Acute Deep Vein Thrombosis (DVT): Evolving Treatment Strategies and Endovascular Therapy

Patrick Conklin, MD, Gregory M. Soares, MD, Gregory J. Dubel, MD, Sun H. Ahn, MD, and Timothy P. Murphy, MD

Deep vein thrombosis (DVT) is a manifestation of **venous thromboembolic (VTE)** disease. VTE encompasses both DVT **and pulmonary embolism (PE).** DVT itself refers to thrombus which has formed in the deep veins of the body which usually parallel an artery of the same or similar name and follow a deep course within an extremity. Formation of thrombus in these vessels frequently results in local and systemic complications leading to significant morbidity and mortality. The Acting Surgeon General Steven K. Galson, MD, MPH, recently released a call to action to reduce the number of cases of DVT and pulmonary embolism in the United States, stressing that collectively DVT and PE contribute to at least 100,000 deaths each year.[1]

An often overlooked yet significant complication of DVT is the **post-thrombotic syndrome** (**PTS** – formerly post-phlebitic syndrome). PTS is characterized by chronic pain and swelling in the affected limb. PTS patients are considered a subset of those with chronic venous insufficiency. They are prone to the skin changes of chronic venous stasis disease, namely hyperpigmentation, lipodermatosclerosis, and atrophie blanche. In the most advanced cases, venous stasis ulcers may occur. Overall, PTS leads to lower quality of life.[2,3]

This article focuses on the epidemiology and treatment of DVT and PTS, including the most recently updated management guidelines from the **American College of Chest Physicians** (**ACCP** 2008) and **the Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis** (**ATTRACT**) Trial. The goal is to enable the reader to understand the appropriate management of DVT and recognize the indications for more aggressive treatment of acute symptomatic DVT.

Epidemiology

Approximately 350,000 individuals are affected by DVT/PE each year in the United States. Many cases are not recognized and the actual number of cases could be twice as high.[1] Studies show that patients with PE demonstrate a 3 month all-cause mortality of 15% to 30%.[1,4,5] As many as 4% of patients with PE will progress to **chronic thromboembolic pulmonary hypertension** (**CTEPH**).[6] PTS will affect nearly 30% of individuals with DVT over a five-year period.[7] It is estimated that the annual direct cost in the United States for PTS is $200 million, with an indirect cost of 2 million lost work days annually due to leg ulcers.[8]

Ultrasound studies have shown that patients with symptomatic venous thromboembolism are most likely to have DVT in the proximal deep veins of the legs; however, only 11% will have upper extremity clot and 15% will have isolated calf DVT.[9] There is general agreement that proximal or iliofemoral distribution DVT is clinically significant and warrants treatment with anticoagulation and or more aggressive measures for severe cases; however, there is with less uniform agreement on the management of calf or infrageniculate DVT.[10] Furthermore, patients with an initial episode of symptomatic DVT are at high risk for recurrent episodes. In a study of 355 patients followed for 8 years after a symptomatic DVT, the cumulative incidence of recurrent VTE was 17.5% after 2 years, 24.6% after 5 years, and 30.3% after 8 years.[11] Recurrence rates are higher if there is residual thrombus in the vessel.[12] Recurrence, particularly of ipsilateral DVT, is a strong risk factor for PTS.[2,7] The cumulative incidence of PTS in these patients increased likewise from 22.8% at 2 years to 29.1% at 8 years.[7]

Risk Factors

There are many risk factors for the development of VTE all of which remain rooted in Virchow's triad of hypercoaguability, stasis and endothelial injury. Hypercoaguability as an etiology for venous thrombosis requires investiga-

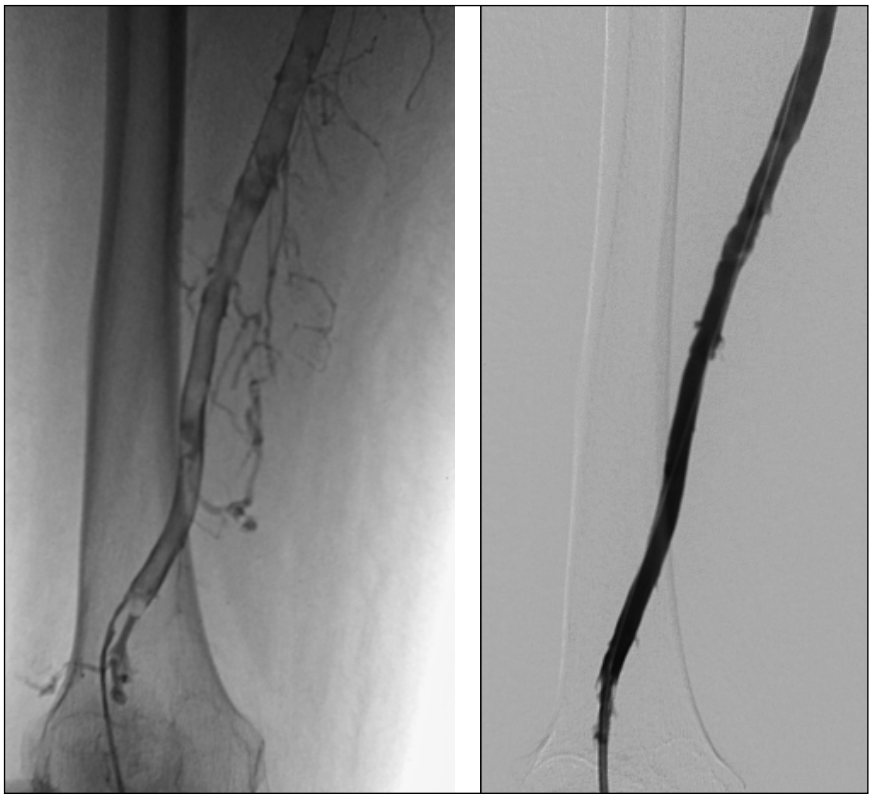

Figure 1: Femoral vein acute DVT pre (left) and post (right) PCDT. Post image reveals >95% thromboreduction.

tion of inherited or acquired thrombophilia. Of the numerous causes for an inherited thrombophilia, the factor V Leiden mutation is the most frequent. Less frequent genetically transmitted thrombophilias include Factor II G20210A mutation, protein C and S deficiencies, and hyperhomocysteinemia.[10] Commonly acquired hypercoaguable states include the presence of known or occult malignancy, recent trauma and other causes of decreased calf-muscle contraction or immobility. Prior DVT may be the greatest risk factor for DVT recurrence with a likelihood of approximately 30% at eight years.[7] The incidence of recurrent DVT is often due to a combination of all three components of Virchow's triad being present following an initial episode of VTE.

Adequacy of Current Treatment Strategies

Aside from the risk of mortality due to PE, early DVT morbidity is directly related to the presence of thrombus. Symptoms of acute proximal DVT include pain and swelling in the extremity and a decreased ability to ambulate. Late complications are primarily related to the development of PTS. The underlying mechanism for long-term venous insufficiency related to PTS involves an inflammatory response followed by recanalization of the acute thrombus, which in turn can causes valvular failure and reflux in the vein.[8] Reflux leads to venous hypertension and may result in edema, venous stasis skin changes and in severe cases to ulceration.[2,6] Once present, PTS can lead to significant limitations in activity, with significant impairment of quality of life. Unfortunately, the treatment options for established PTS are extremely limited, largely palliative and costly.[6]

Since DVT results in both marked early symptomatology and risk of long-term adverse sequelae, comprehensive treatment of acute DVT should address three key therapeutic goals:

1. Decrease risk of mortality due to PE.

2. Decrease early morbidity due to DVT. This may be accomplished through the use of compression, early ambulation, and thromboreduction. Thromboreduction refers to a reduction in thrombus burden by mechanical or pharmacological means.[13]

3. Decrease late morbidity through thromboreduction and valve preservation.[14]

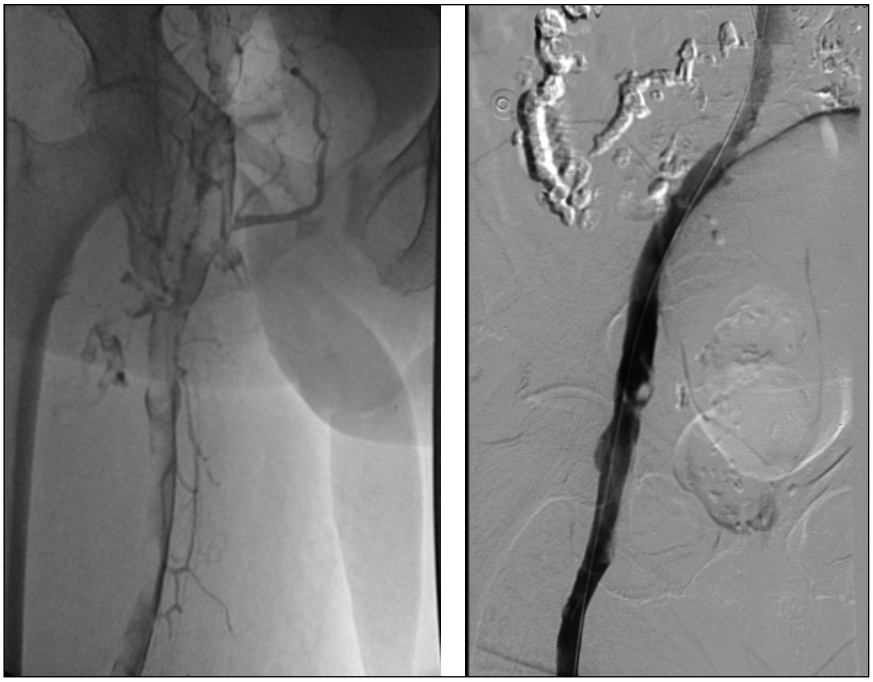

Figure 2: Occlusive common femoral vein DVT (left) and post PCDT (right). Note antegrade flow and lack of collateral veins post PCDT.

Widely accepted and well supported approaches to the prevention of PE through early, effective anticoagulation exist.[15] Less uniformly practiced, but effective guidelines for early graded compression and ambulation have recently become available.[15] Institution of these easily employed means of symptom relief can quickly improve the overall health of those with acute DVT who are also adequately protected from PE. Finally, natural history studies of acute DVT and randomized trial data of the management of iliofemoral DVT offer important observations that the late morbidity of PTS can be prevented or at least mitigated. It is likely that the key to decreasing late sequelae of DVT is valve preservation through early rapid clot removal.[16, 17]

Evolving Treatment Strategies

The treatment of acute DVT remains controversial. The American College of Chest Physicians recommends intravenous anticoagulation as bridge therapy to oral warfarin, along with elevation while at rest, compression of affected limb and early ambulation.[15] Though effective for prevention of clinically significant PE, anticoagulation alone is ineffective for clot removal in the majority of cases, with complete resolution of DVT accomplished in only 10% of patients.[18, 24] The clinical manifestation of anticoagulation's lack of effectiveness for clot dissolution is prolonged acute symptomology of swelling and discomfort. Treatment with anticoagulation alone also does not prevent PTS.[19] Long term follow up data of patients with proximal DVT treated with heparin alone versus heparin and fibrinolysis have shown poorer symptom improvement and worse restoration of venous patency in the heparin alone group.[24]

Finally, Konstantinides and colleagues treated 256 patients who had acute pulmonary embolism with placebo plus heparin or t-PA plus heparin.[20] The incidence of in hospital death or clinical deterioration was significantly higher and the probability of event-free survival was significantly lower in the placebo plus heparin group. In fact, treatment with placebo plus heparin was associated with almost three times the risk of death or treatment escalation compared with t-PA plus heparin. No fatal intracranial hemorrhage occurred in patients who received t-PA plus heparin in that study.

Therefore, heparin treatment alone may carry a higher risk of death or treatment escalation and also falls short in achieving an important long-term goals of DVT management; the minimization of risk of PTS. [20, 21]

Given the fact that anticoagulation alone may be inadequate for acute symptom reduction as well as for PTS prevention, the benefit of thromboreduction has been evaluated. Overall, thromboreduction by surgical thrombectomy has proven beneficial versus anticoagulation alone in randomized trials.[22,23] Unfortunately, surgical thrombectomy is relatively expensive and morbid.[22] Similarly, intravenous systemic thrombolysis (pharmacologic dissolution of thrombus) has shown significant benefit versus anticoagulation alone.[24] Thrombolysis has been shown effective in preservation of valve function, and overall PTS risk may be reduced with thrombolysis.[22,23,25] Systemic thrombolysis for DVT has not been embraced due to fears of significant hemorrhagic complications related to the large doses of thrombolytics required. Studies have suggested a 2-10% risk of major hemorrhagic complication rate when administering systemic anticoagulation.[26] By comparison, **catheter directed thrombolysis (CDT)** can be performed with a lower dose of thrombolytic infused over a longer period of time. The benefits of CDT include improved physical functioning, decreased PTS symptoms, less valvular reflux at 6 months and improved 5-year symptom resolution in a randomized controlled trial.[16,24,27] Significant disadvantages to CDT persist and include long infusions times (48-72 hrs), a necessary ICU stay and the risk for significant bleeding at 11.4% and intracranial hemorrhage at 0.4%.[28] Though CDT offers a promising alternative to surgical thrombectomy and systemic thrombolysis, these drawbacks have tempered wholesale adoption of CDT for thromboreduction.

Contemporary Thromboreduction: Potential For a Paradigm Shift

Pharmacomechanical **Catheter Directed Thrombolysis (PCDT)** may offer a promising solution to the limitations of CDT, systemic thrombolysis and surgical thrombectomy. PCDT combines low-dose thrombolysis with a mechanical device that is placed percutaneously using image guidance via a 2 to 3 millimeter incision to improve and speed thromboreduction. (Figures 1 and 2) The benefits include a decreased level of invasiveness compared to open surgery, as well as, a decreased infusion time and dose of thrombolytic compared with traditional CDT. Moreover, PCDT eliminates the need for a routine ICU stay since it is usually achieved in a single treatment session. The drawbacks include longer initial procedure time and expense than CDT due primarily to the cost of the thrombectomy device. However, since the number of procedures is reduced and the need for post and intraprocedural ICU level monitoring is eliminated, the overall cost-effectiveness of this approach may be greater than that of traditional CDT. Furthermore, any cost-effectiveness analysis must take into consideration both the acute episode of care as well as the potential savings in terms of reduced long-term PTS. This strategy clearly requires further study. Although case series and non-randomized data suggest the possibility of long-term reductions in PTS, there remains a lack of randomized controlled trial data confirming the procedure's efficacy for PTS elimination. To address this paucity of data, the NIH/NHLBI has sponsored the **ATTRACT trial (Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis).** ATTRACT is a Phase III, open-label, multicenter randomized controlled trial which will compare PCDT plus standard anticoagulation versus standard anticoagulation alone. The study seeks to enroll at least 692 patients with proximal DVT in 28 centers and will be multidisciplinary involving Interventionalists, Internal medicine specialists and Emergency room physicians in the US and here in RI (patients may be enrolled at Rhode Island Hospital as well as the Miriam Hospital). The outcomes endpoints include PTS, quality of life, symptom relief, cost, and safety, over a two year follow-up period.

The ATTRACT trial will enroll patients at both Miriam and RI Hospitals

The results of the ATTRACT trial will allow an evidence based appraisal of appropriate indications for PCDT for acute symptomatic DVT. Endovascular intervention and PCDT are currently indicated in "urgent" cases when there is imminent risk to life or limb loss. Typically this involves either extensive inferior vena cava clot with risk to an internal organ's venous drainage and/or phlegmasia cerulea dolens resulting in venous ischemia.[14] The role for PCDT as a first line therapy in the "non-urgent" acute DVT patient is evolving. PCDT has the potential to improve quality of life and reduce long term complications in a minimally invasive fashion, though currently it is often viewed as a 2nd line "salvage" for clinical or anatomic progression while on anticoagulation therapy. The ACCP 2008 guidelines recommend that in addition to appropriate early anticoagulation, DVT patients should ambulate as tolerated and wear 30-40mm Hg compression hose. The College also recommends thrombolysis or CDT in selected patients with extensive acute proximal DVT who have a low hemorrhagic risk, in order to reduce acute symptoms and PTS if the expertise and resources are available.[15]

Summary

DVT and PE contribute to at least 100,000 deaths each year. In addition, 4% of patients with PE will progress to CTEPH[6] and PTS will affect nearly 30%.[11] Anticoagulation alone appears inadequate to prevent PTS in many patients. Newer treatment strategies, includ-

To learn more about CDT and/or PCDT, go to www.sirweb.org.

To learn more about the ATTRACT trial, please contact the Vascular Disease Research Center at (401) 444-7625 or go to www.scvir.org/news/newsPDF/ATTRACT.pdf

ing PCDT, appear to offer the possibility of reducing the pain, suffering and expense of PTS especially in the most severe cases. The NIH/NHLBI sponsored the ATTRACT trial, which will compare PCDT plus standard anticoagulation versus standard anticoagulation alone in patients with proximal DVT. The ATTRACT trial will enroll patients at both Miriam and RI Hospitals and is expected to add significantly to the research in this area. When successfully completed, results from the trial may guide therapy in the years ahead.

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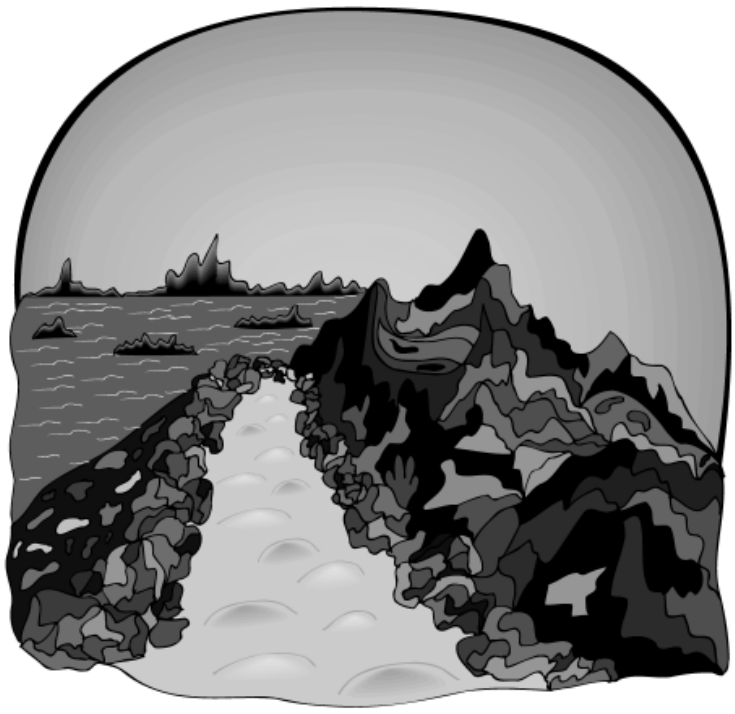

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