Venous stasis syndrome: the long-term burden of deep vein thrombosis

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Currently there is no cure for venous stasis syndrome, a common complication of deep vein thrombosis. Prophylaxis with anticoagulant agents, including new drugs presently under investigation, may decrease the incidence and costs associated with this condition.

Venous thromboembolism (VTE), which consists of deep vein thrombosis (DVT) and pulmonary embolism (PE), can be clinically silent and potentially fatal. In the United States, the annual incidence of VTE has been estimated to be approximately 1 per 1000 persons (Silverstein et al, 1998). Despite the development of newer anticoagulant drugs and improved methods of prophylaxis, the estimated incidence of DVT and PE has remained relatively constant since 1979 (Silverstein et al, 1998). However, the true number of DVT events may be even higher than has been reported in clinical studies because DVT is consistently misdiagnosed or underdiagnosed because of its silent nature.

Clinically important long-term sequelae are frequently associated with DVT. One of the most disabling and disfiguring long-term complications following DVT is chronic venous stasis syndrome (VSS), also known as post-phlebitic or post-thrombotic syndrome (Prandoni et al, 1996; Brandjes et al, 1997; Saarinen et al, 2000). Significant morbidity, including risk of recurrent venous thrombosis, and potential mortality are associated with VSS. Patients with VSS present with symptoms ranging from mild leg swelling to hyperpigmentation, eczematoid dermatitis, lipodermatosclerosis and indurated cellulitis. Long-standing VSS can progress to chronic, incapacitating leg pain and oedema, which may become intractable; and the final stage is skin ulceration (Bernardi and Prandoni, 2000; Mohr et al, 2000). Venous ulcers develop because of severe impairment of tissue perfusion and poor oxygenation; they heal with difficulty, thus increasing susceptibility to infection (Black, 1995).

VSS places a significant economic burden on the health-care system and can have an enormous impact on patients' quality of life. In 1997, the cost of VSS was estimated as ranging from \$6000 to almost \$8000 per event (in 1991 US dollars) (Bergqvist et al, 1997). More recent studies have estimated the cost as \$9300 to almost \$13 000 per event (Olin et al, 1999). Hume (1992) estimated in 1991 that the annual cost of managing venous ulcers in the United States was \$1 billion, while a more conservative assessment reported in 2001 places the cost of treating these disorders (VSS and venous ulcer) at over \$200 million (Heit et al, 2001a).

Venous ulcer is the most costly stage of VSS, requiring wound care, long-term use of antibiotics and other supportive therapy. There are also serious social and economic costs associated with venous ulcers, such as absence from work, forced early retirement and lost leisure activities. It is clear that the burden of treating and managing VSS is substantial and that newer, more effective approaches to prevent its development are warranted.

CLINICAL ASPECTS OF VSS

Incidence and prevalence

VSS is a complication of DVT, varicose veins and other conditions. Because of the paucity of data and non-uniform criteria for diagnosing VSS, the precise incidence of the syndrome is indeterminate. However, using the resources of the Rochester Epidemiology Project, Heit et al identified the inception cohort of Olmsted County, Minnesota, residents with a first lifetime diagnosis of VSS and or venous ulcer over the 25-year period 1966–1990 (Heit et al, 2001a). The age- and sex-adjusted incidence of VSS and venous ulcer was 76.1 and 18.0 per 100 000 person years respectively, and was higher among women than among men (VSS = 83.7 *vs* 67.4 per 100 000 person years; venous ulcer = 20.4 *vs* 14.6 per 100 000 person years).

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More is known about the relationship between DVT and the development of VSS. It is estimated that one quarter to one third of patients with a first lifetime episode of DVT will develop VSS within 8 years (Prandoni et al, 1997; Bernardi and Prandoni, 2000). In a study of 61 patients followed for 39 months after the first DVT episode, 67% of patients developed leg pain and/or swelling, 23% showed signs of pigmentation and 5% demonstrated ulceration (Strandness et al, 1983). In 1991, Nelzen et al published the results of 382 leg ulcer patients in Sweden, showing that prior DVT had occurred in 25% of the patients. The results of these studies support the most recent population-based evaluation of incidence conducted by Mohr et al (2000). This showed a cumulative incidence of VSS in patients diagnosed with DVT, with or without PE, or with PE alone, after 1, 5, 10 and 20 years was 7.3%, 14.3%, 19.7% and 26.8% respectively. The cumulative incidence of venous ulcer was 0.7% after 5 years and 3.7% after 20 years. These findings suggest that the cumulative incidence of VSS continues to increase for at least 20 years after a venous thromboembolic event.

The incidence of VSS is high, even when patients are given adequate treatment for DVT. A cohort study of 528 patients with venographically confirmed DVT found a cumulative incidence of VSS of 30% at 8 years (Prandoni et al, 1997). These patients were treated with adjusted high-dose unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH), followed by at least 3 months of warfarin, and were instructed to wear compression stockings for 2 years. In a small study, Saarinen et al (2000) monitored 26 patients using colour-flow Doppler imaging for 2 years after an initial episode of DVT. The patients were conservatively treated with LMWH and warfarin for 3–6 months; the unaffected extremity was used for comparison. By 20 months, venous valvular incompetence or venous outflow obstruction in the popliteal segment had developed in 50% of the patients. Leg pain, oedema and pigmentation were observed in 62%, 46% and 35% respectively. Only 27% of the study population remained asymptomatic after 2 years.

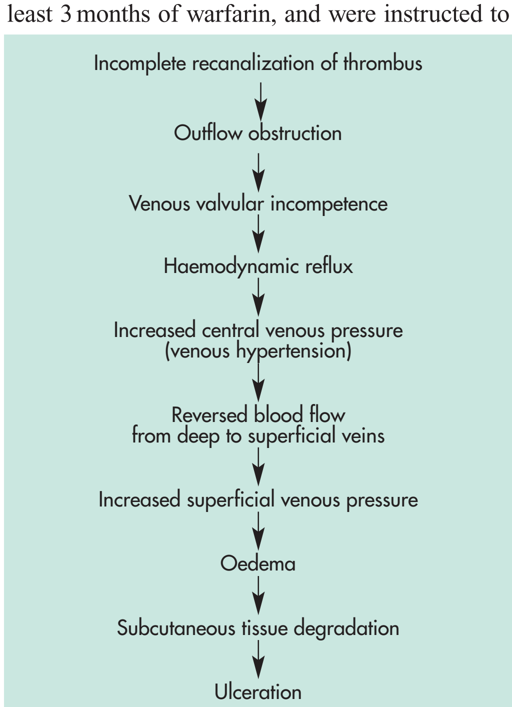

Figure 1. Progression of venous stasis syndrome (VSS) from incomplete recanalization of the thrombus to venous ulcer. VSS usually develops as a complication of proximal deep vein thrombosis, although moderate to severe stasis occurs in calf veins in 4–20% of patients (Mohr et al, 2000).

In another study, Brandjes et al compared the efficacy of graduated compression stocking therapy with that of no prophylaxis in preventing recurrent DVT and VSS in patients with venographically proven DVT (Brandjes et al, 1997). The incidence of VSS following the first episode of DVT was 70% in patients without prophylaxis and 31% in patients with stocking therapy during the median follow-up period of 6.3 years. Most cases of VSS occurred within the first 24 months.

Pathophysiology and risk factors

An important factor in the development of VSS is venous valvular incompetence in the distal valves, leading to haemodynamic reflux (*Figure 1*) (Mohr et al, 2000). Incompetent valves compromise the function of the muscular pumping mechanism that normally supports venous return, resulting in increased pressure in the deep calf veins (Hirsh and Hoak, 1996; Rutherford, 1996). During muscle contraction, the direction of blood flow is reversed from the deep to the superficial veins. Increased superficial venous pressure leads to oedema formation, degradation of subcutaneous tissue and, finally, skin ulceration which typically involves the medial ankle.

The only clearly identifiable risk factor for VSS is DVT (Prandoni et al, 1996; Mohr et al, 2000). In the Olmsted County population, patients with DVT (with or without PE) had a 2.4-fold increased risk of developing VSS compared with patients with PE alone (Mohr et al, 2000). Thus, DVT is the strongest risk factor for VSS. Risk factors for VTE are presented in *Table 1* (Heit et al, 2000a,b).

Clinical presentation

The clinical presentation of VSS generally depends on the stage of the disease (Black, 1995). Varicose veins are a common complaint, usually because of adverse changes in leg appearance. Patients may also experience pressure, heaviness, or a dull ache and oedema in the affected leg brought on by long hours of standing. Elevating the leg can bring symptom relief. In the later stages of VSS, patients present with itching, burning and discolouration of the skin as well as ulcers. The subacute presentation of VSS may mimic acute recurrent DVT (Hirsh and Hoak, 1996).

Diagnosis

Definitive diagnosis of VSS depends upon excluding acute recurrent DVT as the cause of symptoms as well as ruling out the contribution of any coexisting diseases that are arterial, neurological or musculoskeletal in origin (Hirsh and Hoak, 1996). Diagnosis begins with a detailed clinical history and examination to assess signs and symptoms, and disease severity. Physiological diagnosis of VSS depends upon demonstrating deep venous incompetence by determining calf muscle pump function, and also the severity and anatomical sites of venous reflux or obstruction using morphological and haemodynamic tests (*Tables 2* and *3*) (Nicolaides, 2000).

TABLE 1.
Risk factors for venous thromboembolism

Factor	Relative risk	95% confidence interval
Age*	1.38	1.09–1.74
Institutionalization† without recent surgery	7.98	4.49–14.18
Institutionalization with recent surgery	21.72	9.44–49.93
Trauma	12.69	4.06–39.66
Malignant neoplasm without chemotherapy	4.05	1.93–8.52
Malignant neoplasm with chemotherapy	6.53	2.11–20.23
Prior central venous catheter or transvenous catheter	5.55	1.57–19.58
Prior superficial vein thrombosis	4.32	1.76–10.61
Neurological disease with extremity paresis	3.04	1.25–7.38
Varicose veins, age 45 years	4.19	1.56–11.3
Varicose veins, age 60 years	1.93	1.03–3.61

* Per decade increase in age, univariate logistic analysis; † Institutionalization defined as current or recent hospitalization, or nursing home confinement. Adapted with permission from Heit et al (2000b)

TABLE 2.
Imaging methods for detecting venous valvular incompetence or outflow obstruction

Test	Utility	Advantages	Disadvantages
Ascending venography	Shows patency of veins Defines anatomy Distinguishes between primary and secondary disease Detects incompetent perforating veins	Useful when duplex scanning inadequate, equivocal or unavailable	Invasive Does not give quantitative functional assessment of disease severity or show patency of collateral veins
Descending venography	Shows deep or superficial venous reflux Finds leakage points from deep to superficial veins or from pelvis to legs Also has same utility as ascending phlebography		Invasive Costly Potential complications Non-physiological test: blood is lighter than contrast agent
Duplex scanning (colour-flow)	Provides instant view of blood flow and direction Finds reflux or obstruction and anatomical extent Is sensitive to individual veins	Improved accuracy Decreased examination time	Some test positions or manoeuvres depend on cooperative patient who can perform them Operator dependent Difficult test when patient is obese or has swollen legs or when scanning above the inguinal ligament

From Nicolaides (2000)

TABLE 3.
Haemodynamic methods for detecting venous valvular incompetence or outflow obstruction

Test	Utility	Advantages	Disadvantages
Photoplethysmography and light reflection rheography	Detects changes in blood content of tissue Distinguishes deep and superficial venous incompetence	Non-invasive	Poor indicator of severe deep venous insufficiency Not reliable indicator of anatomical distribution of venous insufficiency
Quantitative digital photoplethysmography	Test self-standardizes Measures time-related parameters Measures calf muscle pump effectiveness	Test results have quantitative relationship with symptoms Long-term monitoring possible	
Air plethysmography	Measures venous reflux and obstruction, calf muscle pump ejection Detects presence of obstruction to venous outflow Distinguishes legs with oedema or ulcer from venous vs other causes Measures arterial inflow	Measures venous haemodynamics in entire leg	
Foot volumetry	Measures venous insufficiency Distinguishes deep and superficial insufficiency Indicates calf muscle pump effectiveness Indicates venous reflux	Examines most distal part of leg Useful to monitor therapy Monitors valve damage after deep vein thrombosis	

From Nicolaides (2000)

MANAGEMENT OF VSS

To date, there is no effective pharmacological treatment for established VSS. Destruction of venous valves appears to be permanent. Altered venous pressures and volumes contribute progressively abnormal valve and muscle pump function, perpetuating the condition (Rutherford, 1996).

TABLE 4.
Antithrombotics approved for the prevention of venous thromboembolism

Method	Description	
Low-dose UFH	Heparin 5000 U SC every 8–12 hours starting 1–2 hours before operation	
Adjusted-dose UFH	Heparin starting at approximately 3500 U SC and adjusted by ±500 U SC per dose every 8 hours to maintain a midinterval activated partial thromboplastin time at high normal values	
LMWH	General surgery (moderate risk)	Dalteparin 2500 U SC 1–2 hours preoperatively and once daily postoperatively
		Enoxaparin 20 mg SC 1–2 hours preoperatively and once daily postoperatively
		Nadroparin 2850 U SC 2–4 hours preoperatively and once daily postoperatively
		Tinzaparin 3500 U SC 2 hours preoperatively and once daily postoperatively
	General surgery (high risk)	Dalteparin 5000 U SC 8–12 hours preoperatively and once daily postoperatively
		Enoxaparin 40 mg SC 1–2 hours preoperatively and once daily postoperatively
		Enoxaparin 30 mg SC every 12 hours starting 8–12 hours postoperatively
	Total hip and knee replacement surgery	Dalteparin 5000 U SC 8–12 hours preoperatively and once daily starting 12–24 hours postoperatively
		Dalteparin 2500 U SC 6–8 hours postoperatively then 5000 U SC once daily
		Enoxaparin 30 mg SC every 12 hours starting 12–24 hours postoperatively
		Enoxaparin 40 mg SC once daily starting 10–12 hours preoperatively
		Nadroparin 38 U/kg SC 12 hours preoperatively, 12 hours postoperatively, and once daily on postoperative days 1, 2, and 3, then increased to 57 U/kg SC once daily
		Tinzaparin 75 U/kg SC once daily starting 12–24 hours postoperatively
		Tinzaparin 4500 U SC 12 hours preoperatively and once daily postoperatively
	Major trauma	Enoxaparin 30 mg SC every 12 hours starting 12–36 hours post-trauma if haemostatically stable
	Acute spinal cord injury	Enoxaparin 30 mg SC every 12 hours
	Medical conditions	Dalteparin 2500 U SC once daily
		Enoxaparin 40 mg SC once daily
		Nadroparin 2850 U SC once daily
Fondaparinux sodium	Hip and knee replacement surgery and hip fracture repair 2.5 mg SC once daily started 6–8 hours postoperatively	
Perioperative warfarin	Daily dose starting at approximately 5–10 mg the day of or the day after surgery, and adjusted to a target INR of 2.5 (range 2–3)	

INR = international normalized ratio; LMWH = low molecular weight heparin; SC = subcutaneously; UFH = unfractionated heparin. Adapted from Geerts et al (2001)

The only approach currently available to prevent the development of VSS is to prevent DVT by utilizing prophylaxis in medical and surgical patients at risk (Geerts et al, 2001; Nicolaides, 2001). Prevention of primary and recurrent episodes of DVT with antithrombotic regimens and proper use of elastic stockings are the mainstays of preventing venous insufficiency in the lower limbs (Bernardi and Prandoni, 2000). Conservative management with leg elevation, compression stockings and antithrombotic medications leads to improvement or clinical stability in more than 50% of patients presenting with VSS (Bernardi and Prandoni, 2000).

Effective thromboprophylaxis must balance the patient's risk level for DVT with that for serious bleeding complications (Geerts et al, 2001; Nicolaides, 2001). The Sixth American College of Chest Physicians Consensus guidelines (*Table 4*) (Geerts et al, 2001) outline recommendations for the prevention of VTE and comprehensively describe risk factors and their stratification. The guidelines also explain methods of prophylaxis in various types of surgical, trauma, cardiac and medical patients.

PHARMACOLOGICAL PREVENTION OF VTE

Antithrombotic medications traditionally used for the prevention of VTE include warfarin, which is an oral anticoagulant that affects the synthesis of vitamin K-dependent coagulation factors, and UFH and LMWHs, both of which inhibit multiple activated coagulation factors. Warfarin has been used extensively for the treatment and prevention of VTE. However, the drug has an unpredictable dose–response profile and poses a risk of bleeding complications. Its efficacy is influenced by significant interindividual variations as a result of genetic factors, dietary changes in vitamin K and numerous drug interactions (Gage et al, 2000). Laboratory monitoring of the international normalized ratio (INR) is required to adjust the dose without compromising safety.

UFH and LMWHs inhibit thrombin and factor Xa indirectly as a ternary complex with antithrombin III and the coagulation factors (Hirsh et al, 2001). Factor X is unique because it is activated by both the intrinsic and extrinsic coagulation pathways. The anti-Xa/thrombin ratio for UFH is 1.0, whereas for LMWHs it is greater than 1.0, varying from 1.9 to 5.0. The different pharmacokinetic profiles and ratios may be one factor accounting for the differences in the safety and efficacy of the various LMWHs (Hirsh et al, 2001).

UFH has several significant limitations as a thromboprophylactic agent. Its use requires expertise, continuous monitoring of heparinization and dose adjustments to maintain safe levels of anticoagulation. Unpredictable bleeding and the risk of heparin-induced thrombocytopenia (HIT), an antibody-mediated complication of heparin therapy carrying a high risk of thrombosis, are increased in patients receiving UFH.

The LMWHs have a more predictable anticoagulant response and do not require monitoring except in the aged and in patients with impaired renal function, and can thus be used in an outpatient setting. In addition, the LMWHs are less likely than UFH to cause HIT (Hirsh et al, 2001). LMWHs are used extensively for thromboprophylaxis in patients undergoing major lower limb orthopaedic surgery. However, their use is associated with a high risk of residual VTE, especially following knee replacement surgery (Geerts et al, 2001), and multiple LMWH drug regimens can complicate therapy.

NEW ANTITHROMBOTIC AGENTS FOR REDUCTION OF VTE AND VSS EVENTS

Newer anticoagulants with improved efficacy profiles for use in the prophylaxis of DVT could significantly reduce the long-term costs of VSS. Selective inhibition of coagulation factors provides significantly better prophylaxis without increasing the short-term risk of bleeding complications.

Direct thrombin inhibitors

Direct thrombin inhibitors interact with thrombin by inhibiting its active site. Hirudin is a natural thrombin inhibitor extracted from the salivary glands of the leech (Weitz and Hirsh, 2001). Direct thrombin inhibitors based on this natural anticoagulant include recombinant hirudin (e.g. lepirudin) and smaller synthetic derivatives of hirudin's C-terminal thrombin binding domain (e.g. hirulog, bivalirudin) (Weitz and Hirsh, 2001). Argatroban belongs to a family of small, direct thrombin inhibitors that bind non-covalently to the enzyme's active site (Weitz and Hirsh, 2001). Similar agents include napsagatran, melagatran and ximelagatran (Weitz and Hirsh, 2001). The advantages of these compounds include a targeted specificity for thrombin, the ability to inactivate clot-bound thrombin, and an absence of plasma protein and platelet interactions that can lead to complications such as HIT (Weitz and Hirsh, 2001). Two direct thrombin inhibitors, argatroban and lepirudin, are approved for use in thromboembolic disease, but only as alternative anticoagulants to UFH and LMWHs in patients with HIT (Hirsh et al, 2001).

Ximelagatran is under clinical development for the prevention of VTE in patients undergoing major orthopaedic surgery. Several phase II studies comparing ximelagatran with other antithrombotic agents have yielded positive findings (Heit et al, 2001b; Eriksson et al, 2002a,b; Francis et al, 2002). However, in a clinical trial, ximelagatran failed to show significant benefit over the LMWH enoxaparin sodium in patients undergoing total hip replacement (Colwell et al, 2001).

Selective factor Xa inhibitors

Targeting factor Xa of the coagulation cascade may provide increased therapeutic efficacy over current antithrombotic agents and with similar and safety. Fondaparinux is the most clinically advanced synthetic selective Xa inhibitor in development and has been evaluated extensively in phase II and III clinical trials (Bauer et al, 2001; Eriksson et al, 2001; Turpie et al, 2001, 2002; Lassen et al, 2002).

The safety and efficacy of fondaparinux as a prophylactic agent against VTE has been evaluated in four large studies involving 7344 patients undergoing major orthopaedic surgery (hip replacement, hip fracture surgery and major knee surgery) (Bauer et al, 2001; Eriksson et al, 2001; Lassen et al, 2002; Turpie et al, 2002). Compared with enoxaparin, treatment with fondaparinux resulted in a >50% reduction in the risk of VTE (P<0.001) (Turpie, 2001). The safety profile was similar to that of enoxaparin in terms of clinically relevant bleeding. Fondaparinux is approved for use in prevention of VTE after major lower extremity orthopaedic surgery in the United States and Europe. Major orthopaedic surgery of the lower extremities is a particularly strong risk factor for VTE.

CONCLUSIONS

VSS is a debilitating clinical condition that is a common complication of DVT, which itself is the strongest risk factor for VSS. Significant morbidity and social- and health-care costs are associated with VSS. At this time, no medical or pharmacological therapies effectively treat this condition, once established. Continued research into anticoagulation therapy will help provide clinicians and DVT patients with comprehensive, evidence-based information regarding prognostic indicators and new preventive strategies. Primary prevention of DVT is the most rational approach to reducing the clinical impact and cost of VSS, and this may be enhanced in the future by some of the newer anticoagulants which are on the market as well as those antithrombotic agents that are now in clinical development. HM

Table 4 *is reproduced courtesy of the American College of Chest Physicians.*

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KEY POINTS

- Venous thromboembolism, consisting of deep vein thrombosis and pulmonary embolism, is a clinically silent and potentially fatal disease.
- Clinically important long-term sequelae are frequently associated with deep vein thrombosis.
- One of the most disabling and disfiguring complications following deep vein thrombosis is chronic venous stasis syndrome.
- The only clearly identifiable risk factor for venous stasis syndrome is deep vein thrombosis.
- To date, there is no effective pharmacological therapy for the treatment of established venous stasis syndrome.
- Primary deep vein thrombosis prevention is the most rational means to reduce the clinical morbidity associated with venous stasis syndrome.
- Novel antithrombotic agents are available to reduce venous thromboembolism events and improve long-term patient outcomes.

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