE. Although the completed studies had significant methodological limitations, the preponderance of the evidence suggests that clinical outcomes are likely to be superior with use of endovascular therapy in such patients. Therefore, patients with acute iliofemoral DVT who are at low projected risk of bleeding should be provided with a balanced discussion of the risks and possible benefits of nonurgent first-line endovascular thrombolytic therapy for the purpose of PTS prevention. Given the lack of conclusive evidence of benefit, a very low threshold should be applied to exclude patients if there are risk factors for bleeding. Patients with asymptomatic DVT and isolated calf DVT should not undergo thrombolysis because the risks of major PTS are low. Patients with chronic femoropopliteal DVT should not undergo CDT because it is ineffective in that scenario.

Life Expectancy, Baseline Ambulatory Capacity, and Comorbidities

Patients who are chronically unable to walk or who have very short life expectancy are less likely to benefit meaningfully from aggressive therapy to prevent PTS. In addition, some patients are likely to have difficulty in tolerating aggressive intervention—for example, patients with significant respiratory compromise who cannot lie prone and safely receive sedation for the procedure.

Patients’ Personal Values and Preferences

For aggressive therapies, such as DVT thrombolysis, for which the benefits have not been conclusively established, it is important for the patient to receive a balanced discussion regarding the rationale, the intended benefits (and possible lack of benefits), the attendant risks and inconveniences, and treatment alternatives. Patients may arrive at different conclusions regarding their own suitability for aggressive therapy.

Conclusion

The long-term patient disability associated with DVT is quite substantial and should be routinely considered by treating physicians. Evidence-based methods of preventing late DVT sequelae, such as anticoagulant therapy and elastic compression stockings, should be routinely used. The potential for endovascular thrombolysis to dramatically improve long-term treatment outcomes for patients with proximal DVT appears to be strong. Two multicenter RCTs are ongoing to determine which patients with proximal DVT should be treated in this manner.
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References


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