

Kicking the Can Down the Road: Why Recent Developments in DVT and PTS May Increase Cost of Care and Disease Burden in the Mid-21st Century

The benefits of rheolytic therapy with AngioJet™ ZelanteDVT™.

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For many years, our understanding of venous thromboembolism (VTE) was based mainly on studies of arterial thrombosis. Recent animal models of deep venous thrombosis (DVT) and basic science research have uncovered new details of the mechanisms specific to venous thrombosis. Clinical trials of new anticoagulants and recent epidemiologic studies improved our understanding of VTE recurrence. Still, only a small group of researchers is endeavoring to shed light on the transition from acute DVT to chronic venous disease (CVD).

CONTINUUM OF CHRONIC VENOUS DISEASE

The open vein hypothesis has led to improved techniques and broader utilization of thrombolysis and mechanical and pharmacomechanical thrombectomy in patients with acute iliofemoral venous thrombosis. With treatment of more patients, it became apparent that a significant proportion of acute DVTs are recurrent events, and although thrombolysis is successful in resolving acute thrombi, up to 80% of patients have chronic lesions in the affected veins.¹

Varicose veins are a known risk factor for DVT. A recent study showed that 66% of all patients with acute DVT have preexisting venous reflux.² This means that the majority of patients who clinically presented with acute venous thrombosis have either primary or secondary (post-thrombotic) preexisting CVD. This is not a new revelation; it is a well-known component of Virchow's triad—the damaged wall. However, it emphasizes an important aspect of the definition of CVD. CVD is defined based on the underlying pathology. For example, according to CEAP classification, a patient can have no clinical manifestations (symptoms or signs) but still have CVD provided there is identifiable venous obstruction or reflux. A patient with asymptomatic reflux in the superficial veins should

be classified as C0a, Ep, As, Pr, whereas a patient with asymptomatic iliac vein obstruction should be classified as C0a, Es, Ad, Po.

Because of the high prevalence of venous reflux and wall changes in DVT patients, it is unclear if the reflux or obstruction detected after a DVT episode is post-thrombotic or if it is a manifestation of preexisting CVD. To answer this question, one needs to know if this pathology was present before the acute event or at least at the time of DVT, because changes in unaffected acute thrombus veins cannot develop acutely. In routine clinical settings, this information is usually unavailable. However, in clinical research studies, it is easily obtainable by performing standard venous insufficiency ultrasonography at the time of enrollment; yet, none of the major trials has attempted to do this. Not knowing the pre-DVT condition makes it impossible to correctly assess the natural history of the disease post-DVT. The symptoms and signs observed in patients after an acute event may be new or preexisting. The severity of preexisting symptoms may increase, remain the same, or even decrease after an acute DVT. Without knowledge of pre-DVT status, all changes are noted as the result of DVT, and the treatment outcomes in patients with preexisting CVD are lumped together with those who had no preexisting venous disease.

Primary disease develops at a young age³ and remains subclinical for 20 to 30 years.^{4,5} An estimated 37% of patients with reflux and no clinical manifestations within 13 years develop clinical class CVD of C2 or higher.⁵ More than one-third of these patients progress to chronic venous insufficiency (CVI) in the following decade.⁶

It is estimated that at least half of all DVTs are asymptomatic. In some patients, the thrombus may spontaneously lyse with no visual damage to the venous wall and valves. In others, thrombus evolu-

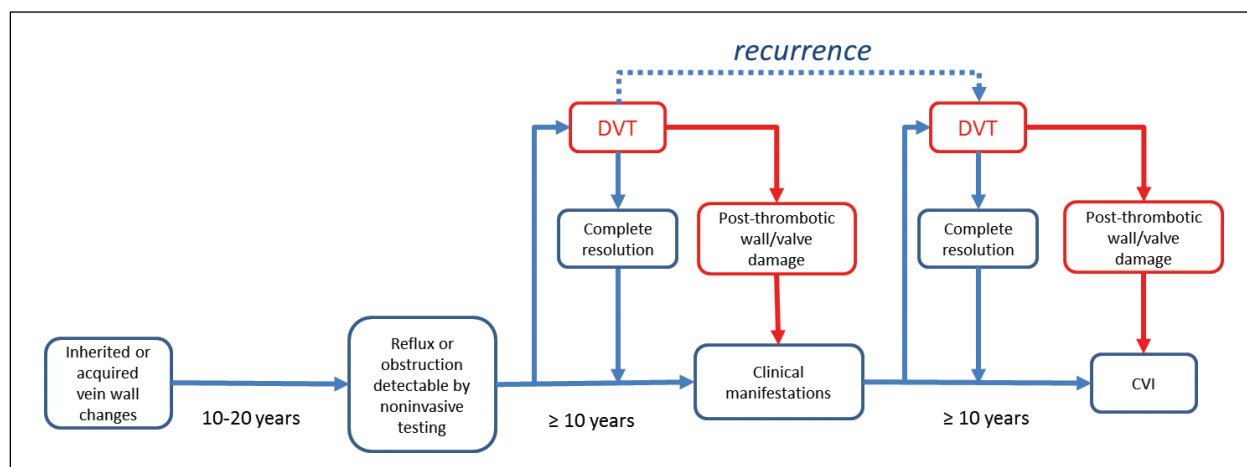


Figure 1. The continuum of chronic venous disease. The blue lines represent the expected natural history of the disease. The red lines represent acceleration of the natural history.

tion results in different degrees of venous obstruction, reflux, or both. In latter cases, an acute disease transitions to secondary CVD. The timing of subclinical stage of the secondary disease remains unknown, and unless a recurrent DVT or early clinical deterioration occurs, it remains in its latency for many years, similar to primary CVD. Thus, in the majority of the cases, acute DVT should be viewed as a continuum of CVD, not as an isolated event (Figure 1). In such patients, with complete lysis of the thrombus, they are simply returned to the previous stage of CVD and not to a healthy state. Newly developed post-thrombotic changes in these patients may accelerate the natural history of their CVD or the disease may remain latent for a long time. Considering these patients as healthy and not having venous disease is a mistake.

SHIFTS IN CLASSIFICATION AND TREATMENT

Pursuing simplification of trial logistics and cost savings, the majority of clinical trials evaluating CVD replaced the pathologic definition of secondary (post-thrombotic) CVD with a syndromic definition of post-thrombotic syndrome (PTS). Instead of defining disease by the underlying pathology, certain severity scores have been used, such as the Villalta scale, Ginsberg scale, and Venous Clinical Severity Score. As a result, a patient with manifestations that are not severe enough would be classified as not having PTS. Although such definition can be justified, using this approach, patients with fewer symptoms but severe underlying pathology (eg, iliac vein occlusion) are classified as having a perfect treatment outcome or that treatment was not necessary. If such an approach

were used in cancer, patients with early stages would be untreated, and treatment of symptoms would be considered a cure. Utilization of a severity score-based definition of disease in clinical trials has led to misclassification of patient outcomes. Although less symptomatic patients are misclassified as having been successfully treated, patients with preexisting CVD are misclassified as having poor outcomes even if their clinical manifestations were less severe but not below the threshold level.

Recent years are also marked by a shift toward ambulatory risk-based treatment of VTE. Current guidelines do not recommend immediate imaging and lean toward conservative therapy for the majority, if not all, DVT patients.⁷ Availability of new oral anticoagulants makes this trend practical and sustainable. Clinical trials that use the severity-based definition of CVD and disregarded the clinical and pathologic manifestations of CVD prior to the acute episode contribute to this trend by denying the benefits of potentially effective treatment modalities. As the incidence of VTE is increasing, the likely result of this trend will be an increased number of patients with iliofemoral DVT who will reach the severity threshold and require treatment much later in life. Many of these patients who are now in their 40s and 50s will reach their severity threshold 15 to 20 years from now, making treatment more difficult and likely more expensive. This trend is also likely to shift the cost of treatment from private insurance to Medicare.

SUMMARY

Clinical guideline and medical policy writers and contributors should recognize the deficiencies of these clinical trials, and clinical investigators should consider a

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more meaningful approach to defining post-thrombotic disease and clinical outcomes of treatment of acute venous thrombosis. ■

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