

ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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Superficial Vein Thrombosis: New Perspectives and Observations From Recent Clinical Trials



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H&O What is superficial vein thrombosis, and how common is it?

BC *Superficial vein thrombosis* (SVT) is the preferred term to indicate thrombosis of any segment of the superficial vein system. SVT encompasses some older terms, such as *superficial phlebitis* (also called superficial thrombophlebitis); *suppurative thrombophlebitis* (also called septic thrombophlebitis); and *superficial femoral vein thrombosis* (a misnomer). SVT also encompasses many current terms, such as *infusion thrombophlebitis* (thrombosis caused by catheter insertion, venipuncture, or intravenous drug infusion); *varicose vein thrombosis* (thrombosis involving dilated varicose veins, usually in the subcutaneous tissue of the legs); *Mondor disease* (thrombophlebitis involving the breast veins or the dorsal penile vein); and *Trousseau syndrome* (migratory thrombophlebitis associated with malignancy).

This variety of terms reflects the multiple sites and causes of SVT. The lower limbs are the most common site of SVT, especially in association with varicose veins. Studies conducted in secondary and tertiary care centers have found that lower limb SVT, which typically is diagnosed in outpatients, appears to occur more frequently than deep vein thrombosis (DVT). In the STEPH (Incidence of Superficial Vein Thrombosis) study,¹ however, which was conducted in a community of 265,687 people in France, the yearly rate of lower limb SVT was 0.64 per 1000. This is lower than the estimated yearly rate of venous thromboembolism (VTE), which is 1 per 1000. In the STEPH study, SVT involved the long saphenous

vein in 50% to 60% of cases, the short saphenous vein in 11% to 15% of cases, and tributaries of the long and short saphenous veins in 30% to 40% of cases. SVT of the upper limbs can affect as many as 25% to 35% of hospitalized patients, in whom upper limb SVT is especially likely to develop. In rare cases, thrombosis can affect superficial veins in other parts of the body, such as the abdominal wall, thoracic wall, and neck.

H&O What causes SVT, and who is at risk?

BC Lower limb SVT and DVT have multiple risk factors in common, including advanced age, obesity, active cancer, previous thromboembolic episodes, pregnancy, the use of oral contraceptives or hormone replacement therapy, recent surgery, autoimmune disease (particularly Behçet disease and Buerger disease), and thrombophilia. However, unlike for DVT, varicose veins are the main risk factor for lower limb SVT; they are present in 80% to 90% of cases. Upper limb SVT is associated with the use of short peripheral venous catheters; it also may occur after peripheral vein infusion or venipuncture.

H&O How is SVT diagnosed?

BC No gold standard diagnostic tests are available for SVT. Inflammation of the vein walls and surrounding tissues causes most of the signs and symptoms of SVT, so that detection is relatively easy. For many years, clinical diagnosis alone—which was based solely on the observation of red, tender, palpable cords on the skin along

Table. Conditions That Mimic Superficial Vein Thrombosis

• Lymphangitis
• Chronic dermatitis
• Erysipelas
• Cellulitis
• Erythema nodosum
• Lyme disease
• Cutaneous manifestations of immunologic or rheumatologic disorders

segments of superficial veins—was considered adequate. Therefore, some do not consider confirmatory objective testing to be mandatory for an SVT diagnosis. Other conditions may mimic SVT, however, which is why compression ultrasound has become the objective test of choice for confirming clinically suspected SVT. In compression ultrasound, the lack of compressibility of a superficial vein segment and impairment of blood flow through the same venous segment can be applied to an SVT diagnosis, just as they can to a DVT diagnosis.

H&O Is SVT often misdiagnosed?

BC Many conditions can mimic SVT, especially skin conditions (Table). Therefore, clinical characteristics alone may not be enough to confirm a diagnosis of SVT. Furthermore, clinical assessment alone can underestimate the true extent of thrombosis, which may propagate from superficial to deep veins. Compression ultrasound allows diagnostic confirmation of SVT in the lower or upper limbs, along with evaluation of the extent of SVT and the exclusion of concomitant DVT.

H&O What are the potential complications of SVT?

BC SVT of the lower limbs is associated with a risk for thromboembolic complications because of the potential for extension into deep veins. SVT of the great and small saphenous veins can easily extend into the deep veins through the saphenofemoral junction (SFJ) and saphenopopliteal junction (SPJ), respectively, leading to the SVT complications of DVT and possibly pulmonary embolism (PE). Other superficial veins of the lower limbs, such as the tributaries of the great and small saphenous veins—especially in patients with varicose vein disease—also can be affected by thrombosis. However, the risk for extension into the deep veins through the perforating veins is lower in such cases.

An analysis of 2 observational studies, the POST

(Prospective Observational Superficial Thrombophlebitis) study and the OPTIMEV (Optimisation de l'Interrogatoire pour l'Estimation du Risque de Maladie Thromboembolique Veineuse) study, showed that 23% of patients presenting with isolated lower limb SVT also had DVT, with the DVT noncontiguous in half of the cases and occurring in the contralateral limb in 17%.² These findings indicate that compression ultrasound of both lower limbs should be mandatory in cases of suspected SVT. The analysis of the POST and OPTIMEV studies also examined the characteristics noted on ultrasound that were associated with an increased risk for DVT. Perforating vein involvement or an SVT less than 3 cm from the SFJ was found to increase the risk for DVT significantly. Close proximity of an SVT to the SFJ has long been accepted as a risk factor for complications, such as extension into the deep veins and PE.

H&O What is the standard treatment of patients with SVT?

BC No consensus has been reached at present regarding the optimal management of patients with symptomatic SVT that is isolated, meaning without concomitant DVT or PE. Because the clinical manifestations of SVT have a strong inflammatory component, empiric evidence has suggested that topical anti-inflammatory agents are sufficient for symptom relief. Variations in disease severity, however, lead to a greater or lesser thrombotic burden and differences in the risk for thromboembolic complications. SVT that is associated with a small thrombus (defined as <4-5 cm long on ultrasound) is considered minor, benign, and self-limiting and requires only symptomatic relief. However, SVT that is associated with a significant thrombus (>4-5 cm long) carries a higher risk for extension and requires a more aggressive treatment.³ Randomized clinical trials have included patients with SVT in the most frequent locations—that is, the long and short saphenous veins—because of the increased risk for extension into the deep vein system through the SFJ or SPJ. In general, SVT of the long saphenous vein in which the thrombus head is within 3 cm of the SFJ traditionally has been excluded from interventional studies because it is considered equivalent to a DVT owing to the high risk for progression (10%-70%).

A recent Cochrane Review on the treatment of SVT of the lower limbs led to inconclusive results because most of the randomized controlled trials were small and of poor quality.^{4,5} Only a minority of the studies compared treatment with placebo, and none evaluated the same treatment comparisons on the same study outcomes (which precluded meta-analysis). Treatments ranged from surgery to medication, which included nonsteroidal

anti-inflammatory drugs; oral agents (vasotonin, heparan sulfate, sulodexide, oxyphenbutazone, vitamin K antagonists, and oxerutins); intramuscular agents (dermatan sulfate); intravenous agents (enzyme therapy); and parenteral anticoagulants (eg, fondaparinux, low-molecular-weight heparin [LMWH], and unfractionated heparin).

According to the review, surgery, which has traditionally been an option for treating isolated lower limb SVT, may provide the dual benefits of relieving symptoms and reducing the incidence of PE by halting the progression of thrombi into the deep venous system. Interventions range from ligating the SFJ to ligating and stripping the phlebotic veins. Unfortunately, the review on the treatment of lower limb SVT included only 3

Compression ultrasound has become the objective test of choice for confirming clinically suspected superficial vein thrombosis.

randomized clinical trials of surgical treatment, and all the studies had major design flaws. Therefore, surgery should not be considered for lower limb SVT. This recommendation is consistent with recent guidelines from the British Committee for Standards in Haematology, which suggest that only medical therapy be given.⁶ A traditional treatment for the relief of SVT symptoms has been the use of elastic stockings in addition to nonsteroidal anti-inflammatory drugs, which may be administered in oral form or in a topical preparation. Although no data are available on the optimal duration of use or degree of compression, treatment usually lasts for 7 to 14 days. Compression hosiery also may be recommended for patients who have varicose veins.

CALISTO (Comparison of Arixtra in Lower Limb Superficial Vein Thrombosis With Placebo) evaluated use of the pentasaccharide fondaparinux, a synthetic heparin derivative, in SVT treatment.⁷ This double-blind, randomized, placebo-controlled trial, the largest study of SVT treatment, enrolled 3004 patients with SVT of the long saphenous vein with a thrombus at least 5 cm long in 93% of cases. It was found that a prophylactic dose of fondaparinux (2.5 mg) for 6 weeks was more effective than placebo at reducing complications. At a follow-up of

up to 77 days, the composite endpoint of death from any cause and symptomatic events (PE/DVT or symptomatic extension to the SFJ or SVT recurrence) was significantly lower in the fondaparinux group (0.9%) than in the placebo group (5.9%).

The second largest trial of SVT treatment was STE-FLUX (Superficial Thromboembolism and Fluxum).⁸ Investigators studied 664 outpatients with SVT of the long or short saphenous vein or collateral veins that was at least 4 cm long. Patients were randomly assigned to 1 of 3 different doses and durations of LMWH. The researchers found that the 30-day intermediate dose of LMWH was superior to either the 30-day prophylactic dose or the 10-day intermediate dose in reducing the primary outcome, which was a composite of symptomatic and asymptomatic DVT, symptomatic PE, and relapse and/or symptomatic or asymptomatic SVT recurrence in the first 33 days, with 60-day follow-up. No increase in major bleeding occurred.

H&O What have we learned about superficial thrombophlebitis in recent years?

BC Many studies have shown that SVT is not always a benign, self-limiting disorder, as it can be associated with extension into deep veins. Therefore, an objective diagnosis is required, both to confirm the clinical suspicion and to evaluate the degree of extension. Moreover, treatment with anticoagulants may significantly reduce thromboembolic complications in lower limb SVT.

H&O How have recent clinical trials affected the management of patients with SVT?

BC Clinical trials have included patients with objectively diagnosed SVT of the lower limbs and generally have excluded patients who have SVT with a small thrombotic burden and those who have high-risk SVT. The most appropriate treatment for patients who have SVT with a small thrombotic burden (thrombus length <4-5 cm and location >3 cm from the SFJ or SPJ) is a topical or oral NSAID for 8 to 12 days. The most appropriate treatment for patients who have high-risk SVT (thrombus location <3 cm from the SFJ and possibly from the SPJ) is therapeutic anticoagulation with vitamin K antagonists or possibly direct oral anticoagulants for 3 months.⁹ Patients who have intermediate-risk SVT (thrombus length >4-5 cm and location >3 cm from the SFJ or SPJ) should receive 2.5 mg of fondaparinux once daily for 45 days, or else intermediate-dose LMWH for 4 to 6 weeks.¹⁰

H&O What other trials are in the works or should be planned?

BC There is still a need for randomized, controlled trials addressing the best way to treat lower limb SVT that is related to cancer or pregnancy, as well as the best way to treat DVT of the upper limb or neck, abdominal wall, or penis.

Although we do not yet have any data on the treatment of SVT with direct oral anticoagulants, 2 ongoing trials are examining this issue: the phase 3 SURPRISE trial (Superficial Vein Thrombosis Treated With Rivaroxaban Versus Fondaparinux; NCT01499953) and the RASET trial (Rivaroxaban Anticoagulation for Superficial Vein Thrombosis; NCT02123524). RASET is a phase 3, randomized, placebo-controlled, blinded, multicenter trial that will compare 10 mg of rivaroxaban (Xarelto, Janssen) daily with placebo in patients who have symptomatic leg SVT (≥ 5 cm in length) that otherwise would not initially be treated with anticoagulant therapy.

Disclosure

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