NATURAL HISTORY OF POSTTHROMBOTIC DISEASE: TRANSITION FROM ACUTE TO CHRONIC DISEASE

—Susan R. Kahn, MD, MSc, FRCPC, Montreal, Canada

Despite appropriate anticoagulant therapy, at least 1 of every 2 to 3 patients with acute symptomatic deep-vein thrombosis (DVT) of the lower extremities will develop postthrombotic disease (PTD), which is severe in 1 of 5 patients. The reported incidence of PTD after confirmed symptomatic venous thrombosis has varied between 20% and 100%. Rates have been higher in earlier studies than in reviews of later (last 20 years) studies, which could be due to improved diagnostic and therapeutic approaches to patients with DVT, but also to differences among studies in study design, definition of PTD, sample size, length of follow-up, and use of elastic compression stockings. PTD can develop, although less frequently, after an asymptomatic episode of postoperative DVT. According to the results of the most recent studies, most patients who develop PTS become symptomatic within 2 years of the acute episode of DVT, which is severe in 1 of 5 patients. These findings challenge the view that PTD requires many years to become apparent. Furthermore, a recent study showed that the degree of severity of persistent venous symptoms or signs as early as 1 month after DVT predicted PTD in a “dose-response” fashion during the subsequent 2 years.
It is believed that PTD occurs primarily as a consequence of venous hypertension. Venous hypertension leads to impaired venous return, reduced calf muscle perfusion, abnormal function of the microvasculature with increased tissue permeability, and consequently the characteristic clinical manifestations of PTD.^{2,20} DVT can lead to chronic venous hypertension by two main mechanisms, persistent (residual) venous obstruction, and valvular reflux, which may occur in combination.^{17,21-28} Of the two mechanisms, persistent venous obstruction may be more important than reflux, as based on two recent reports, lack of vein recanalization within 6 months after DVT alone or in combination with venous reflux significantly predicted the development of PTD, whereas the presence of venous reflux alone had only modest predictive value.^{16,29} Anticoagulant treatment of DVT prevents thrombus extension and pulmonary embolization, but does not lyse the acute clot. Follow-up studies of patients with DVT treated with anticoagulants have revealed that often only partial clearance of thrombus occurs.^{29-32} Damage to venous valves with subsequent reflux occurs often after DVT, likely via thrombus-induced activation of inflammation, fibrous scarring associated with acute and resolving thrombosis, or by venous dilation distal to the obstructed venous segment.^{33,36} Of interest, in two recent reports, increased levels of inflammatory cytokines or adhesion molecules were linked with the subsequent development of PTD.^{37,38} suggesting that inflammation at the time of acute DVT or residual inflammation after the acute episode of DVT may play a role in the transition from acute DVT to chronic PTD.

Clinical predictors of chronic PTD identifiable at the time of acute DVT include proximal DVT (especially common femoral or iliac veins), elevated body mass index, previous ipsilateral DVT and older age.^{2,39} One study has reported that patients with DVT with subtherapeutic international normalized ratios >50% of the time during the initial 3-month treatment with vitamin K antagonists had a threefold higher risk of developing PTS.^{40} Despite the common belief that patients with PTD have a uniformly poor prognosis, a few recent studies have suggested that prognosis might be better than previously reported, with more than 50% of patients remaining stable or even improving during long-term follow-up.^{3,41,42} However, currently, it is not possible to reliably predict the course of PTD in individual patients.

REFERENCES


CRITICAL ISSUES IN DEEP VEIN THROMBOSIS PREVENTION
—J.A. Caprini, MD, Chicago, Ill

Despite a great deal of literature including thousands of studies showing the value of thrombosis prophylaxis in medical and surgical patients, only 50% of the patients “at risk” for thromboembolism worldwide receive appropriate prophylaxis. Although there is a great fear of bleeding from prophylactic anticoagulants, large studies have shown that people die from thrombosis without prophylaxis rather than bleeding from anticoagulation. These statistics are astonishing given the fact that approximately 900,000 individuals suffer venous thromboembolism (VTE) in the United States yearly including 300,000 deaths. The majority of VTE events occur after discharge where prophylaxis is uncommon. The expense and inconvenience of out-of-hospital prophylaxis and lack of randomized control trials (RCTs) for most patient groups have limited this approach. A further problem is that health care providers have been taught to follow CHEST consensus guidelines that are a good source of RCT data but do not apply to many patients in clinical practice.

Part of the solution is to perform individual risk assessment for each patient and calculate a score that has been shown to correlate with the 30-day incidence of imaging-proven clinical VTE events. The score needs to be linked to a care pathway that is mandatory but includes a provision to opt out for valid contraindications.

The second approach is to expand and develop real world clinical databases and have a section in the CHEST guidelines document that analyzes and rates these databases. Furthermore, recommendations and clinical care plans based on these databases can be suggested. Mechanical methods of prophylaxis have to be critically analyzed and differences between stockings and pneumatic devices that have been identified in the literature need to be widely disseminated. There needs to be a method developed to track compliance with pneumatic devices and also standardize them. Head to head studies need to be done to see which of several approaches has the best efficacy (long leg, short leg, uniform compression, sequential compression, rapid inflation).

Finally, the most important need for the prophylaxis field is the development of safer but effective modalities. Research involving the P-selectin or its ligand, PSGL-1, (a leukocyte cellular adhesion molecule) is a critical issue because preliminary data have shown that these compounds have been shown to be effective in reducing inflammation and thrombus resolution comparable to the low molecular weight heparin in animals.

CRITICAL ISSUES

1. The use of individual risk assessment as a guide to thrombosis prophylaxis including risk-scoring tied to 30-day known thrombosis rates to identify which patients would benefit from out-of-hospital prophylaxis.

2. Development of studies designed to explore new anticoagulants including the value of P-selectin inhibition as a possible replacement for low molecular weight heparin for thrombosis prophylaxis.

3. Meta-analysis of clinical databases to develop clinical guidelines to supplement the CHEST consensus guide-