

# The post-thrombotic syndrome: progress and pitfalls

Susan R. Kahn

Department of Medicine, McGill University, and Center for Clinical Epidemiology & Community Studies, Sir Mortimer B. Davis Jewish General Hospital, Montreal, QC, Canada

## Summary

The post-thrombotic syndrome (PTS) develops in up to one half of patients after symptomatic deep venous thrombosis (DVT) and is the most common complication of DVT. Typical features of PTS include chronic pain, swelling, heaviness, oedema and skin changes in the affected limb. In severe cases, venous ulcers may develop. The frequency of PTS is likely to be reduced by preventing DVT with the use of effective thromboprophylaxis in high-risk patients and settings and by minimising the risk of ipsilateral DVT recurrence. Use of compression stockings for 2 years after DVT appears to reduce the incidence and severity of PTS but issues remain regarding their use and effectiveness. Future research should focus on elucidating the pathophysiology and risk factors for PTS, assessing the safety and effectiveness of catheter-directed thrombolysis to prevent PTS and evaluating the optimal use of compression stockings to prevent and treat PTS. In addition, new therapies to treat PTS should be sought and evaluated.

**Keywords:** deep venous thrombosis, post-thrombotic syndrome, epidemiology, risk factors, prevention, treatment.

Post-thrombotic syndrome (PTS) is a chronic condition that develops in 20–50% of patients after deep venous thrombosis (DVT) (Prandoni *et al*, 1996; Kahn & Ginsberg, 2004; Stain *et al*, 2005; Schulman *et al*, 2006). As such, it is the most common complication of venous thromboembolism (VTE). PTS reduces quality of life (Kahn *et al*, 2002) and incurs significant direct and indirect societal costs (Bergqvist *et al*, 1997). To date, however, PTS has received little attention within the field of VTE research. For example, in the numerous clinical trials of therapies for VTE that have directly influenced our current-day clinical practices, PTS has almost never been included as a measure of outcome. Possible reasons for the lack of attention to this common

condition on the part of physicians and researchers include lack of knowledge of the high incidence of PTS, uncertainty as to how to diagnose PTS as no ‘gold standard’ test exists, or the perception that PTS is untreatable, inevitable, or takes years to develop after DVT.

This article reviews the current understanding of the clinical presentation, pathophysiology, diagnosis, risk factors, epidemiology and management of PTS. The burden of PTS from the patient’s and society’s perspective is discussed. Finally, PTS research priorities are highlighted.

## How does PTS present clinically?

Post-thrombotic syndrome is termed a ‘syndrome’ because it is associated with groupings of symptoms and clinical signs, which may vary from patient to patient. Patients with PTS experience pain, heaviness, swelling, cramps, itching or tingling in the affected limb. Symptoms may be present in various combinations and may be persistent or intermittent. Typically, symptoms are aggravated by standing or walking and improve with resting, leg elevation and lying down. Signs that may be noted on physical examination of the limb include oedema, telangiectasias, hyperpigmentation, eczema, varicose collateral veins and, in severe cases, lipodermatosclerosis and ulceration (Kurz *et al*, 1999) (Table I).

## What is the underlying pathophysiology of PTS?

When DVT is diagnosed, standard anticoagulant treatment prevents thrombus extension and embolisation to the pulmonary arteries, but does not directly lyse the acute thrombus. Follow-up studies of patients with DVT who were treated with anticoagulants have shown that in most cases, only partial clearance of thrombus occurs and return of normal physiological function of the vein is rare (Piovella *et al*, 2002; Prandoni *et al*, 2002). Even in patients who do achieve clot lysis, permanent damage to venous valves occurs frequently, conceivably via thrombus-induced activation of inflammation (Roumen-Klappe *et al*, 2002) or scarring associated with acute and resolving thrombosis, leading to valve incompetence (reflux). Indeed, the use of thrombolysis to treat DVT, while achieving high rates of clot lysis, has not been definitively shown to improve venous haemodynamics or reduce the risk

Correspondence: Dr Susan R. Kahn, Department of Medicine, McGill University, and Center for Clinical Epidemiology & Community Studies, Sir Mortimer B. Davis Jewish General Hospital, 3755 Cote Ste. Catherine, Room A-127, Montreal, QC, Canada H3T 1E2.  
E-mail: susan.kahn@mcgill.ca

**Table I.** Typical clinical features of the post-thrombotic syndrome.

Leg symptoms	Signs
Heaviness	Oedema
Pain	Peri-malleolar telangiectasiae
Swelling	Venous ectasia
Itching	Hyperpigmentation
Cramps	Redness
Paresthesia	Dependent cyanosis
Bursting pain	Lipodermatosclerosis
	Healed ulcer
	Open ulcer
<i>Symptom pattern</i>	
Worse with activity, standing, walking	
Better with rest, recumbency	

of PTS, compared with standard anticoagulation (Wells & Forster, 2001).

Based on the above and on results of venous haemodynamic studies in patients with PTS, it is likely that the pathophysiology of this syndrome involves the interplay of two processes: (i) damage to delicate venous valves by the thrombus itself or by associated inflammatory mediators, which causes valvular reflux; and (ii) residual venous obstruction because of incomplete thrombus clearance, which leads to impaired venous return. Both processes lead to increased venous pressure (venous hypertension), which results in reduced calf muscle perfusion, increased tissue permeability and the associated clinical manifestations of PTS (e.g. pain, effort intolerance, swelling).

### How is PTS diagnosed?

By definition, PTS is a syndrome and there is no gold standard laboratory, imaging or functional test that establishes the diagnosis. In patients with objectively confirmed prior DVT who have typical PTS symptoms and signs, PTS is usually the correct diagnosis. In some patients, it may take up to 3–6 months for the initial pain and swelling associated with acute DVT to resolve, hence a diagnosis of PTS should be deferred until after the acute phase has passed. While objective evidence of venous valvular incompetence by Doppler ultrasound or by plethysmography may help to confirm the diagnosis of PTS in symptomatic patients, PTS should not be diagnosed if clinical symptoms are absent. This is because, while many patients with symptomatic PTS have valvular incompetence, many DVT patients develop valvular incompetence but do not have symptomatic PTS (Milne *et al*, 1994; Kahn *et al*, 2006a).

Three clinical scales for the diagnosis of PTS have been developed (Villalta *et al*, 1994; Porter *et al*, 1995; Ginsberg *et al*, 2000) and are summarised in Table II. These have been used to assess the presence and grade the severity of PTS in a number of clinical studies, including trials of therapies to prevent or treat PTS. However, none has undergone full evaluation of reliability, validity or responsiveness to change

and their use for the routine clinical monitoring of DVT patients has not been assessed. Moreover, differences in the test characteristics of these measures could help to explain the differing rates of PTS that have been reported in long-term follow-up studies of patients with DVT. For example, in a recent study of a population of patients evaluated 1 year after symptomatic DVT, the proportion of patients classified as having PTS was almost fivefold higher with the Villalta measure than with the Ginsberg measure, and the agreement between the two measures was poor (Kahn *et al*, 2006a). Another recent study detected substantial differences in the ability of various PTS measures to discriminate between legs affected by DVT and those of controls (Kolbach *et al*, 2005). Research aimed at validating and standardising diagnostic criteria for PTS to improve the uniformity of its' diagnosis in clinical studies and to enhance the ability to compare results of different studies would be of value.

### Which DVT patients are at risk of developing PTS?

#### *Risk factors that are apparent at the time of DVT diagnosis*

**Age and sex.** Two studies found that increasing age was associated with a higher risk of developing PTS (Prandoni *et al*, 2004; Van Dongen *et al*, 2005), but other studies did not (Kahn *et al*, 2002; Kahn *et al*, 2005a; Stain *et al*, 2005). In one study, male sex was a weak risk factor for PTS (Stain *et al*, 2005). Overall, there do not appear to be consistent relationships between age or sex and the development of PTS.

**Body mass index (BMI).** Results of prospective studies suggest that higher BMI is associated with a greater risk of PTS. In a small cohort study of patients with symptomatic proximal DVT who were followed for 12 months, patients who developed PTS had significantly higher mean BMI than those who did not develop PTS and BMI >28 was associated with an odds ratio for PTS of 3.5 (Ageno *et al*, 2003). In a substudy to a trial that compared two intensities of long-term warfarin anticoagulation for unprovoked (idiopathic) proximal DVT, adjusted analyses indicated that higher BMI was associated with increased severity of PTS (Kahn *et al*, 2005a). Similarly, Van Dongen *et al* (2005) found that BMI >25 was a significant independent predictor of PTS after proximal DVT. As obesity is a potentially modifiable risk factor, the role of weight reduction in the prevention or management of PTS merits evaluation.

**Thrombophilia.** Inherited and acquired thrombophilic disorders increase the risk of developing a first episode of VTE (Bauer, 2005) and in some studies, increased the risk of recurrent VTE (Palareti & Cosmi, 2004). Whether these disorders also increase the risk of developing PTS is of interest and relevance. In a longitudinal cohort study of predictors of PTS, there were no associations between the risk

**Table II.** Clinical scales for the diagnosis of post-thrombotic syndrome (PTS).

PTS scale	Criteria used to diagnose PTS	Developed specifically for PTS	Rates severity of PTS
Villalta scale (Villalta <i>et al</i> , 1994)	Five symptoms (pain, cramps, heaviness, pruritus, paresthesia) Six signs (oedema, skin induration, hyperpigmentation, venous ectasia, redness, pain during calf compression) Each rated as 0 (absent), 1 (mild), 2 (moderate) or 3 (severe) Points are summed to yield total score: 0–4: No PTS 5–14: Mild/moderate PTS 15 or more, or presence of ulcer: Severe PTS	Yes	Yes
Ginsberg measure (Ginsberg <i>et al</i> , 2000; Ginsberg <i>et al</i> , 2001)	Pain and swelling of limb of $\geq 1$ month duration, typical character (worse end of day or with prolonged sitting/standing, better after night's rest and leg elevation) that occurs $\geq 6$ months after acute DVT	Yes	No
CEAP classification* (Porter <i>et al</i> , 1995)	Patients with chronic venous disease classified into one of seven clinical classes (Class 0–6) according to presence of clinical signs. Each class may include signs present in lower-order class. Class: 0. Symptoms only; no visible or palpable signs of venous disease 1. Telangiectasias, reticular veins, malleolar flare 2. Varicose veins 3. Oedema, no skin changes 4. Skin changes (e.g., pigmentation, eczema, lipodermatosclerosis) 5. Skin changes with healed ulcer 6. Skin changes with active ulcer Each clinical class is then subclassified as to: Aetiology (congenital, primary, secondary) Anatomy (superficial, deep, perforator veins) Pathophysiology (reflux, obstruction, both)	No†	No‡

\*CEAP: Clinical-Etiology-Anatomic-Pathophysiologic. Modifications of CEAP (Clinical Severity Score, Venous Segmental Disease Score) have been proposed (Rutherford *et al*, 2000).

†Developed for chronic venous disease in general.

‡Increasing CEAP class is intended to reflect increased severity of signs of chronic venous disease; symptoms and their severity are not considered. PTS = postthrombotic syndrome.

of developing PTS and deficiencies of antithrombin, Protein C or Protein S or the presence of lupus-like anticoagulants (Prandoni *et al*, 1996). As this was an older study, testing for the common genetic thrombophilias was not yet available. In a recent cohort study, the presence of factor V Leiden, Prothrombin gene mutation or elevated factor VIII levels were not predictive of the development of PTS (Van Dongen *et al*, 2005). A study by our group found that in patients with idiopathic (unprovoked) DVT, the presence of factor V Leiden or Prothrombin mutation was an independent predictor of both a lower risk and reduced severity of PTS (Kahn *et al*, 2005a), a finding which was unexpected and is currently undergoing further evaluation in prospective studies. Hence, from the limited data available, it does not appear that thrombophilia increases the risk of developing PTS.

*Characteristics of the initial VTE.* In recent prospective studies, the likelihood of developing PTS was not influenced according to whether DVT was idiopathic (unprovoked) or secondary (because of surgery, trauma or cancer) (Prandoni *et al*, 2004; Stain *et al*, 2005; Van Dongen *et al*, 2005). With regard to the

relationship between the severity or location of the initial thrombus and the subsequent development of PTS, results have been inconsistent, which may be due at least in part to a combination of differing study methodologies, patients and definitions of PTS. In some studies, the risk of PTS was higher in patients with proximal rather than distal (calf) DVT (Lindner *et al*, 1986; Monreal *et al*, 1993) while in other studies neither the site nor the extent of the initial thrombus predicted the development of PTS (Browse *et al*, 1980; Philbrick & Becker, 1988; Prandoni *et al*, 1996). Indeed, some prospective studies reported rates of PTS after distal DVT that were as high as 20–80% (Schulman *et al*, 1986; McLafferty *et al*, 1998). Hence, distal (calf vein) DVT appears to be associated with a substantial risk of subsequent PTS.

*Asymptomatic DVT.* Deep venous thrombosis is sometimes diagnosed in asymptomatic patients by performing screening imaging tests in high-risk situations, for example postoperatively. Such imaging tests have included  $^{125}\text{I}$ -fibrinogen uptake testing, contrast venography or venous duplex ultrasound. A recent meta-analysis (Wille-Jørgensen

*et al*, 2005) pooled seven studies of patients with asymptomatic, objectively confirmed postoperative DVT and reported that the overall relative risk of developing PTS was 1.6 [95% confidence interval (CI) 1.24–2.02] as compared with patients without asymptomatic DVT on imaging tests. Moreover in 2005, Schindler and Dalziel reported among total knee and total hip arthroplasty patients that 18 months after ultrasound-diagnosed and treated asymptomatic postoperative DVT, about 24% of patients had developed persistent oedema in the affected leg, compared with 1% of patients without postoperative DVT (Schindler & Dalziel, 2005). These findings indicate that asymptomatic DVT can lead to PTS, which could help to explain the lack of a clinical history of DVT in some patients who have postthrombotic changes in their limbs.

#### *Risk factors that manifest during long-term follow-up after DVT*

*Intensity, quality and duration and of oral anticoagulation* A few recent studies have provided interesting data regarding the relationship between the duration, intensity and quality of oral anticoagulation and the subsequent development of PTS. Intensity of long-term anticoagulation does not appear to influence the risk of developing PTS, as shown in a recent study by our group (Kahn *et al*, 2005a) of patients with unprovoked proximal DVT treated with anticoagulants for an average of 2.2 years. After an initial 3 month period of treatment with warfarin targeted to an International Normalised Ratio (INR) of 2.0–3.0, there was no difference in the risk of developing PTS among patients who were randomised to a target warfarin intensity of 1.5–1.9 vs. 2.0–3.0 (Kahn *et al*, 2005a). However, the quality of anticoagulation in the first months after DVT may influence the risk of developing PTS. In a study of 244 DVT patients treated with vitamin K antagonists (target INR 2.0–3.0) for 3 months, those who spent >50% of the time with a subtherapeutic INR (INR <2.0) had an almost threefold higher risk of developing PTS (Van Dongen *et al*, 2005). This suggests that poor quality of anticoagulant therapy early after DVT may promote PTS, perhaps because of suboptimal clot resolution. Finally, with regard to the duration of anticoagulant therapy, in a cohort study of 406 patients followed for a median of 60 months after diagnosis of a first DVT, there was no difference in the risk of PTS among patients who received anticoagulation for <6 months, 6–12 months or >12 months (Stain *et al*, 2005).

Taken together, these results suggest that factors that trigger PTS may occur in the first weeks to months after acute DVT, appear to be promoted by inadequate initial anticoagulation, but are little influenced by intensity or duration of long-term anticoagulation.

*Recurrent DVT.* The most important risk factor for PTS is recurrent ipsilateral DVT, which in a number of studies was found to increase the risk of PTS as much as 10-fold (Prandoni

*et al*, 1996; Prandoni *et al*, 2004; Van Dongen *et al*, 2005), probably by causing further damage of compromised venous valves or by aggravating venous outflow obstruction. By extension, it is therefore important to prevent recurrent DVT by providing an adequate intensity and duration of anticoagulation for the initial DVT and by using thromboprophylaxis to prevent DVT in high-risk patients and settings as recommended in regularly updated evidence-based consensus guidelines (Geerts *et al*, 2004).

*Residual thrombosis on ultrasound.* The presence of residual thrombosis on ultrasound appears to be a risk factor for recurrent DVT after anticoagulant treatment of acute DVT (Piovello *et al*, 2002; Prandoni *et al*, 2002) and could plausibly promote the development of PTS because of persistent venous obstruction or valve damage. However, in recent studies that have examined this issue, modest [odds ratio (OR) 1.69; 95% CI 1.23–2.32] (Prandoni *et al*, 2005) or no associations (Kahn *et al*, 2005a) between the presence of residual vein thrombosis and the development of PTS were found.

*Persistent elevation of D-dimer.* Elevated D-dimer is a risk factor for first and recurrent DVT (Cushman *et al*, 2003; Cosmi *et al*, 2005). Elevated levels of D-dimer (defined as cut-off of >500 ng/ml on an enzyme-linked immunosorbent assay), measured 3 weeks after withdrawal of oral anticoagulant therapy, were found to be a modest risk factor (OR 1.9, 95% CI 1.0–3.9) for PTS in a recent study (Stain *et al*, 2005). These results require confirmation in large prospective studies.

#### **How often does PTS occur after DVT?**

Over the last two decades, the annual incidence of VTE has remained stable and is estimated to be 1.0–1.6 per 1000 persons per year, with a per-person lifetime incidence of *c.*5% (Silverstein *et al*, 1998). Approximately 250 000 new cases of VTE occur in the United States each year. Hence, the prevalence of PTS is on the rise in the population. A recent population-based study showed that cumulative rates of venous stasis after DVT were 7% at 1 year, 14% at 5 years, 20% at 10 years and 27% at 20 years and the cumulative risk of ulcer was 4% by 20 years (Mohr *et al*, 2000). More than a quarter of the *c.*170 000 new cases of venous stasis per year are considered to represent cases of PTS.

Prospective studies have provided important information on the frequency of PTS after symptomatic DVT. In a longitudinal cohort study of patients with a first episode of symptomatic DVT, the cumulative incidence of PTS was 17% after 1 year (severe in 3%), 23% after 2 years, 28% after 5 years (severe in 9%) and 29% after 8 years (Prandoni *et al*, 1996). In the control arm of a recent trial to evaluate the use of compression stockings to prevent PTS in patients with symptomatic proximal DVT, the cumulative rate of PTS at 2 years was 49%, and severe PTS occurred in 12% of patients by the end of

5 years follow-up (Prandoni *et al*, 2004). In both studies, the majority of cases of PTS occurred within 2 years of the initial DVT. Our recent systematic review, of European and North American studies of the occurrence of PTS in prospectively followed DVT patients, showed that the pooled incidence of any PTS was 46%, of severe PTS (including venous ulcers) was 15%, and that in most cases, the condition developed within 1–2 years of the acute DVT (Kahn & Ginsberg, 2004). Indeed, PTS is a very frequent complication of DVT.

### What is the impact of PTS on patients and society?

Post-thrombotic syndrome is not merely a cosmetic or 'nuisance' problem. Rather, PTS is costly and burdensome to patients and society, both in terms of money spent and effect on quality of life and productivity. A US study estimated that the annual direct cost of PTS is at least \$200 million dollars (Heit *et al*, 2001). A Swedish study estimated that over a 15 year follow-up, the average cost of treating PTS was c.US\$4700, or 75% of the cost of treating the primary DVT (Bergqvist *et al*, 1997). In a Brazilian study, the mean annual cost of treating PTS was the equivalent of US\$426 for mild-to-moderate PTS and US\$1188 for severe PTS (Ramacciotti *et al*, 2006). In a recent Canadian study, the annual cost of venous ulcer care in Ottawa alone was >\$1 000 000 and a large number of these cases are secondary to previous DVT (Harrison *et al*, 2001). The indirect costs of PTS are also significant as DVT and PTS affect persons of working age. For example, it is estimated that 2 million workdays are lost annually in the United States because of leg ulcers (Phillips *et al*, 1994). Research performed by our group has shown that patients with PTS have significantly poorer quality of life than DVT patients without PTS (Kahn *et al*, 2002; Kahn *et al*, 2005a), that quality of life is lower than in patients with other forms of chronic venous disease (Kahn *et al*, 2004) and that impairment in quality of life is, on average, worse than in patients with osteoarthritis or chronic lung disease (Kahn *et al*, 2002; Kahn *et al*, 2005b).

### How does should PTS be managed? (Table III)

#### Prevention of PTS

**Thromboprophylaxis.** As PTS is a consequence of DVT and thromboprophylaxis is an effective means of preventing DVT, it is highly likely, by extrapolation, that use of thromboprophylaxis in high risk patients and settings as recommended in evidence-based consensus guidelines (Geerts *et al*, 2004) will prevent cases of PTS. However, practice audits continue to demonstrate that thromboprophylaxis is underutilised (Kahn *et al*, 2006b). Further, while thromboprophylaxis is effective, its use does not eliminate the risk of VTE. Moreover, nearly 50% of VTE events occur unpredictably and are therefore not preventable with thromboprophylaxis. Strategies that focus on

Table III. Strategies for the prevention and management of PTS.

#### Prevention

Prevent index DVT with the use of thromboprophylaxis in high-risk patients and settings as recommended in evidence-based consensus guidelines.

Prevent recurrent ipsilateral DVT by providing anticoagulation of appropriate intensity and duration for the initial DVT and by targeted use of appropriate thromboprophylaxis if long-term anticoagulation is discontinued.

Use of knee-length, 30–40 mm Hg ECS elastic compression stockings for up to 2 years after DVT; optimal duration uncertain

The role of thrombolysis for the prevention of PTS is not yet established. Catheter-directed thrombolysis requires further evaluation in properly designed trials before it is endorsed as being effective in reducing the risk of PTS.

#### Management

Elastic compression stockings reduce odema and may improve PTS symptoms.

Intermittent pneumatic compression units are effective for severe symptomatic PTS.

Venoactive agents, such as aescin (e.g. as found in horse chestnut) or rutosides, may offer short term improvement of PTS symptoms; large controlled trials addressing long-term effectiveness and safety are needed.

Compression therapy, skin care and topical dressings are used to treat venous ulcers.

preventing the development of PTS after DVT are therefore more likely to be effective in reducing the frequency of PTS than are attempts to prevent the index DVT. As ipsilateral DVT recurrence is an important risk factor for PTS, preventing recurrent DVT by providing anticoagulation of appropriate intensity and duration for the initial DVT is an important goal (Kearon, 2004).

**Thrombolysis.** Thrombolytic therapy used in conjunction with heparin for the treatment of acute DVT leads to higher rates of vein patency and better preservation of valve function than does the use of heparin alone (Goldhaber *et al*, 1984; Ng & Rivera, 1998). However, the effectiveness and safety of thrombolysis for the prevention of PTS is as yet uncertain (Wells & Forster, 2001). A few trials of systemic thrombolysis for the treatment of DVT have assessed PTS as a study endpoint. Among 51 patients with acute proximal DVT, symptoms and signs of PTS were less frequent at the 19-month follow-up in those who received streptokinase compared with those who received heparin alone (35% vs. 92%) (Elliot *et al*, 1979). Similarly, in a trial of 42 patients with acute proximal DVT, signs of PTS at 6-year follow-up were less frequent in streptokinase than in heparin recipients (24% vs. 67%) (Arnesen *et al*, 1982). In a blinded trial of 83 proximal DVT patients, those treated with a 4-hour systemic infusion of tissue plasminogen activator had higher rates of achieving >50% clot lysis than heparin-treated patients (58% vs. 0%,  $P = 0.002$ ) and among trial patients who achieved >50% clot lysis, PTS

occurred less frequently (25% vs. 56%,  $P = 0.07$ ) (Turpie *et al*, 1990). While suggestive, these results are not considered to be definitive due to small numbers of patients studied, differing definitions of PTS, and for some trials, retrospective assessment for PTS.

Catheter-directed thrombolysis, which involves direct delivery of a fibrinolytic drug into the clot via a catheter introduced within the thrombosed vein, may be safer and more effective than systemic thrombolytic therapy and could hold promise as a means of preventing PTS. Results of a non-randomised study of 68 iliofemoral DVT patients enrolled in a registry who underwent successful catheter-directed thrombolysis suggested that such patients had fewer PTS symptoms, better physical functioning and less health distress at the 16-month follow-up than 30 similar patients who received anticoagulation alone (Comerota *et al*, 2000). In a prospective, single centre, non-randomised study of 51 patients with acute iliofemoral DVT, those who chose to receive multimodality therapy that included catheter-directed thrombolysis with balloon angioplasty or stenting followed by anticoagulation, had significantly better resolution of venous symptoms at 5 years than those who chose anticoagulation alone (78% vs. 30%,  $P = 0.0015$ ) (AbuRahma *et al*, 2001). Finally, a small single-centre randomised trial of 35 patients with acute iliofemoral DVT reported better venous physiological outcomes (venous function, valve patency) at the 6-month follow-up among catheter-directed thrombolysis recipients compared with those who received anticoagulation alone, but signs and symptoms of PTS were not reported (Elsharawy & Elzayat, 2002).

While the above results are of interest, as yet, there is no clear, high quality evidence to support the use of thrombolysis as a means to prevent PTS, and because of the lack of such evidence, consensus bodies recommend against the routine use of systemic or catheter directed thrombolysis for the initial treatment of DVT (Buller *et al*, 2004). In order to definitively address this important issue, large, rigorously conducted multicentre controlled trials of standard anticoagulation versus catheter-directed thrombolysis to prevent PTS are required.

*Elastic compression stockings.* Graduated elastic compression stockings (ECS) decrease oedema and improve tissue microcirculation (Pierson *et al*, 1983). Knee-length and thigh-length ECS appear to have equal physiological effects, but the former are easier to apply and more comfortable (Benko *et al*, 2001).

To date, three trials have evaluated the effectiveness of long-term use of ECS for the prevention of PTS after DVT. In the first, 194 patients with symptomatic proximal DVT were randomly allocated to daily use of a custom, made-to-measure 30–40 mm Hg knee-length ECS for at least 2 years or no stocking (Brandjes *et al*, 1997). PTS was diagnosed using a scoring system that incorporated symptoms and signs. Use of ECS resulted in a decrease from 47% to 20% of mild/moderate PTS and a decrease from 23% to 11% of severe PTS. A subsequent randomised trial conducted by Ginsberg *et al*

(2001) compared the effect of active stockings to sham stockings (no haemodynamic effect; one or two sizes too large) to prevent PTS in proximal DVT patients who had venous valvular incompetence but no symptoms or signs of PTS 1 year after the initial event. PTS was diagnosed using the Ginsberg PTS measure (Table II). No benefit of daily ECS was shown; 0 (0%) of the 24 patients in the active stocking group developed PTS, compared with one (4.3%) of 23 participants treated with sham stockings ( $P = 0.49$ ) (Ginsberg *et al*, 2001). Finally, a recent trial by Prandoni *et al* (2004) evaluated the effectiveness of 'off the rack' 30–40 mm Hg ECS versus no stockings in 180 patients with a first episode of symptomatic proximal DVT. The 2-year cumulative incidence of PTS, diagnosed using Villalta's scale (Table II), was 25% in the stocking group compared with 49% in the control group (hazard ratio 0.49;  $P = 0.011$ ).

A recent meta-analysis that pooled these three studies ( $n = 421$ ) reported an overall 54% relative risk reduction in PTS with use of ECS (Kolbach *et al*, 2003a). However, a number of important questions remain. Firstly, the lack of blinding in the two positive studies reduces confidence in the results because scales used to diagnose PTS and to assess its severity have subjective elements that are susceptible to reporting bias. Moreover, it is not yet known how long stockings need to be worn, which compression strength is optimal and whether they are of benefit to patients with distal DVT. Although ECS are unlikely to cause harm, they are difficult to apply, uncomfortable, expensive and require replacement every few months. Pending results of ongoing multicentre, placebo-controlled studies, providing stockings to patients who have residual leg pain or swelling after DVT and continuing them for as long as the patient derives symptomatic benefit is a reasonable approach.

### *Treatment of PTS*

There are few treatment options for PTS. To date, there is no evidence that long-term use of diuretics is effective for the treatment of PTS-related oedema. Clinicians often prescribe physical compression methods to counteract increased venous pressure. ECS on an as-needed basis may reduce swelling in some patients with PTS (Prandoni, 2005) and should be tried. However, their treatment benefit has not been definitively shown in the setting of PTS and is primarily extrapolated from studies of patients with chronic venous disease (Kurz *et al*, 1999). Indeed, a recent Cochrane review (Kolbach *et al*, 2003b) concluded that there is no evidence to support the use of ECS to treat PTS, and while intermittent pneumatic compression units may be of benefit for the management of severe, intractable PTS symptoms or severe oedema, they are cumbersome, expensive and there are no data on their long-term effects. Regarding medications to treat PTS, there is limited evidence that 'venoactive' agents, such as aescin or rutosides, may reduce symptoms of chronic venous insufficiency (Diehm, 1996) and in one study, improved PTS

symptoms in the short-term (Prandoni, 2005). However, the long-term benefit and safety of these medications have not been evaluated in large controlled trials. Post-thrombotic venous ulcers are generally treated with compression therapy, leg elevation and topical dressings but are often refractory to therapy and tend to recur (Kurz *et al*, 1999). Finally, surgical treatments for PTS, such as venous valve repair or venous bypass have been evaluated primarily in small patient series at single, specialised centres and appear to be of limited value (Eklof *et al*, 1998).

## Future areas for research

Post-thrombotic syndrome research has significantly lagged behind research in acute VTE. Studies are needed to better elucidate the pathophysiology and risk factors for PTS. Large-scale, ideally placebo-controlled, trials are needed to evaluate the effectiveness, optimal timing, strength and duration of use of ECS in preventing and treating PTS. Multicentre trials of catheter-directed thrombolysis to prevent PTS in patients with proximal DVT are also required. The potential value of venoactive agents, diuretics, anti-inflammatory medications and emerging novel therapies should be evaluated in well-designed trials that use a standardised approach to PTS diagnosis.

## Conclusion

Post-thrombotic syndrome is burdensome and costly to patients and society. At present, effective, evidence-based treatments for PTS are lacking, which is a source of difficulty and frustration for patients with PTS. Until effective treatments are found, prevention of PTS is the key to reducing its overall impact on patients and society. Preventing DVT recurrence is likely to reduce the risk of PTS. Daily use of graduated ECS after DVT may reduce the risk of PTS. As of yet, there is no established role for thrombolysis in preventing PTS.

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