Emerging themes in the treatment of venous thromboembolism

Jeffrey I. Weitz

Departments of Medicine and Biochemistry and Medical Sciences, McMaster University and Henderson Research Centre, Hamilton, Ontario, Canada

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common disorder. The annual incidence of VTE among Caucasians of European origin is 1 to 2 per 1,000 up to the age of 40, and the incidence doubles each decade thereafter (1). There are racial differences in the incidence of VTE; those of African origin likely have a higher incidence of VTE, while the incidence is lower in Asians (1).

An already common disorder is likely to become even more common with the aging population and the rising prevalence of obesity. Thus, not only does the risk of VTE increase with age, but it also increases as a function of body mass index (BMI). A BMI over 30 increases the risk of VTE 2.5-fold (2), and obesity compounds the risk associated with other VTE risk factors, such as hormonal therapy (3). With over 40% of the North American population now overweight or obese (4), and many other parts of the world catching up, we are likely to soon see the impact of obesity on the incidence of VTE. As the burden of disease increases, it is timely to have a Theme Issue devoted to emerging concepts in the treatment of VTE.

How is the treatment of VTE evolving? This Theme Issue outlines advances in initial medical and interventional approaches to VTE treatment. Anticoagulant therapy remains the mainstay of therapy with prompt treatment essential to prevent fatal PE. Up to one-third of VTE patients present with symptomatic PE, which, if untreated, is associated with a fatality rate of 20% to 25% (5). In patients with DVT, the risk of thrombus extension, and subsequent PE, is increased if anticoagulant treatment is inadequate (6). With appropriate treatment, however, the risk of fatal PE in patients who present with PE or DVT is reduced to about 1.5% and 0.4%, respectively (7).

How can we optimize anticoagulation therapy yet streamline the care of VTE patients and keep healthcare costs down? As outlined in the paper by Becattini et al. (8), we have seen a shift from inpatient treatment with continuous intravenous infusion heparin, a drug that requires frequent monitoring to ensure that a therapeutic level of anticoagulation is achieved, to largely out-of-hospital management with subcutaneous low-molecular-weight heparin (LMWH) or fondaparinux, agents that need little or no monitoring. New long-acting parenteral anticoagulants that can be given subcutaneously on a once-weekly basis and/or rapidly acting oral anticoagulants have the potential to simplify treatment even further. Such agents are in advanced stages of clinical development (9).

Although anticoagulation therapy remains the mainstay of treatment of both DVT (Fig. 1) and PE (Fig. 2), careful patient assessment is needed to identify those who may benefit from more aggressive management. In patients with DVT, those with extensive iliofemoral involvement can present with severe leg pain and swelling. Because of the potential for damage to the valves in their deep veins, such patients also are at greatest risk for post-thrombotic syndrome. Catheter-directed fibrinolysis, with or without thrombus extraction, can restore blood flow in the proximal veins producing rapid improvement in leg symptoms. Although there is a risk of bleeding, technical refinements and the introduction of new devices have improved both the safety and efficacy of these invasive procedures (10). With promising short-term results (11), long-term studies are needed to determine whether the use of these procedures in conjunction with anticoagulation therapy reduces the risk of post-thrombotic syndrome compared with anticoagulation alone.

What about treatment of PE? Patients with massive PE and associated haemodynamic compromise require aggressive treatment (Fig. 2). Traditionally, these patients have been given systemic fibrinolytic therapy. Newer options include catheter-directed fibrinolysis and/or thrombus extraction. In addition, the results of surgical embolectomy have improved in centers that have established a rapid response team with specialized expertise in this procedure (12).

Recent data suggest that some patients with submassive PE may also benefit from systemic fibrinolytic therapy. Such patients exhibit echocardiographic evidence of right ventricular dysfunction and often have increased serum levels of troponin and brain natriuretic peptide (13). The emerging role of fibrinolysis and interventional therapy in acute VTE treatment is reviewed by Emmerich et al. (14) in this Theme Issue.

Correspondence to:
Dr. Jeffrey Weitz
Henderson Research Centre
711 Concession Street
Hamilton, Ontario
LBV 1C3
Tel.: +1 905 574 8550, Fax: +1 905 575 2646
E-mail: jweitz@thrombosis.hhscr.org
Patients with VTE who are bleeding, or are at high risk for bleeding, represent a special challenge. Those presenting with symptomatic calf DVT and offers that haemostasis is intact. Patients with extensive iliofemoral DVT should be considered for interventional therapy to restore blood flow in the proximal veins. Interventions include catheter-directed fibrinolysis with or without thrombus extraction. Anticoagulation therapy is contraindicated for DVT patients who present with major bleeding or are at high risk for bleeding. It is safe to withhold anticoagulant treatment in patients whose DVT is localized to the calf provided that serial compression ultrasound (CUS) examinations show no evidence of proximal extension. If calf thrombi extend into the proximal veins, an intracaval filter should be placed to prevent PE. Likewise, an intracaval filter also is also indicated for patients who present with proximal DVT and have a contraindication to anticoagulant therapy. Because a filter does not address the primary problem, anticoagulation treatment should be initiated in these patients once it is safe to do so.

What about long-term management of VTE? Here, again, there have been several advances. We now have better information on the optimal duration and intensity of warfarin therapy. There now is good evidence that a three-month course of anticoagulation therapy is adequate for patients whose VTE occurred in the setting of a well recognized and reversible risk factor, such as major surgery (15). In contrast, patients with unprovoked VTE require more extended treatment. If anticoagulation therapy is stopped after three, six or 24 months, these patients have a 10% risk of recurrence at one year, and a 30% risk of recurrence at five years. Recurrence rates are even higher if the patient has certain underlying congenital or acquired thrombophilic defects, such as antithrombin deficiency or antiphospholipid antibody syndrome. As discussed by White et al. (16) in this Theme Issue, race and gender also impact on the risk of recurrence. Although the risk of recurrence gradually declines over time, the optimal duration of treatment for these patients remains unclear. Current practice guidelines recommend a minimum of six months of treatment (17). The decision to continue treatment beyond six months must be individualized based on the balance between the risk of recurrent VTE if anticoagulant therapy is stopped and the risk of major bleeding with extended anticoagulant treatment. Patient preference also plays into this decision; some patients are anxious to stop warfarin, whereas others are willing to tolerate the inconvenience of long-term anticoagulant therapy to avoid recurrent VTE. An approach to assessing this
risk balance is provided by Schulman et al. (18) in this Theme Issue.

Not only is there more information on the optimal duration of treatment, there also is new information on the optimal intensity of warfarin therapy for extended VTE treatment. Thus, warfarin therapy that is dose-adjusted to achieve a target international normalized ratio (INR) of 2.0 to 3.0 is more effective than lower intensity warfarin regimen (target INR of 1.5 to 1.9) and does not increase the risk of major bleeding (19).

Where do we go from here? Simple tests, such as persistently elevated levels of D-dimer or residual abnormalities on compression ultrasonography, may help to identify subgroups of VTE patients at high risk for recurrence (20, 21). These patients could then be targeted for extended anticoagulation therapy. Studies are underway to explore these possibilities. As I outline in this Theme Issue (22), we also need oral anticoagulants that are easier to administer and, ideally, cause less bleeding than warfarin. New oral factor Xa or thrombin inhibitors that can be given in fixed doses without coagulation monitoring may provide the answer. Phase III clinical trials comparing these agents with warfarin for VTE treatment are ongoing. Finally, we also need more effective and convenient anticoagulants to treat VTE patients who are at high-risk for both recurrence and bleeding, such as those with underlying cancer. LMWH has proven to be more effective than warfarin in this patient population. Even with LMWH, however, there is a substantial risk of recurrence. Studies are needed to determine whether the new oral agents have a role in this setting.

Finally, Algue et al. (23) provide evidence suggesting that women with a history of VTE are prone to pre-eclampsia and pregnancy loss. These findings are not surprising because women with previous VTE are more likely to have underlying thrombophilic defects and complications of pregnancy are more common in women with thrombophilia (24). There is emerging evidence that prophylactic treatment with LMWH during pregnancy improves pregnancy outcome (25) and such treatment is now recommended, together with low-dose aspirin, in women with multiple early pregnancy losses or one or more late pregnancy loss (26). Prophylactic LMWH also is recommended in women with a past history of unprovoked VTE.

VTE remains a major healthcare burden despite the array of effective anticoagulants currently available for prophylaxis. The treatment of VTE is evolving and this theme issue will bring readers up to date. Stay tuned for further advances in upcoming issues of Thrombosis and Haemostasis.

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