Thrombolytic Therapy for Acute Deep Vein Thrombosis and the Venous Registry

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Randomized clinical trials have defined anticoagulation with unfractionated or low molecular weight heparin followed by warfarin as standard therapy for acute deep venous thrombosis (DVT). Such treatment is highly effective in preventing recurrent venous thromboembolism, but provides imperfect protection against development of the postthrombotic syndrome. By restoring venous patency and preserving valvular function, catheter-directed thrombolytic therapy potentially affords an improved long-term outcome in selected patients with DVT. A national venous registry, compiling data from 63 participating centers, was established to collect data regarding the technical details of the procedure and early outcome. Data from the registry have established the optimal technical approach and patient population. An antegrade catheter-directed approach using urokinase in patients with acute iliofemoral DVT of less than 10 days duration and no prior history of DVT may achieve complete lysis in 65% of patients. Analysis of the clinical outcome is pending, but early results suggest improved valve function and fewer symptoms at 1 year in patients with complete thrombolysis. These promising data should serve as the basis for future randomized trials of catheter-directed thrombolysis for the treatment of acute DVT.
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The treatment of acute deep venous thrombosis (DVT) is directed toward preventing pulmonary embolism and minimizing the long-term manifestations of the postthrombotic syndrome. Pulmonary embolism, with its attendant mortality, is the most devastating complication of acute DVT. Inadequate treatment of proximal venous thrombosis is associated with a 20%–50% risk of clinically significant recurrent thromboembolism.[1] However, postthrombotic sequelae, including pain, edema, hyperpigmentation, and ulcer-

ation may be associated with substantially greater socioeconomic morbidity. Some postthrombotic manifestations will develop in up to two thirds of patients, while 7% to 23% will have severe manifestations, and 4% to 6% will develop an ulcer.[2-6] Severe chronic venous disease has been estimated to be present in 5% of the U.S. population,[7] corresponding to a prevalence of between 6 million and 7 million individuals with stasis changes and 400,000 to 500,000 with leg ulcers. The medical cost associated with these postthrombotic complications has been estimated to account for 40% of the total cost of acute DVT.[8]

The treatment of acute deep venous thrombosis has been defined by randomized clinical trials that have relied on recurrent venous thromboembolism and bleeding as clinical endpoints. Standard anticoagulation with unfractionated or low molecular weight heparin followed by warfarin for at least 3–6 months is effective in preventing pulmonary embolism, with only 5% of patients sustaining a recurrent thromboembolic event during treatment.[9,10] Unfortunately, prevention of the postthrombotic syndrome has been all but ignored by most clinical trials. Adjunctive treatments such as compression stockings have been shown to reduce the incidence of the postthrombotic syndrome by 50%,[11] and data from natural history studies suggest that adequate anticoagulation may be important in reducing the deleterious effect of recurrent thrombotic events.[12,13] However, no major randomized trials of acute treatment have included the postthrombotic syndrome as a primary endpoint.

Pathophysiology of the Postthrombotic Syndrome

Prevention of the postthrombotic syndrome requires some understanding of the underlying pathophysiology. Severe manifestations of the postthrombotic syndrome result from ambulatory venous hypertension, and the incidence of ulceration is linearly related to the venous pressure measured in a dorsal foot vein.[14] Ambulatory venous pressure, which reflects the global hemodynamics in the extremity, is determined by a number of factors, including valvular reflux and persistent venous obstruction, as well as, the anatomic distribution of these abnormalities. Postthrombotic symptoms are more closely correlated with a reduction in venous refilling time than with abnormalities of venous outflow, suggesting that valvular incompetence is the most important determinant of the postthrombotic syndrome.[15] However, extremities with skin changes and ulceration are more likely to have a combination of reflux and obstruction than either abnormality alone.[16,17] Not surprisingly, the highest ambulatory venous pressures also occur in limbs with both reflux and obstruction.[18,19]

Postthrombotic symptoms are more closely correlated with a reduction in venous refilling time than with abnormalities of venous outflow, suggesting that valvular incompetence is the most important determinant of the postthrombotic syndrome.

An understanding of the factors leading to the development of valvular incompetence, or reflux, may give some insight into its prevention. Valvular destruction is not a universal consequence of acute DVT. Only 33%–59% of initially thrombosed venous segments show ultrasound evidence of reflux 1 year later.[20] Valvular incompetence is at least partially determined by the rate of recanalization and recurrent thrombotic events. Segments developing reflux have been found to require 2.3 to 7.3 times longer for complete recanalization than segments in which valve function is preserved.[21] Venous segments that sustain a recurrent thrombotic event have also been shown to have a considerably higher incidence of valvular incompetence.[22] Consistent with these observations, Prandoni has noted a six-fold increase in risk of the postthrombotic syndrome among patients with recurrent thrombosis.[4]

While anticoagulation may be effective in preventing recurrent thrombosis, it does little to promote rapid recanalization.

These observations have important implications for the treatment of acute DVT, since measures that promote rapid and complete recanalization and prevent recurrent thrombosis may decrease the incidence of the postthrombotic syndrome. While anticoagulation may be effective in preventing recurrent thrombosis, it does little to promote rapid recanalization. Less than 20% of patients treated with heparin alone will show any evidence of early thrombolysis by venography[18] and only 24% of iliofemoral thrombi treated with anticoagulation will be patent at 1 year.[23] Thrombolytic therapy may theoretically prevent the postthrom-

botic syndrome by promoting rapid recanalization, thereby preserving valve function and avoiding the detrimental consequences of persistent venous obstruction.

Thrombolytic Therapy for Acute DVT

Virtually all clinical trials evaluating thrombolytic therapy for acute DVT have used systemically administered agents. Although at least some degree of lysis has been reported in 53%–70% of patients treated with thrombolysis, no single study has had sufficient power to prove its efficacy in comparison with standard anticoagulation. However, meta-analyses of appropriately randomized trials have suggested that systemically administered streptokinase is 3.7 times more likely[24] and recombinant tissue plasminogen activator (rt-PA) 7 times more likely[25] to produce at least some degree of thrombolysis than is unfractionated heparin alone. Similarly, in reviewing pooled data from 13 studies, Comerota and Aldridge[18] found that complete, partial, and no thrombolysis were reported in 4%, 14%, and 82% of patients treated with heparin compared with 45%, 37%, and 18% of patients treated with thrombolytic agents. Late venous patency is also better among patients treated with thrombolytic agents. While anticoagulation alone reduced the number of occluded segments at 1 year by 37%, a variety of essentially systemic thrombolytic regimens reduced this number by 48% to 58%.[26] There is thus little doubt that thrombolytic agents are effective in removing thrombi from the deep venous system.

Unfortunately, the risk of complications and lack of rigorous long-term follow-up have limited the use of thrombolysis for acute DVT. Potential complications of thrombolytic therapy include bleeding and pulmonary embolism. In a meta-analysis of five randomized trials, Lensing and Hirsh[27] reported major bleeding events in 13.2% of patients treated with systemic streptokinase or tissue plasminogen activator compared with 3.5% of patients treated with heparin. Systemic thrombolysis with rt-PA resulted in one major hemorrhage for every 15 patients treated.[25] In contrast to the hemorrhagic risk of these agents, the incidence of clinically significant pulmonary embolism is quite low.

Systemically administered thrombolytic agents are associated with long infusion times, a high incidence of partial thrombolysis, and a significant rate of bleeding complications.

In addition, in the absence of data demonstrating the clinical benefit of recanalization, the degree of recanalization has not been widely accepted as a valid endpoint in thrombolytic therapy trials. However, the available data, although often imperfect, do at least suggest some long-term benefit from thrombolytic therapy. Of studies providing follow-up of patients treated with systemically administered thrombolytic agents, seven have suggested successful preservation of valve function,[26,28-33] one report was negative,[34] and one was inconclusive.[35] Of these studies, the most recent has also suggested less severe postthrombotic manifestations 1 year after treatment with systemic thrombolysis.[26] Ambulatory venous pressure was also reported to be lower among those treated with systemic thrombolysis than among those treated with anticoagulants alone or with thrombolytics administered via a pedal vein.

Unfortunately, systemically administered thrombolytic agents operate only at the margins of the thrombus and are quite inefficient. They are correspondingly associated with long infusion times, a high incidence of partial thrombolysis, and a significant rate of bleeding complications. Forster and Wells[25] concluded that four patients needed to be treated with systemic rt-PA to achieve greater than 50% lysis in one patient. These findings have led to consideration of infusion of thrombolytic agents directly into the thrombus as an alternative to systemic lysis. This approach is attractive because, as with the use of thrombolytic agents in the arterial system, a high concentration of the drug can be delivered directly into the thrombus, prolonged systemic infusions can be avoided, and direct intravenous access allows adjunctive procedures such as balloon angioplasty to be performed. Although streptokinase and rt-PA have also been used, urokinase has been the most widely used agent for catheter-directed thrombolysis.[36]

Measures that promote rapid and complete recanalization and prevent recurrent thrombosis may decrease the incidence of the postthrombotic syndrome.

Such techniques require that a multiside-hole catheter or infusion wire be embedded within the thrombus and must be differentiated from "loco-regional" approaches, in which the thrombolytic agent is

Table 1
Venous Access Sites for Catheter-Directed Thrombolysis

Site	Urokinase Infusions (N = 312)
Popliteal vein	131 (42%)
Common femoral vein	86 (28%)
Internal jugular vein	66 (21%)
Pedal vein (systemic)	60 (19%)
Other	36 (12%)

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administered via a pedal vein.[25,26,37] Such regional approaches suffer the same disadvantages as systemic thrombolysis. Furthermore, these approaches have frequently used lower thrombolytic doses and the results have often been worse than for systemically administered agents.[26]

Semba and Dake[38] were among the first to report the results of catheter-directed thrombolysis for acute DVT. Urokinase at a dose of 150,000–200,000 IU/hr was administered directly into the thrombus through either a dual-lumen multiside-hole catheter or a coaxial system with an infusion wire. Among 25 limbs in which the occlusion was successfully crossed, complete lysis was achieved in 72%, partial lysis in 20%, and no significant lysis in 8%. As importantly, 18 (72%) of these limbs were found to have an underlying venous stenosis, 16 of which were treated by angioplasty with (14) or without (2) a stent. Other series have reported a total of 263 patients treated with a catheter-directed approach.[36] The average duration of thrombolytic infusion in these patients was 51 hours, and complications included bleeding requiring transfusion in 4.9%, pulmonary embolism in 0.8%, and death in 0.4% of patients.

The Venous Registry

To better define the role of catheter-directed thrombolysis in the treatment of DVT, a multicenter registry was established to prospectively compile technical and follow-up data regarding the procedure. Enrollment criteria were based upon a consensus of participants and included patients with both acute (≤ 10 days) and chronic (> 10 days) symptoms and those with iliofemoral and femoropopliteal DVT. Patients with isolated calf vein thrombosis; thrombosis following surgical thrombectomy; and contraindications to the use of contrast media, anticoagulants, or thrombolytic agents were specifically excluded from enrollment. Percent thrombolysis was determined venographically, scoring seven proximal venous segments according to the Society for Vascular Surgery/North American Chapter of the International Society for Cardiovascular Surgery reporting standards in venous disease.[39] Patients were followed clinically and with venous duplex ultrasonography at hospital discharge and at intervals of 4 to 6 weeks, 3 months, 6 months, and 12 months. Residual

Table 2
Venous Registry Demographics

Patients (N = 287)	
Age, mean, y	47.5
Sex	
Female	150 (52%)
Male	137 (48%)
Limb	
Right	61%
Left	39%
Previous DVT history	90 (31%)
Symptoms	
Acute (≤ 10 days)	188 (66%)
Chronic (> 10 days)	45 (16%)
Acute on chronic	54 (19%)
Thrombus location (N = 312 infusions)	
Inferior vena cava	2 (< 1%)
Isolated iliac	10 (3%)
Iliofemoral	221 (71%)
Femoropopliteal	79 (25%)

DVT, deep venous thrombosis.

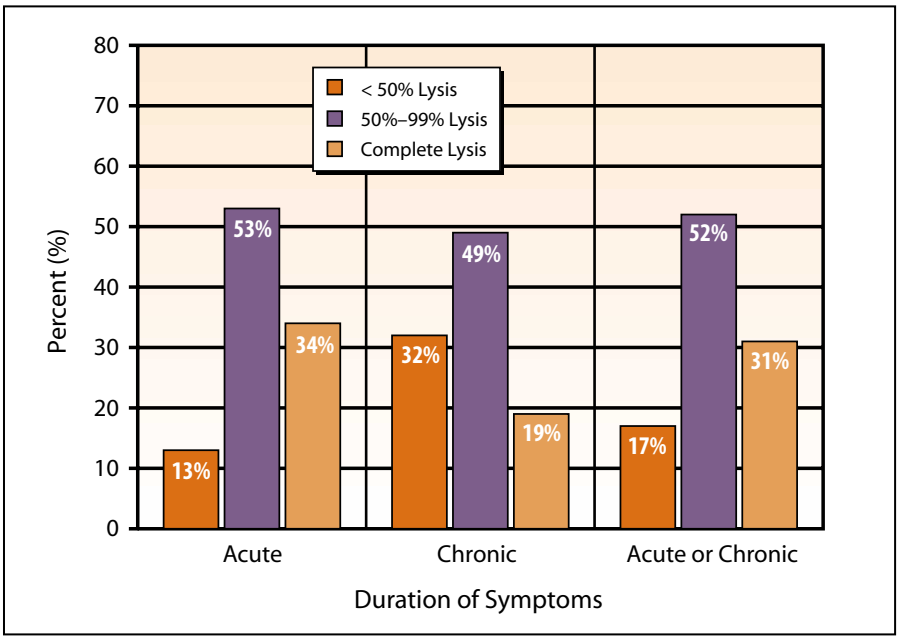

Figure 1. *Degree of thrombolysis according to duration of symptoms among venous registry patients undergoing catheter-directed lysis (N = 312 infusions). Percent thrombolysis was calculated as (Initial thrombus score − Final thrombus score / Initial thrombus score × 100) and categorized as complete, 50%–99%, or < 50%. Differences in the frequencies of complete and < 50% lysis among those with acute and chronic symptoms are statistically significant (P < .01). Data from Mewissen et al.*[40]

venous thrombosis was defined by standard ultrasound criteria, whereas valvular incompetence was assessed using standing distal cuff deflation. The early technical results from the Venous Registry have been previously reported.[40]

Although the use of urokinase via a catheter-directed approach was mandated by the protocol, access sites (Table 1) and the need for adjunctive procedures such as balloon angioplasty or stent deployment were determined by the physicians performing the procedures. With experience, an antegrade approach using ultrasound-guided puncture of the popliteal vein for placement of a 5-French sheath became the preferred method. Thrombolytic infusion was instituted with either a coaxial catheter and infusion wire or multiside-hole system and continued until lytic stagnation on serial venograms 12 hours apart. Treatment averaged 7.8 million IU of urokinase infused over 53.4 hours. Notably, systemic pedal vein infusions were associated with significantly longer infusion times and higher lytic doses.

Between January 1995 and December 1996, initial data were submitted for 473 patients undergoing catheter-directed thrombolysis at 63 institutions. Adequate data were submitted for an assessment of the technical results in 287 patients undergoing 312 lytic infusions in 303 limbs. The demographics of these patients are shown in Table 2. Complete lysis was achieved in 31% of infusions; 50%–99% lysis in 52%; and less than 50% lysis in 17%. Although these results are not substantially different from those reported for systemic thrombolysis of acute DVT,[41] it is critical to remember that the Venous Registry included both acute and chronic venous disease. The degree of thrombolysis was significantly related to the duration of symptoms and a history of DVT, whereas early patency was related to thrombus location. Complete lysis was achieved in 36% of limbs without a previous thrombosis compared with only 20% of those with a DVT history. Similarly, complete lysis was more common in limbs with acute symptoms than in limbs with chronic symptoms, while those with acute on chronic symptoms showed results similar to those with acute symptoms alone (Figure 1). Patency at 1 year was related to both the degree of initial thrombolysis and the anatomic location of the thrombus. Seventy-five percent of limbs with complete lysis remained patent at 1 year, whereas only 32% of limbs with less than 50% lysis were patent. Although the initial degree of thrombolysis was independent of thrombus location, 1-year patency was significantly better for iliofemoral thrombosis (64%) than for femoropopliteal thrombosis (47%).

Major and minor bleeding complications occurred in 11% and 16% of patients, respectively. The largest category of bleeding complications was related to the access site (Figure 2). Intracranial bleeding occurred in 2 (0.4%) patients, whereas 6 (1%) patients sustained a pulmonary embolism. One patient each died from an intracranial hemorrhage and a pulmonary embolism for an overall mortality rate of 0.4%.

Despite the efficacy of catheter-directed thrombolysis in removing thrombus, the goal of such therapy is to reduce the incidence of the postthrombotic syndrome by preserving valvular function and eliminating residual venous obstruction. One-year follow-up data regarding symptoms, residual venous obstruction, and valvular incompetence suggest that complete lysis does minimize postthrombotic symptoms and

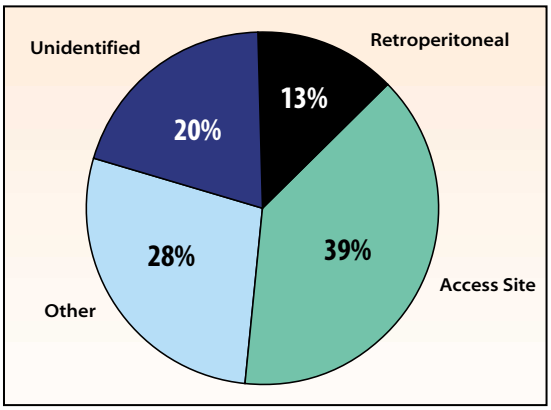

Figure 2. *Major bleeding complications among patients enrolled in the venous registry (n = 473). Bleeding requiring transfusion occurred in 54 (11%) patients. Bleeding designated as "other" includes musculoskeletal, gastrointestinal, or genitourinary bleeding. Data from Mewissen et al.*[40]

their surrogate hemodynamic markers. Complete analysis of these data is currently awaiting publication. However, successful lysis has been correlated with improved health-related quality of life in these patients; patients classified as lytic failures have outcomes similar to those of patients treated with heparin alone.[42]

The Importance of the Venous Registry

Despite the promise of these data, the Venous Registry was not a randomized clinical trial and lacked a control group treated with standard anticoagulation. Therefore, these data cannot establish a new standard of care for the treatment of acute DVT. The data are, however, very important in defining how such therapy should be administered and identifying those patients most likely to benefit from catheter-directed thrombolytic therapy. Such considerations are very important in the design of future randomized trials. Forster and Wells[25] have noted that inclusion of older thrombi as well as older and higher-risk patients will tend to bias studies against thrombolytic therapy. The Venous Registry confirms that results for patients with chronic DVT are significantly worse than for patients with acute symptoms, particularly for femoropopliteal DVT. Future trials should be directed toward optimal patients, who include those with acute iliofemoral DVT, symptoms of less than 10 days duration, and no prior history of DVT. In this select population, complete lysis occurred in 65% of patients and the 1-year patency rate was 96%. The Venous Registry further establishes that systemic infusions via the pedal vein are inefficient and ineffective, as suggested by randomized trials.[25,26] An ultrasound-guided antegrade approach via the popliteal vein is the preferred access. The Registry further establishes the safety and efficacy of urokinase when used for catheter-directed thrombolysis. The relevance of this data to other thrombolytic agents is unknown. Pulmonary embolism occurred in only 1% of patients, and routine inferior vena cava filtration is not warranted.

Data from the Venous Registry also lends further support to the use of catheter-directed thrombolysis for phlegmasia cerulea dolens. This condition, which may culminate in venous gangrene and limb loss in 12%–50% of patients, results when extensive iliofemoral venous occlusion leads to massive fluid sequestration, increased interstitial pressure, decreased capillary perfusion, and ultimately ischemia.[43] The diagnosis is suggested by severe edema in a cyanotic, painful lower extremity. Although initial treatment with heparin is required to prevent propagation and preserve collaterals, thrombectomy was historically the only means available to treat tissue ischemia refractory to anticoagulation. However, several case reports[43-45] have established the efficacy of catheter-directed thrombolysis in restoring venous outflow and arresting tissue ischemia. The Registry extends this evidence with 26 such patients treated with catheter-directed thrombolysis.

Finally, data from the Venous Registry give new insight into the pathophysiology of iliofemoral venous thrombosis. Underlying stenoses or short-segment venous occlusions requiring metallic stents were uncovered by thrombolysis in one third of the registry limbs, 94% of which were in the iliac segment and 71% of which were in the left limb. Such lesions are frequently related to the May-Thurner or Cockett syndrome, arising from compression of the left iliac vein by the overlying right common iliac artery.[46] The importance of these lesions has been unappreciated, as they usually thrombose in the setting of other recognized risk factors such as hospitalization, surgery, or pregnancy.[46] Treatment of such lesions has a statistically significant, beneficial effect on 1-year patency, with 74% of stented limbs maintaining patency compared with 53% of limbs without stents. Other investigators have similarly used venous stents in approximately one third of patients undergoing thrombolysis.[36] Small series of iliac stents for acute DVT have demonstrated patency rates of 83%–93% at 1–2 years.[47,48] Although others[48] have reported acceptable results for infrainguinal stents, the Venous Registry found that four of five

infrainguinal stents thrombosed early after implantation.

Conclusions

The safety and efficacy of anticoagulation with intravenous unfractionated heparin or subcutaneous low molecular weight heparin followed by warfarin for the treatment of acute DVT have been well validated by randomized clinical trials. Less than 5% of patients treated with appropriate anticoagulation will sustain a recurrent thromboembolic event. However, anticoagulation is substantially less efficacious in preventing the postthrombotic syndrome. The use of thrombolytic agents to restore venous patency and preserve valvular function is an attractive adjunct to anticoagulation in selected patients. Data from the Venous Registry suggest that optimal results are achieved when an antegrade catheter-directed approach is used in patients with acute iliofemoral DVT of less than 10 days duration and no prior history of DVT. Although adjunctive measures, such as stenting residual venous lesions, clearly improve the results, the role of other approaches such as the use of mechanical thrombectomy devices requires further definition. Early experience with these devices has not been uniformly favorable.[48] Clinical outcome studies from the Venous Registry are pending, although smaller series have reported long-term symptom resolution in 78% of those treated with catheter-directed thrombolysis compared with only 30% of those treated with standard anticoagulation.[23] Although the design of the Registry has many limitations, the results clearly warrant randomized clinical trials comparing catheter-directed thrombolysis with standard anticoagulation in at least a select group of patients. For the present, the American College of Chest Physicians' consensus guidelines suggest that "the use of thrombolytic agents in the treatment of venous thromboembolism continues to be highly individualized and clinicians should have some latitude in using these agents. In general, patients with … massive iliofemoral thrombosis, who are at low risk to bleed, are the most appropriate candidates."[49] ■

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Main Points

- Randomized clinical trials have defined anticoagulation with unfractionated or low molecular weight heparin followed by warfarin as standard therapy for acute deep venous thrombosis (DVT).
- While this therapy effectively prevents recurrent venous thromboembolism, it is less effective at preventing the post-thrombotic syndrome, which is associated with substantial socioeconomic morbidity.
- Thrombolytic therapy may theoretically prevent the postthrombotic syndrome by promoting rapid recanalization, thereby preserving valve function and avoiding the detrimental consequences of persistent venous obstruction.
- The Venous Registry has compiled data regarding catheter-directed thrombolysis from 63 centers using urokinase.
- Findings from the registry suggest that patients with acute iliofemoral DVT of less than 10 days duration and no prior history of DVT are most likely to benefit from thrombolytic treatment. An antegrade catheter-directed approach using urokinase provides optimal technical results.

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