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Contemporary Issues in the Prevention and Management of Postthrombotic Syndrome

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Abstract

OBJECTIVE—To provide an evidence-based review and clinical summary of postthrombotic syndrome (PTS).

DATA SOURCES—A literature review was performed via MEDLINE (1950–July 1, 2009) and *International Pharmaceutical Abstracts* (1970–June 2009) searches using the terms post-thrombotic syndrome, post-phlebitic syndrome, deep vein thrombosis, and compression stockings.

DATA SYNTHESIS—PTS is best characterized as a chronic syndrome of clinical signs and symptoms including pain, swelling, parasthesias, and ulceration in the affected limb following deep vein thrombosis (DVT). It occurs in up to half of patients with symptomatic DVT, usually within the first 2 years. Although the pathophysiology of PTS is not well understood, a thrombus may cause venous hypertension and valvular incompetence resulting in edema, tissue hypoxia, and in severe cases, ulceration. Risk factors for PTS include recurrent ipsilateral DVT, obesity, and poor quality of anticoagulant therapy. PTS diagnosis is based on the presence of typical signs and symptoms and may be made using one of several clinical scoring systems. Prevention of PTS should focus on DVT prevention and the use of elastic compression stockings following DVT, while fibrinolysis remains under investigation as an effective method for PTS prevention. The treatment of PTS may include either pharmacologic or mechanical modalities, although none of these regimens has been rigorously tested. Pharmacists have the opportunity to provide more comprehensive antithrombotic management by educating patients and providers on PTS, recommending appropriate preventive therapy, assisting patients in obtaining and adhering to this therapy, and assisting providers with the management of PTS.

CONCLUSIONS—Providers should be proactive in preventing PTS, with pharmacists taking an active role in optimal DVT prevention, identifying patients at risk for PTS, and counseling and directing preventive therapies.

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Keywords

compression stockings; deep vein thrombosis; edema; postphlebitic syndrome; postthrombotic syndrome; venous thromboembolism

Postthrombotic syndrome (PTS) is a chronic and often debilitating complication of deep vein thrombosis (DVT). The classic symptoms of PTS are pain, swelling, edema, and venous ectasia in the affected limb following a DVT. Severe PTS can lead to chronic lower extremity ulceration, resulting in limited mobility and the need for frequent medical care. Even in less severe cases of PTS, the quality of life (QoL) of patients may be significantly limited.[1,2]

In the US, an estimated 600,000 cases of venous thromboembolism (VTE) occur annually, with over 375,000 cases of DVT. Similar estimates report an additional 296,000 fatal VTE events.[3] Other studies have reported the overall annual incidence of VTE to be approximately 120 per 100,000.[4] While pulmonary embolism and recurrent DVT are well-recognized complications of DVT, it is becoming clearer that PTS is a potentially severe, costly, and debilitating condition that is underrecognized by many health-care practitioners. The aim of this article is to increase awareness of PTS by providing a review of its incidence, burden, and pathophysiology, as well as current prevention and treatment modalities. Additionally, we highlight areas where pharmacists can play a significant role in the prevention and management of PTS.

Data Sources

A literature review was performed via MEDLINE (1950–July 1, 2009) and *International Pharmaceutical Abstracts* (1970–June 2009) searches using the terms post-thrombotic syndrome, post-phlebitic syndrome, deep vein thrombosis, and compression stockings. We reviewed English-language publications, including randomized controlled trials, meta-analyses, case reports, and literature reviews, and selected publications deemed most clinically relevant to the topic of PTS.

Epidemiology

HOW COMMON IS PTS?

PTS is the most common complication of DVT, with symptoms occurring in up to half of patients following a first episode of symptomatic DVT, typically within the first 2 years. Most studies have reported an overall incidence of 20–50% for PTS,[5–10] but differences in the definition of PTS, diagnostic modalities, and PTS scales have limited a more precise estimation of the true incidence.

The reported incidence of PTS following asymptomatic DVT is less clear. While some studies have shown that as many as 25–33% of patients with asymptomatic DVT develop PTS, other investigations have found either low rates of PTS or no significant difference in the rates of PTS with asymptomatic proximal DVT or calf DVT, compared with no DVT.[5,11,12] Most of these studies examined postoperative orthopedic surgery patients, were limited by smaller sample sizes, and differed in the definition of PTS and the methods employed for the diagnosis of DVT.

WHAT IS THE EFFECT OF PTS ON QUALITY OF LIFE?

Because PTS symptoms are typically more severe with standing or physical activity, PTS has been associated with a reduced QoL. For example, Kahn et al.[13] studied both validated

generic and venous disease–specific QoL measures. They found that of 387 patients with acute DVT, those who developed PTS had lower scores and significantly less improvement in QoL when assessed 2 years following the index event. QoL scores were negatively correlated with the severity of PTS symptoms. PTS was the only independent predictor of venous disease–specific QoL, suggesting that the development of PTS may have the largest effect on QoL after DVT. Additionally, multiple studies have demonstrated that patients with PTS have a significantly poorer QoL than DVT patients without PTS or patients with other forms of chronic venous disease.[2,14,15]

WHAT IS THE COST OF PTS?

The estimated healthcare costs of treating PTS add significantly to the cost of treating DVT. The annual cost of PTS in the US has been estimated at approximately $200 million, with costs over $3800 per patient in the first year alone.[16] Annual per-patient cost increases with disease severity.[1,8,17] Venous ulceration is the most expensive complication, costing nearly an additional $8000 per patient.[18] The indirect costs of PTS are significant as well. It is estimated that over one quarter of the 170,000 cases of venous stasis syndrome are a result of PTS and that up to 2 million work days are lost per year due to complications related to leg ulcers.[1,2,8]

HOW DOES PTS DEVELOP?

Despite ongoing investigations into the pathophysiology of PTS, the mechanisms and processes leading to its development are not entirely clear. Inflammatory mediators and the acute thrombus itself may damage the venous wall and cause valvular incompetence which, in turn, leads to venous hypertension and reduced calf muscle perfusion with subsequent altered muscle metabolism.[19,20] Increased tissue permeability present in PTS likely results from a combination of increased venous pressure augmented by angiostatic chemokines. Thus, as vessel diameter increases due to valvular incompetence and inflammatory-mediated chemokine changes, fluid accumulates and permeability markedly increases.[21] Taken together, these processes lead to edema, tissue hypoxia, and in severe cases, lipodermatosclerosis and ulceration (Figure 1).[5,8]

WHAT ARE RISK FACTORS FOR PTS?

The location and size of the initial DVT may predict the risk of PTS.[6] For example, proximal DVT has been associated with a 30% higher risk of developing PTS compared with distal DVT.[10] In addition, ipsilateral DVT increases the risk of PTS 6- to 10-fold.[6,8,22] This higher risk may reflect the additional damage of recurrent thrombosis on the venous valves and endothelium. The presence of residual thrombus on ultrasound has not been definitively shown to increase the risk of PTS.[14,23]

Although neither age nor sex has been shown to definitively increase the risk of PTS,[10,14,22,24–26] obesity (body mass index ≥30 kg/m^2), which is a major risk factor for DVT, is associated with an increased risk and severity of PTS. This higher risk may be due to increased venous pressure promoting venous reflux in already compromised veins in the setting of chronic debilitation and poor muscle function.[8,10,14,24] The presence of an identified thrombophilia is associated with an increased risk of venous leg ulcers but does not increase the risk of PTS.[10,22,27]

DO THE DURATION, INTENSITY, AND QUALITY OF ANTICOAGULATION THERAPY AFFECT THE RISK OF PTS?

Neither the duration (6 wk vs 6 mo) nor the intensity (international normalized ratio [INR] target 2.5 vs 1.7) of anticoagulation affects the risk of PTS.[14] The quality of anticoagulation

management, however, does correlate with the risk of PTS. van Dongen et al.[26] reported that patients with DVT with subtherapeutic anticoagulation (INR <2.0) more than 50% of the time during their first 3 months of warfarin treatment had an increased risk of developing PTS during the 5-year follow-up period (OR 2.71). Importantly, tight INR control may mitigate the risk of PTS. When comparing patients who had a subtherapeutic INR over 30% of the time with those whose INR was therapeutic over 30% of the time, the OR for developing PTS was 1.89. When patients' INRs were outside the therapeutic range 90% of the time, the OR for developing PTS increased to 3.69.

Since pharmacists often provide anticoagulation management and monitoring, they are uniquely positioned to identify patients at risk for PTS and can help to ensure that patients are educated on the importance of maintaining therapeutic anticoagulation to prevent complications of DVT, such as PTS.

Diagnosis

Typically, PTS is characterized by lower extremity swelling and pain. These symptoms are often worse with activity and improved with rest or elevation of the affected limb. Other symptoms include cramping, tingling, and itching. On examination, patients with PTS may have edema, erythema, varicose veins, and eczema; severe cases may be associated with chronic ulcers.[28] When a patient presents with these unilateral symptoms, has a history of DVT, and new or recurrent DVT is excluded, a diagnosis of PTS may be made clinically.[5,28] Ideally, the diagnosis of PTS should be deferred until 3–6 months after the index DVT, as symptoms due to acute DVT may take this long to completely resolve.

There are now 4 clinical scoring systems that may be helpful for the diagnosis of PTS. These include Widmer staging,[29] Villalta scale,[30] Ginsberg measure,[11,31] and Clinical-Etiologic-Anatomic-Pathophysiologic (CEAP) classification[32] (Table 1). There is no clear advantage of using one of these scales over the others. Both the CEAP and Widmer scales are more general classifications and may be used in evaluating both PTS and chronic venous disease, while the Villalta scale and Ginsberg measure are specific for PTS. Although the Villalta scale appears to be gaining in use and popularity, none of these scales has undergone rigorous validation. Differences in the interrater reliability of these scales may be one of the reasons why reported rates of PTS vary in published studies.[33]

Documenting valvular incompetence by Doppler ultra-sonography or by plethysmography is not necessary if typical PTS signs and symptoms are present in a patient with a history of DVT. If valvular incompetence is identified by imaging without the presence of typical signs and/or symptoms of PTS, a diagnosis of PTS should not be made,[28,34] as many patients with a history of DVT will have evidence of valvular incompetency on imaging studies. A recent article calls for an established uniform definition of PTS to provide greater validity between researchers and practical use for clinicians.[35]

Prevention

DVT PREVENTION

Arguably, the most effective way to prevent PTS is to prevent DVT from occurring. We now have a number of well-designed, randomized studies demonstrating that pharmacologic prophylaxis effectively reduces the risk of DVT and pulmonary embolism in patients at risk.[36] Unfortunately, despite these high-quality data, many hospitalized patients are either not correctly identified as being at risk (and thus do not receive appropriate thromboprophylaxis) or receive a prophylaxis regimen that is not supported with current recommendations (eg, aspirin alone or mechanical devices alone when a pharmacologic

agent is more appropriate and there is no appreciable bleeding risk).[36,37] All providers, including nurses, pharmacists, and physicians, should be engaged in recognizing at-risk patients and ensuring that appropriate prophylaxis is ordered and administered in a timely fashion.

ELASTIC COMPRESSION STOCKINGS

What Are They and How do They Work?—One method of preventing the development of PTS is the use of elastic compression stockings (ECS). ECS provide graduated levels of compression (highest pressure at the ankle, lowest pressure at the knee or thigh) to assist the calf muscle and improve tissue circulation, although the exact mechanism is not well understood.[38,39] In general, the lower strength stockings are used for prevention or treatment of minor venous conditions, and the higher strength are used for more severe venous conditions (Table 2).

What is the Evidence?—The benefit of using ECS for the prevention of PTS was first seen in a small number of observational trials.[34,40,41] Four randomized, controlled trials have been published with conflicting results regarding the efficacy of ECS in the prevention of PTS (Table 3).[22,31,42,43] Both the Brandjes et al.[43] and Prandoni et al.[22] trials demonstrated benefit of ECS for PTS prevention, while the Ginsberg et al.[31] and Aschwanden et al.[42] trials did not. Each of these trials has limitations. The 2 positive studies were nonblinded, contrasted with the Gins-berg trial, which utilized a placebo stocking (stocking 1–2 sizes too large, thus producing no hemodynamic effect) for comparison. Some state that the use of a placebo stocking may have actually been a confounder, since it is possible the placebo stocking could have provided some unknown degree of compression.[44] Finally, the Aschwanden trial was actually underpowered for its primary outcome of detecting post-thrombotic skin changes.

A meta-analysis of the Brandjes, Ginsberg, and Prandoni trials by Kolbach et al.[44] reported that the use of ECS significantly reduced the incidence of all PTS (OR 0.31; 95% CI 0.20 to 0.48) and of severe PTS (OR 0.39; 95% CI 0.20 to 0.76). A meta-analysis by Giannoukas et al.[45] also found that the use of ECS reduced the risk of PTS (RR 0.52; 95% CI 0.40 to 0.67). The Giannoukas meta-analysis included the above 3 trials plus an additional 37-patient trial that randomized patients to either bed rest and no compression or early ambulation (plus either Unna boot bandages or 30- to 40-mm Hg strength compression stockings) for 9 days.[46]

Limitations of both meta-analyses were the lack of a uniform definition of PTS, varying compression regimens (specifically with regard to strength, timing, and duration), varying assessments of adherence, and varying duration of anticoagulation. Further, the trial[46] included in the second meta-analysis assessed early ambulation combined with compression therapy as a preventive strategy, so we are unable to assess the source of treatment benefit.

A large, randomized, multicenter controlled trial in progress may clarify these issues.[47] The SOX trial investigators are randomizing patients to a 30- to 40-mm Hg strength stocking or a 5-mm Hg placebo stocking, which is similar to a store-bought trouser sock (Table 3). Results from the SOX trial are not expected for several more years.

What Strength ECS to Prescribe?—The compression strength of stockings used in these randomized trials ranged from 20 to 40 mm Hg.[22,31,42,43] The clinical trials using 30- to 40-mm Hg strength stockings demonstrated the most efficacy in reducing the risk of PTS and is reflected in current recommendations for PTS prevention[48] (Appendix I). However, currently, there are no data directly comparing the efficacy of different strengths of ECS for PTS prevention and further studies are needed to determine the minimum effective strength.

What is the Timing and Duration of ECS Therapy?—The optimal time of initiation and duration of ECS therapy after a diagnosis of DVT remain controversial. No published studies to date have specifically evaluated the timing of stocking application on the incidence of PTS. The randomized controlled trials cited above employed ECS at various time points (immediately upon DVT diagnosis up to 1 y after diagnosis).[22,31,42,43] One randomized trial assessed the effects of early versus later application of ECS on vein recanalization following DVT.[49] Patients were prescribed 25.5–32.5 mm Hg ECS within the first 14 days after the initiation of DVT treatment. Fifty-two patients completed 90 days of follow-up. In the early compression therapy group, 82% of occluded venous segments were completely recanalized at 90 days, as compared with 60% complete recanalization in the control group (OR 0.27; 95% CI 0.07 to 0.89). No patients in either group demonstrated PTS symptoms at 90 days (method of PTS diagnosis not defined). However, PTS was a secondary endpoint, with the number of patients too small and study duration too short to make a definitive assessment.

The early application of ECS may have opposing effects on adherence. Patients usually experience the most leg pain and swelling in the first few weeks following DVT diagnosis and may associate improvement in their symptoms with the use of ECS. The randomized trials that applied ECS early (within the first month following DVT diagnosis) had excellent adherence rates (76–93%).[22,42,43] The one trial that employed a late application of ECS (at 1 y following DVT diagnosis) did not report adherence data.[31] However, if patients have significant lower extremity swelling immediately following DVT diagnosis, they may require a different size stocking early in therapy as opposed to later in therapy, requiring additional purchases of stockings. Also, the early leg pain and swelling may actually prohibit many patients from using the stockings.

Regarding the duration of ECS, trial data demonstrate that the incidence of PTS is highest in the first 2 years following a diagnosis of proximal DVT and does not change appreciably after 2 years.[22,42,43] These reports imply that compression therapy will likely be beneficial at least for this duration of time, although indefinite use may be reasonable in patients with ongoing signs or symptoms of PTS.

Consistent with current recommendations from the American College of Physicians, the American Academy of Family Physicians, and the American College of Chest Physicians (ACCP), providers should discuss PTS with and prescribe ECS for all patients within the first month following acute proximal DVT diagnosis, preferably within the first 2 weeks after diagnosis, and continuing for a minimum of 2 years[48,50] (Appendix I).

What Are the Barriers to Patient Adherence to ECS?—Patient adherence is perceived to be a barrier to the routine use of ECS due to discomfort, difficulty with putting them on, and cost.[51] Clinical trials, which used varying definitions for “regular” use of ECS, reported adherence rates between 54% and 93%.[22,40–43] Although one might expect to see a lower rate of adherence outside the setting of a clinical trial, of 78 patients surveyed in routine clinical settings, 87% reported daily use of ECS.[51] Adherence rates are significantly lower in patients with distal DVT, as these patients generally have fewer or less severe symptoms.[40,51]

To improve patient adherence to ECS, providers may prescribe knee-length ECS, similar to what was used in most clinical trials. Compared with thigh-length ECS, the knee-length products are just as effective but may be much more comfortable for patients.[52] Based on the mechanism and design of the stockings, it is thought that as long as the highest pressure is applied at the ankle, the stocking will provide the desired effect of reducing pain and edema, regardless of the location of the clot.[38] As was the practice in most clinical trials,

patients should be instructed to wear the stocking only on the affected leg during waking hours.[22,31,38,39,43] Difficulty putting on the stockings is often a barrier to patient adherence.[51] There are several things that patients can do to make this process easier (Appendix I).

Cost was also cited as a perceived barrier to adherence.[51] ECS 30– 40 mm Hg can be purchased at most medical supply stores with a prescription; the average cost is approximately $40–50 per pair (results of an informal survey of local medical supply stores, May 18, 2009), which may not be reimbursed by some third-party insurers.

There are other important items to remember when prescribing ECS (Appendix I). Patients' ankle and calf circumferences should be measured to obtain the appropriate size stocking. For optimal accuracy, these measurements should be taken in the earliest part of the day when leg swelling is minimal. The stockings should be replaced every 6 months so that proper elasticity and, hence, efficacy is maintained.[22,31,43] Despite the demonstrated benefit of ECS for the prevention of PTS, patients with peripheral arterial insufficiency should not receive compression therapy.[22,38,42,47]

Does Exercise Prevent PTS?—Some have proposed that exercise and/or early ambulation (with or without compression therapy) following a diagnosis of DVT may help to reduce the risk of PTS. In one study, patients who received compression therapy plus early mobilization had significantly lower Villalta scores 2 years post-DVT compared with patients who were prescribed bed rest and no compression therapy.[46] Another study demonstrated that patients may continue to wear ECS during exercise, but that stockings will not necessarily help to improve symptoms during or caused by exercise, nor will they increase exercise capacity.[53]

How Can PTS Prevention with ECS Be Improved?—As providers, we should ensure that ECS are prescribed for all patients with proximal DVT to optimize PTS prevention efforts. Despite recommendations from evidence-based guidelines, a survey conducted by Kahn et al.[51] revealed that only one third of 34 Canadian physicians routinely prescribe ECS following DVT diagnosis, and only half prescribe the recommended strength stocking (30–40 mm Hg). Recent data suggest that rates of ECS prescription may not be higher in specialty anticoagulation providers.[54] Pharmacists can improve the rate of ECS prescribing by initiating protocols and policies for prescribing ECS, so that this becomes standard practice across institutions. The pharmacist who interacts regularly with patients who have DVT is in the position to identify patients at risk for PTS and to recommend appropriate preventive therapy. The pharmacist can also assist patients in obtaining ECS and educating them in their proper use. By taking this active role, pharmacists can improve patient adherence to use of ECS, prevent PTS, and make a major impact on decreasing this long-term complication of DVT.

DOES USING FIBRINOLYTICS FOR ILIOFEMORAL DVT PREVENT PTS?

Patients with acute iliofemoral DVT appear to be at higher risk of developing severe PTS.[55] Although conventional treatment for iliofemoral DVT is a parenteral anticoagulant followed by warfarin, this therapy does not reliably lead to recanalization of affected vein segments.[56] Studies investigating the use of systemic fibrinolytics in conjunction with un-fractionated heparin (UFH) reported that vein patency and valve function appeared to be better compared with the use of heparin alone.[57,58] In addition, meta-analysis data from 5 studies encompassing 110 patients demonstrated that the incidence of PTS was lower in patients with DVT who were treated with streptokinase and UFH compared with those treated with UFH alone (42.5% vs 69.6%, OR 0.46, 95% CI 0.21 to 0.99).[59] These data, of course, are

limited by the small sample sizes, significant heterogeneity in the different study designs, the lack of a uniform definition of PTS, and incomplete study follow-up.[60]

In comparison, catheter-directed thrombolysis (CDT) is a method by which a fibrinolytic agent is delivered via catheter into a clot within a thrombosed vein. Several recent trials have studied the benefit of CDT in iliofemoral DVT. Although different in study design and outcome measures, these trials reported that in carefully selected patients, the use of CDT as an adjunct to standard treatment (ie, a heparinoid and warfarin) improved venous patency and was associated with fewer long-term symptoms of PTS.[61–64] For example, a retrospective survey in patients with iliofemoral DVT reported that patients treated with CDT in addition to standard anticoagulation (n = 68) had significantly fewer PTS symptoms ($p = 0.006$) than did those treated with anticoagulation alone (n = 30).[62] Subsequently, the ACCP now recommends that CDT (or systemic thrombolysis if CDT is unavailable) be used in select patient populations (iliofemoral DVT, symptoms for <14 days, good functional status, life expectancy ≥1 y, low bleeding risk) for the purpose of reducing acute symptoms and postthrombotic morbidity.[48]

Treatment

MECHANICAL

Studies have employed various mechanical methods to treat PTS, including compression, elevation, and dressings (Table 4). Most authors have focused primarily on edema as a measurable outcome in response to PTS treatment.[65] Physical compression methods include any type of circular pressure on the leg. Utilized techniques include adherent tape, Unna's paste boot, ECS, and newer venous return assist devices, such as the Venowave. Although these treatments are frequently prescribed, their benefit has not been clearly established. A review of patients with Widmer stage I and II PTS found no benefit of ECS (30–40 mm Hg at the ankle) compared with placebo.[66] In patients with severe PTS, intermittent pneumatic compression (IPC) did reduce symptom severity and increase blood oxygenation.[67–69] Clinical guidelines reflect this research, and the ACCP suggests compression therapy for mild leg edema and IPC for severe leg edema.[48]

PHARMACOLOGIC

There are several pharmacologic treatments available for PTS-related edema and venous ulcers (Table 4). Although none of these has proven safety and efficacy in large clinical trials, they may provide symptomatic relief. Patients using pentoxifylline demonstrated significantly improved venous ulcer healing at 6 months.[70] A meta-analysis of 11 randomized trials evaluated and supported pentoxifylline's effectiveness (RR 1.56; 95% CI 1.14 to 2.13),[71] although not all trials reached statistical significance.[72] A pentoxifylline regimen of 400 mg 3 times daily was largely uniform across the studies included in the meta-analysis.[71] One study compared pentoxifylline 400 mg 3 times daily with 800 mg 3 times daily and found no significant difference in ulcer healing rates. Duration of therapy was not specifically studied and varied from as little as 6 weeks (or healing of the ulcer) to 6 months. According to the meta-analysis, pentoxifylline is well tolerated, with gastrointestinal upset as the most common adverse effect. Aescin (or escin), the main active component of horse chestnut, has antiinflammatory, vasoconstrictive, and vaso-protective properties[73]; it is primarily effective in the treatment of venous ulcers. In a 12-week study of patients with chronic venous insufficiency, treatment with aescin 50 mg twice daily reduced PTS symptoms similarly compared with ECS.[74] Rutosides (rutin), naturally occurring, yellow crystalline flavonol glycosides, affect capillary permeability and have been studied more in chronic venous insufficiency than in PTS specifically.[75] When applied either topically or systemically, rutosides do appear to improve leg edema and blood flow in these

patients.[48,76–78] For pharmacologic treatment of PTS, the ACCP recommends pentoxifylline 400 mg 3 times daily in conjunction with localized care and compression or IPC devices for venous leg ulcers. For persistent venous ulcers, the ACCP recommends treatment with rutosides.[48] There are currently no formal recommendations for using aescin as a treatment for PTS-related complications.

Pharmacists can help in the treatment of PTS by making recommendations for appropriate pharmacotherapy and monitoring for drug interactions with any new therapy, as many of these patients may still be taking warfarin for treatment of their DVT.

Upper Extremity PTS

The development of PTS after upper extremity DVT is less well studied than after lower extremity DVT, but the incidence appears to be approximately 15% overall, with a range reported in studies between 7% and 46%.[79] No published trials have evaluated the efficacy of compression devices and/or venoactive drugs in upper extremity PTS. We echo the recommendations of the 2008 ACCP guidelines against the use of preventive therapy for PTS in patients with upper extremity DVT. In patients with upper extremity PTS symptoms that do not resolve, elastic bandages or compression sleeves may provide some symptom relief.[48] Additionally, referring these patients to a lymphedema clinic may be helpful.

Areas of Future Study

There are several areas where additional investigations and studies will help us to better understand how to prevent and treat PTS. First, the clinical scoring systems for diagnosis of PTS have not been validated (Table 1). A validated diagnostic tool will improve the quality and uniformity of clinical trials and allow us to better define and assess the impact of PTS on patients with DVT. Second, there are still unanswered questions regarding the optimal prevention of PTS. Although several trials have demonstrated the efficacy of ECS for PTS prevention, the minimum compression strength necessary and the optimal timing and duration of compression therapy remain unknown. We need data on whether ECS are effective or even necessary for prevention of PTS following either asymptomatic or distal DVT. In addition, the role of fibrinolytic therapy in reducing PTS is still unclear. Finally, additional treatment options for PTS with demonstrated safety and efficacy are needed, particularly in the area of pharmacotherapy.

Summary

PTS is a common and costly complication of DVT and significantly affects a patient's QoL. Acute DVT and the accompanying inflammation cause valvular incompetence and venous hypertension, which result in the pain, swelling, and venous ulceration that are associated with PTS. Preventive efforts should be multifaceted, and we must not forget the importance of evidence-based DVT prophylaxis in patients identified as being at risk. Once DVT has occurred, we should ensure optimal anticoagulation control, monitor for signs and symptoms of PTS, and provide appropriate preventive therapy. ECS, when applied within the first few weeks following DVT and continued regularly for at least 2 years, are effective in preventing PTS. Fibrinolytic therapy for acute iliofemoral DVT may be appropriate for carefully selected patients. Finally, if patients develop PTS, the diagnosis should be made based on clinical signs and symptoms; imaging is usually unnecessary. Treatment of PTS includes pharmacologic agents, such as aescin or horse chestnut, rutosides, and pentoxifylline, and compression therapy and wound care for venous ulcers. Pharmacists have the opportunity to provide more comprehensive antithrombotic management by providing education to all patients with DVT regarding PTS, recommending and/or

prescribing appropriate preventive therapy, assisting patients in obtaining and adhering to this therapy, and assisting providers with the diagnosis and management of PTS.

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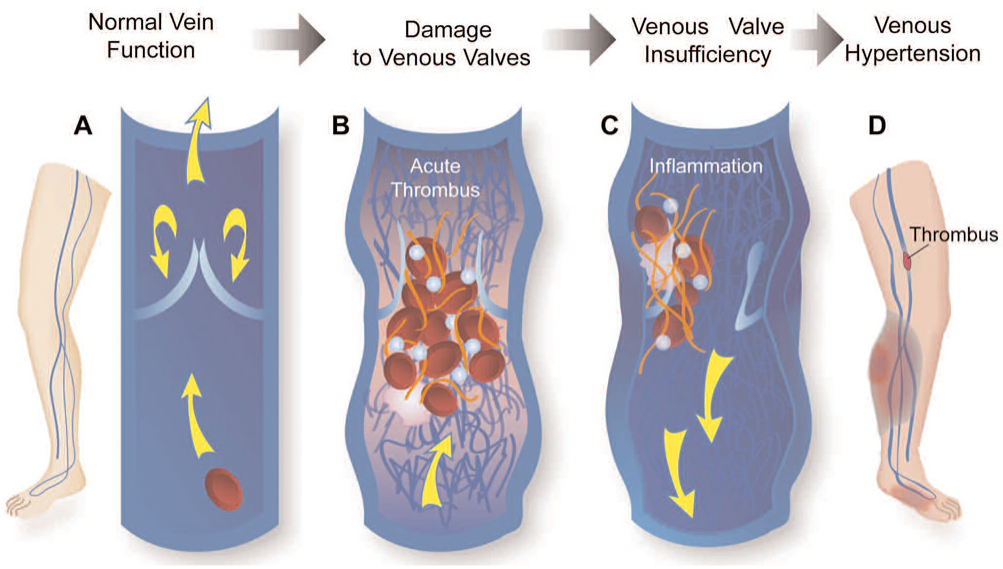

Figure 1.
The pathophysiology of postthrombotic syndrome. Thrombus damages venous valves, leading to valvular insufficiency and venous hypertension. This process may ultimately lead to the erythema, pain, and swelling characteristics of postthrombotic syndrome.

Table 1

Clinical Scales for the Diagnosis of Postthrombotic Syndrome

PTS Scale	Criteria Used to Diagnose PTS
Widmer staging	stage I: ankle flare, subclinical edema
Widmer (1985)[29]	stage II: edema, pigmentation, lipodermatosclerosis, skin atrophy
	stage III: leg ulcer, current or past
Villalta scale	5 symptoms (pain, cramps, heaviness, pruritus, paresthesia)
Villalta (1994)[30]	6 signs (edema, 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 presence of ulcer: severe PTS
Ginsberg measure	pain and swelling of limb of ≥1 mo; typical character (worse end of day or with prolonged sitting/standing, better after night's rest and leg elevation) that occurs ≥6 mo after acute DVT
Ginsberg (2000, 2001)[11,31]	
CEAP classification	pts. with chronic venous disease classified into 1 of 7 clinical classes (0–6) according to presence of clinical signs.
Porter (1995)[32]	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. edema, no skin changes
	4. skin changes (eg, pigmentation, eczema, lipodermatosclerosis)
	5. skin changes with healed ulcer
	6. skin changes with active ulcer
	Each clinical class is then subclassified as to:
	Etiologic (congenital, primary, secondary)
	Anatomic (superficial, deep, perforator veins)
	Pathophysiologic (reflux, obstruction, both)

CEAP = Clinical-Etiologic-Anatomic-Pathophysiologic; DVT = deep vein thrombosis; PTS = postthrombotic syndrome.

Table 2

Types and Uses of Elastic Compression Stockings[a]

Class	Strength (mm Hg)	OTC or Rx	Uses
Lightweight	<20	OTC	minor spider veins, slight varicose veins, varices during pregnancy, prevention of VTE in recumbent pts.
Class 1	20–30	OTC	heaviness and fatigue in the legs; moderate spider veins; minor varicose veins; varices during pregnancy; minor foot, ankle, and leg swelling; superficial thrombosis; post-sclerotherapy
Class 2	30–40	Rx	moderate varicose veins, moderate edema, lymphatic edema, management of venous ulcers, prevention of venous ulcers **prevention of PTS** orthostatic hypotension, post-sclerotherapy, pregnancy with previous phlebitis, stasis dermatitis due to chronic venous insufficiency
Class 3	40–50	Rx	severe varicose veins, severe edema, lymphatic edema, management of venous ulcers **PTS** chronic venous insufficiency, orthostatic hypotension

OTC = over-the-counter; PTS = postthrombotic syndrome; Rx = prescription; VTE = venous thromboembolism.

[a]Data from Medi, supplier of compression stockings, May 15, 2009.

Table 3

Randomized Controlled Trials Assessing the Efficacy of Elastic Compression Stockings for the Prevention of Postthrombotic Syndrome

Reference	Pts.	Control Group	Treatment Group	Outcomes
Brandjes (1997)[43]	N = 194; first-episode proximal DVT	n = 98 no ECS	n = 96 ECS 40 mm Hg, applied 2–3 wk after DVT diagnosis and worn daily for at least 2 y	mild-moderate PTS[a] control: 47% ECS: 20% p < 0.001 severe PTS[b] control: 23% ECS: 11% p < 0.001
Ginsberg (2001)[31]	N = 202; 1 y after first episode of proximal DVT pts. divided into 3 groups study 1: no PTS, no VVI study 2: no PTS, + VVI study 3: + PTS	study 1: n = 120 no intervention study 2: n = 23 placebo stocking study 3: n = 17 placebo stocking	study 2: n = 24 ECS 20–30 mm Hg study 3: n = 18 ECS 30–40 mm Hg	study 1 PTS[c]: 5% study 2 PTS[c]: placebo: 4.3% ECS: 0% study 1 (no intervention) vs study 2 placebo group: no significant difference in PTS study 3 worsened PTS symptoms[c]: placebo: 59% ECS: 61%
Prandoni (2004)[22]	N = 180; first-episode proximal DVT	n = 90 no stockings	n = 90 ECS, 30–40 mm Hg, applied 5–10 days after DVT diagnosis and worn daily for at least 2 y	mild-moderate PTS[d]: control: 49% ECS: 24.5% severe PTS[d]: control: 11.7% ECS: 3.5%
Aschwanden (2008)[42]	N = 169; first or recurrent proximal DVT following at least 6 mo of OAC and ECS	n = 85 no stockings	n = 84 ECS, 26–36 mm Hg, worn daily for 2 y	CEAP class 4 or higher post-thrombotic skin changes[c] control: 20% ECS: 13.1% presence of at least 1 of 5 PTS-associated symptoms[e] control: 16.5% ECS: 12.2%
Kahn (2007)[47]	first-episode proximal DVT (study in progress)	"inactive stocking" 5 mm Hg, applied as early as possible within 14 days after DVT diagnosis and continued for 2 y	ECS 30–40 mm Hg, applied as early as possible within 14 days after DVT diagnosis and continued for 2 y	incidence of PTS[d]

CEAP = Clinical-Etiologic-Anatomic-Pathophysiologic; DVT = deep vein thrombosis, ECS = elastic compression stockings; OAC = oral anticoagulation; PTS = postthrombotic syndrome; VVI = venous valvular incompetence.

[a] Mild-moderate PTS (score ≥3): 1 point each for spontaneous pain in calf, spontaneous pain in thigh, pain in calf on standing/walking, pain in thigh on standing/walking, edema of foot/calf, "heaviness" of leg, calf circumference increased by 1 cm, ankle circumference increased by 1 cm, pigmentation, venectasia, newly formed varicosis, phlebitis.

[b] Severe PTS (score ≥4): 1 point each for spontaneous pain and pain on standing/walking, edema of calf, impairment of daily activities, calf circumference increased by 1 cm, pigmentation, discoloration, and venectasia, 4 points for venous ulcer.

[c] See Table 1 for PTS scoring system.

[d] Used Villalta scale; see Table 1.

[e] Symptoms not described.

Table 4

Treatment of Postthrombotic Syndrome

Agent/Method/Device	Mechanism	Evidence
Compression, elevation, dressings[66]	decreased pooling of blood and subsequent reduction in diameter of vessels; improved oxygenation	meta-analysis of ECS (30–40 mm Hg) in mild-to-moderate cases of PTS failed to show benefits
Intermittent pneumatic compression[67]	same as ECS	prospective crossover trial in 15 pts.; significantly lower mean symptom score in therapeutic vs placebo pressures
Pentoxifylline[71]	uncertain: thought to lead to decreased red and white blood cell filterability, decreased blood viscosity, decreased fibrinogen levels, and decreased platelet aggregation	RR 1.70 (95% CI 1.30 to 2.24) for complete healing of leg ulcers in a meta-analysis of 11 randomized placebo-controlled trials
Aescins (horse chestnut)[73]	uncertain: prevention of leukocyte activation may prevent anti-elastase and anti-hyaluronidase acitivity	evidence limited to mainly small clinical trials with or without randomization; thought to be at least as effective as ECS
Rutosides[75–78]	uncertain: similar to other flavanoid compounds: reduces inflammatory-mediated damage	limited studies available; trials with extensive exclusion criteria; no adverse reactions reported

ECS = elastic compression stockings; PTS = postthrombotic syndrome.

Appendix I

Summary of Recommendations: Elastic Compression Stockings for the Prevention of the Postthrombotic Syndrome

American College of Chest Physicians[48]

For a patient who has had a symptomatic proximal DVT, we recommend the use of an elastic compression stocking with an ankle pressure gradient of 30 to 40 mm Hg if feasible (Grade 1A). Compression therapy, which may include use of bandages acutely, should be started as soon as feasible after starting anticoagulant therapy and should be continued for a minimum for 2 years, and longer if patients have symptoms of PTS.

American College of Physicians and the American Academy of Physicians[50]

Compression stockings should be used routinely to prevent postthrombotic syndrome, beginning within 1 month of diagnosis of proximal DVT and continuing for a minimum of 1 year after diagnosis.

Elastic Compression Stockings

Explain PTS and begin ECS “as soon as feasible” within the first month following DVT diagnosis and continued for at least 2 years.

Prescribe a knee-length stocking (regardless of the location of the DVT) worn only on the affected leg during waking hours.

Prepare the patient with the following information:

- prescription is required for the 30- to 40-mm Hg strength ECS
- replace ECS at least every 6 mo
- approximate cost of ECS
- list of local medical supply stores that stock the appropriate-strength ECS

ECS should be sized to fit based on ankle and calf circumference measurements (sizing should be done at the time of day when extremity is least swollen)

Tips for application of ECS:

If the patient cannot tolerate wearing ECS all day, have him/her wear ECS for a few hours at a time, and gradually increase the amount of time worn.

Put ECS on first thing in the morning when extremity is least swollen.

Do not allow wrinkles in the ECS.

Do not cut or alter ECS.

Never fold or roll down ECS.

Pts. with difficulty bending to put on stockings may try assist devices such as rubber gloves (provides a better grip to pull ECS) or a stocking aid (stocking fits over a metal device, patient slides foot into stocking).

Pay attention to manufacturer instructions for the ECS: wash and dry as directed to prevent shrinkage or damage to the stockings.

ECS = elastic compression stockings; DVT = deep vein thrombosis; PTS = postthrombotic syndrome.